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# The Selection and Use of Essential Medicines

Report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2019 (including the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children)

World Health Organization

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# Contents

# Executive summary

This summary reports the recommendations made by the WHO Expert Committee on the Selection and Use of Essential Medicines for the 2019 Essential Medicines Lists update.

The 22nd meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines took place in Geneva, Switzerland, from 1 to 5 April 2019. The aim of the meeting was to review and update the *20th WHO Model List of Essential Medicines (EML) and the 6th WHO Model List of Essential Medicines for Children (EMLc)*.

The Expert Committee considered 65 applications, including proposals to add 53 new medicines and new formulations of 19 existing medicines, extend the indications for 34 listed medicines, and to remove 10 medicines or formulations from the lists. The Expert Committee also considered reports and recommendations from the EML Antibiotics and Cancer Medicines Working Groups. In accordance with applicable procedures,[1] the Expert Committee evaluated the scientific evidence for the comparative effectiveness, safety and cost-effectiveness of the medicines in question.

In summary, the Expert Committee:

- recommended the addition of 28 new medicines to the EML (12 to the core list and 16 to the complementary list);
- recommended the addition of 23 new medicines to the EMLc (6 to the core list and 17 to the complementary list);
- recommended adding additional indications for 26 currently listed medicines;
- recommended the addition of new formulations of 16 currently listed medicines;
- recommended the deletion of 9 medicines and of specific formulations of a further 4 medicines; and
- rejected 21 applications for inclusion, change or deletion of 31 medicines.

The recommendations are briefly described below in order of their appearance on the Model Lists according to the classification.

A full summary of changes to the Model Lists is shown in Table 1. The applications not recommended are listed in Table 2.

[1] WHO medicines strategy. Geneva: World Health Organization: 2001. See: http://www.who.int/selection_medicines/committees/subcommittee/2/eeb1098%5b1%5d.pdf.

# Section 6: Anti-infective medicines

## Section 6.2: Antibacterials

### AWaRe classification of antibiotics

The Expert Committee noted the adoption and utilization of the Access, Watch and Reserve (AWaRe) classification of antibiotics on the EML by several Member States including the endorsement of AWaRe by the G20 Health Ministers in 2018.[2] Furthermore, a new target indicator based on AWaRe was adopted that specifies a country-level target of at least 60% of antibiotic consumption being from the Access group. This indicator is intended to monitor access to essential medicines and progress towards universal health coverage under the WHO 13th General Programme of Work.[3] The Committee recognized the emerging role of the AWaRe groups for stewardship and quality improvement programmes.

The Expert Committee recommended that specific listing of antibiotics in the EML and the allocation of antibiotics to the different AWaRe groups should be distinguished from each other, recognizing their distinct albeit complementary purposes. The Committee acknowledged that EML-listed antibiotics represent a parsimonious, evidence-based selection of essential narrow spectrum antibiotics for first- and second-choice empiric treatment of most common bacterial infections and a tool for stewardship. However, the AWaRe classification should extend beyond the EML to all commonly used antibiotics globally. The Committee acknowledged the contributions of the EML Antibiotics Working Group and endorsed the Working Group's recommendations for AWaRe classification of 177 commonly used antibiotics, to better support antibiotic monitoring and stewardship activities. The Expert Committee recommended the development of an AWaRe classification database as a searchable resource for countries.

### Antibiotics not classified as Access, Watch or Reserve

The Committee recommended, based on the advice of the EML Antibiotics Working Group, that WHO may wish to consider creating an additional group in the AWaRe classification database for antibiotics whose use is not evidence-based, nor recommended in high quality international guidelines, particularly fixed-dose combinations of multiple broad-spectrum antibiotics. Antibiotics in this group are not included on the Model Lists.

The AWaRe classification database will be published as an Online Appendix to the 2019 Model Lists and Technical Report of the meeting.

The Expert Committee recommended the re-structuring of Section 6.2 to better accommodate AWaRe classification, and that antibiotics on the EML be listed in revised sub-sections according to AWaRe groups, replacing the existing sub-sections based on chemical structure (e.g.,

[2] Declaration: G20 Meeting of Health Ministers (4th October 2018, Mar del Plata, Argentina. See: http://www.g20.utoronto.ca/2018/2018-10-04-health.pdf.

[3] WHO Thirteenth General Programme of Work, 2019–2023;WHO Impact Framework. See: http://apps.who.int/gb/ebwha/pdf_files/EB144/B144_7-en.pdf.

beta-lactam and other antibacterials). The subsequent sub-sections within Section 6.2 are re-numbered accordingly:

- **6.2.1: Access group antibiotics**
- **6.2.2: Watch group antibiotics**
- **6.2.3: Reserve group antibiotics**
- **6.2.4: Antileprosy medicines**
- **6.2.5: Antituberculosis medicines**

### Additions, changes and deletions

The Expert Committee recommended for inclusion three new recently registered antibiotics for treatment of multi-drug resistant infections caused by pathogens ranked as "Critical Priority" on the WHO Priority pathogens list[4] and classified under AWaRe as Reserve antibiotics: ceftazidime + avibactam, meropenem + vaborbactam and plazomicin. Four recently registered antibiotics were not recommended for EML inclusion, but were classified under AWaRE for monitoring purposes (ceftolozane + tazobactam, eravacycline and omadacycline as Reserve; delafloxacin as Watch).

The Committee recommended first- and second-choice empiric antibiotic treatment options for enteric fever, surgical prophylaxis and progressive apical dental abscess on the EML and EMLc, including the addition of cefuroxime (for surgical prophylaxis), classified under AWaRe as a Watch group antibiotic.

The Committee recommended the removal of aztreonam, fourth- and fifth-generation cephalosporins (as classes), tigecycline and daptomycin from the EML and EMLc as these antibiotics did not meet the revised criteria for inclusion on the Model Lists as individual Reserve group agents (see 6.2.3 Reserve group antibiotics, below). Furthermore, the Committee agreed that fourth-generation cephalosporins should be re-classified as Watch group as they did not meet the revised criteria for classification as Reserve. The Committee also recommended the re-classification of faropenem from the Watch to the Reserve group due to its high potential for inappropriate use. It is an orally available formulation with a broad-spectrum activity, inappropriate use of which may further the spread of carbapenemase-producing *Enterobacteriaceae*.

## Section 6.2.1: Access group antibiotics

This category includes antibiotics that have activity against a wide range of commonly encountered susceptible pathogens while showing lower resistance potential than antibiotics in Watch and Reserve groups. The following 19 Access group antibiotics are recommended as first or second choice empiric treatment options for infectious syndromes reviewed by the Expert Committee, and are listed as individual medicines on the Model Lists to promote optimal use and with the goal of improving global "access to Access" antibiotics.

[4] Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. See: https://apps.who.int/iris/handle/10665/311820.

| Access group antibiotics included on the 2019 Model Lists | |
|---|---|
| Amikacin | Cloxacillin |
| Amoxicillin | Doxycycline |
| Amoxicillin + clavulanic acid | Gentamicin |
| Ampicillin | Metronidazole |
| Benzathine benzylpenicillin | Nitrofurantoin |
| Benzylpenicillin | Phenoxymethylpenicillin |
| Cefalexin | Procaine benzylpenicillin |
| Cefazolin | Spectinomycin |
| Chloramphenicol | Sulfamethoxazole + trimethoprim |
| Clindamycin | – |

## Section 6.2.2: Watch group antibiotics

The Watch group includes antibiotics that have higher resistance potential and includes most of the highest priority agents among the list of critically important antimicrobials (CIA) for human medicine[5] and/or antibiotics that are at relatively high risk of selection of bacterial resistance. These medicines should be prioritized as key targets of national and local stewardship programmes and monitoring. The following 11 Watch group antibiotics are recommended as essential first or second choice empiric treatment options for a limited number of specific infectious syndromes and are listed as individual medicines on the WHO Model Lists.

| Watch group antibiotics included on the 2019 Model Lists | |
|---|---|
| Azithromycin | Ciprofloxacin |
| Cefixime | Clarithromycin |
| Cefotaxime | Meropenem |
| Ceftazidime | Piperacillin + tazobactam |
| Ceftriaxone | Vancomycin |
| Cefuroxime | |

[5] Critically important antimicrobials for human medicine, 6th Revision. See: https://apps.who.int/iris/handle/10665/312266.

## Section 6.2.3: Reserve group antibiotics

The Reserve group includes antibiotics that should be reserved for treatment of confirmed or suspected infections due to multidrug-resistant organisms. Reserve group antibiotics should be considered as 'last resort' options. Seven selected Reserve group antibiotics are listed as individual medicines on the WHO Model Lists as they have a favourable benefit-risk profile and proven activity against Critical Priority" or "High Priority" pathogens as identified by the WHO priority pathogens list, most notably carbapenem-resistant *Enterobacteriaceae*. These antibiotics should be globally accessible, but their use should be tailored to highly specific patients and settings, when alternatives are not suitable or have failed. To preserve their effectiveness these Reserve group antibiotics should be prioritized as key targets of national and international stewardship programmes including regular monitoring and reporting of their use.

| Reserve group antibiotics included on the 2019 Model Lists | |
|---|---|
| Ceftazidime + avibactam | Meropenem + vaborbactam |
| Colistin | Plazomicin |
| Fosfomycin (intravenous) | Polymyxin B |
| Linezolid | |

## EML Antibiotics/AWaRe Working Group

The Expert Committee acknowledged that the existing EML listings and the classification of individual medicines to specific AWaRe groups may change slightly over time, due to the evolving epidemiology of infectious diseases and antimicrobial resistance, changes in the availability of antibiotics and emergence of new scientific evidence. The ongoing revision and consolidation of the antibiotics included on the EML and of AWaRe classification is a key activity of the Working Group, with the aim of balancing the objectives of preserving antibiotic effectiveness while guaranteeing necessary access. Therefore, the Committee recommended the continuation of the activities of the EML Antibiotics/AWaRe Working Group.

The Committee recommended that the Working Group should assess the adoption of the AWaRe classification across countries and further explore how AWaRe can assist in activities to promote optimal antibiotic stewardship. Some areas needing more investigation are the incorporation of AWaRe in national essential medicines lists and clinical practice guidelines, and the adaptation of AWaRe for educational activities to improve antibiotic use. The Committee recommended the Working Group develop antibiotic stewardship algorithms for Reserve antibiotics to define how these medicines should be used and how their misuse can be prevented. This includes the identification of evidence gaps for the recommended uses in clinical practice. The Committee noted that the current regulatory approval process for new antibiotics, most of which qualify for the Reserve category due to their activity against priority multidrug-resistant pathogens (usually carbapenem-resistant pathogens), does not result in adequate evidence to judge their role for

their optimal clinical use and guide appropriate policy interventions. The Working Group should identify and document these evidence gaps and propose research strategies for how to address them. In general, the AWaRe groups, the WHO priority pathogens list and the WHO list of critically important antimicrobials should become more closely aligned with regard to definitions and terminology to avoid confusion and the Working Group should support and expand this effort.

Additional proposed activities of the Working Group include the development of policy documents assessing optimal antibiotic dosage and treatment duration for common infectious syndromes in both adults and children. This information, together with the Model Lists and AWaRe classification should inform production of a WHO handbook outlining antibiotic treatment guidance for high-burden bacterial syndromes. This information should also be made available in an easily accessible electronic format, e.g. by incorporating this information into the electronic EML.

## Section 6.2.4: Antituberculosis medicines

The Committee recommended the inclusion of meropenem and of amoxicillin + clavulanic acid on the complementary list of the EML and EMLc for the new indication of treatment for multidrug-resistant tuberculosis (MDR-TB). The Committee recommended that imipenem + cilastatin could be considered as an alternative to meropenem for use in adults. The Committee expressed concern in relation to increased use of carbapenem antibiotics (classified as Watch group) in the empiric treatment of MDR-TB and the development of carbapenem resistance and recommended that ongoing monitoring for the development of resistance be undertaken.

The Committee recommended the addition of several new formulations of currently listed medicines for use in children: cycloserine, ethambutol, ethionamide, isoniazid, levofloxacin, linezolid and moxifloxacin. The addition of child-friendly formulations of antituberculosis medicines is fully in line with the latest WHO guideline recommendations on the management of MDR- and isoniazid-resistant TB.

The Committee recommended the deletion of capreomycin and kanamycin from the complementary list of the EML and EMLc, noting that their use is no longer recommended in WHO guidelines due to increased treatment failure and toxicity when compared to alternative oral therapeutic options. The Committee also recommended the deletion from the EML of fixed-dose combination of ethambutol + isoniazid, and specific formulations/strengths of fixed-dose combinations of isoniazid + pyrazinamide + rifampicin and isoniazid + rifampicin, no longer recommended in WHO guidelines due to their association with higher rates of treatment failure.

The Committee recommended the addition of bedaquiline to the complementary list of the EMLc for the treatment of MDR-TB in children aged 6 years and older, as extrapolation of evidence from adult data suggests good efficacy and benefits outweigh risks. The Committee did not recommend a change to the age restriction (≥6 years) that applies to the listing of delamanid on the Model Lists, as the evidence used to support the lowering of the age limit in the WHO Guidelines used a formulation and strength of delamanid that is not currently commercially available, nor bioequivalent to the formulation and strength included in the EMLc.

The Committee did not recommend the addition of injectable formulations of ethambutol, isoniazid, p-aminosalicylic acid (PAS) and rifampicin: the Committee noted that WHO recommends oral treatment regimens, ideally administered in fixed-dose combinations. The Committee also noted that the availability of the proposed injectable agents was limited and recognized the potential for inappropriate use of prolonged parenteral anti-TB medicines. The Committee did not recommend the addition of a new strength formulation of isoniazid oral liquid, giving preference to dispersible tablet formulations.

### Section 6.4.2: Antiretrovirals

For the treatment of human immunodeficiency virus (HIV) infection, the Committee recommended the addition of the fixed-dose combination of dolutegravir + lamivudine + tenofovir disoproxil fumarate to the EML, and the addition of dolutegravir to the EMLc, in line with recommendations in the latest WHO Guidelines. The Committee also recommended addition of new formulations of raltegravir, ritonavir, and lopinavir + ritonavir. Formulations of abacavir + lamivudine and zidovudine were recommended for deletion, while formulations of raltegravir and ritonavir proposed for deletion were recommended to be retained until the availability of newer, preferred formulations is assured.

### Section 6.4.4.2: Medicines for hepatitis C

This section of the list has been amended to differentiate between pangenotypic and non-pangenotypic direct-acting antivirals, and other antivirals for hepatitis C virus infection.

### Section 6.4.4.2.1: Pangenotypic direct-acting antiviral combinations

The Committee recommended the addition of the fixed dose combination of glecaprevir + pibrentasvir to the EML for the treatment of adult patients with chronic hepatitis C virus infection based on evidence of pangenotypic effectiveness with acceptable safety, as supported by current WHO guidelines. The Committee noted that the EML now contains multiple pangenotypic treatment options for hepatitis C (sofosbuvir + velpatasvir, sofosbuvir/daclatasvir, glecaprevir + pibrentasvir) and recommended that they be considered as therapeutically equivalent to facilitate selection and procurement at country level.

### Section 6.4.4.2.2: Non-pangenotypic direct-acting antiviral combinations

The Committee also recommended the deletion from the EML of simeprevir, whose place in therapy has been superseded by the pangenotypic options. Other non-pangenotypic treatments could be considered for deletion in the future.

### Section 6.5.3.2: (Antimalarial medicines) for chemoprevention

The Committee recommended listing of fixed-dose combination formulations of sulfadoxine + pyrimethamine on the EML for the new indication of intermittent preventive treatment of malaria in pregnancy (IPTp), and on the EMLc for the new indication of intermittent preventive treatment of malaria in infancy (IPTi); and the addition of co-packaged formulations of

amodiaquine and sulfadoxine + pyrimethamine dispersible tablets to the EMLc for seasonal malaria chemoprevention, in line with recommendations in WHO guidelines for the treatment of malaria.

### Section 6.5.5.1: African trypanosomiasis

The Committee recommended the addition of fexinidazole to the EML and EMLc as an orally-administered treatment for treatment of 1st and 2nd stages of human African trypanosomiasis due to *Trypanosoma brucei gambiense* infection.

### Section 6.6: Medicines for ectoparasitic infections (New)

The Committee recommended listing of ivermectin on the EML and EMLc for the new indication of treatment of scabies, in a new sub-section of the list for ectoparasitic infections. The Committee noted the potential advantages of single-dose oral administration of ivermectin compared to topically administered alternatives in terms of improved compliance.

## Section 7: Antimigraine medicines

The Committee did not recommend the addition of sumatriptan to the EML for the treatment of adult patients with acute migraine. The Committee noted that available evidence supports the greater effectiveness of sumatriptan compared to placebo, but evidence comparing sumatriptan with analgesics currently included on the EML for treatment of migraine (aspirin and paracetamol) showed varying results, including no difference in effect. At its next meeting, the Committee would welcome a review of additional data of the role in therapy of sumatriptan in the context of other migraine therapies and current guideline recommendations.

## Section 8: Immunomodulators and antineoplastics (Re-named)

### Section 8.1: Immunomodulators for non-malignant disease (Re-named)

**Anti-TNF biologics for chronic inflammatory conditions:** The Committee recommended the addition of adalimumab to the complementary list of the EML and EMLc for use in the treatment of chronic inflammatory autoimmune disorders – rheumatoid arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and Crohn disease based on a positive benefit-risk profile as second-line treatment (after methotrexate). Adalimumab is listed with a square box, representative of the class of tumour necrosis factor alpha (TNF-α) inhibitors, including biosimilars. Alternatives were limited to etanercept and infliximab on the EMLc and to etanercept, infliximab, certolizumab pegol and golimumab on the EML. The Committee recognized that these medicines are associated with a significant budget impact to health systems as they are used for long periods and are often highly priced. However, the availability of several therapeutically equivalent alternatives and increased availability of biosimilar products could lead to more market competition and reduced prices.

**Medicines for multiple sclerosis:** The Committee recognized the public health need for effective and affordable treatments for multiple sclerosis (MS) but did not recommend the

addition to the EML and EMLc of glatiramer acetate, fingolimod and ocrelizumab at this time. The Committee acknowledged the application's approach to increase access to MS treatments by prioritizing selected treatment options. However, the Committee noted that some relevant therapeutic options for MS were not included in the application (azathioprine and natalizumab) or were not given full consideration (rituximab). The superiority of presented medicines over other therapeutic options in the outcomes considered (benefits, harms, affordability) did not clearly emerge. The Committee would therefore welcome a revised application that comprehensively reviews the relative roles of relevant available medicines for MS.

## Section 8.2: Antineoplastic and supportive medicines (Re-named)

This section has been updated and amended to include sub-sections that better represent the pharmacologically diverse medicines currently listed:

- **8.2.1: Cytotoxic medicines**
- **8.2.2: Targeted therapies**
- **8.2.3: Immunomodulators**
- **8.2.4: Hormones and antihormones**
- **8.2.5: Supportive medicines**

Applications for new cancer medicines were the received from various sources, including a WHO Secretariat-led effort to engage with expert stakeholders through the Cancer Medicines Working Group to identify and prioritize the most effective cancer medicines for indications where they have clinically relevant benefits.

The Committee recommended listing for a number of new high-priced cancer medicines for specific indications on the complementary list of the EML.

Melanoma: nivolumab (with a square box indicating pembrolizumab as a therapeutically equivalent alternative) for first-line monotherapy in patients with unresectable and metastatic melanoma. Both these medicines demonstrated highly relevant increases in overall survival and represent the first medicines on the EML for metastatic melanoma.

Multiple myeloma: bortezomib, lenalidomide, thalidomide and melphalan for the treatment of patients with newly-diagnosed multiple myeloma in both non-transplant and transplant eligible/available settings. These medicines demonstrated large improvements in survival with acceptable safety and represent the first medicines on the EML for multiple myeloma.

Lung cancer: erlotinib (with a square box indicating afatinib and gefitinib as therapeutically equivalent alternatives) for first-line treatment of epidermal growth factor receptor (EGFR) mutation-positive advanced non-small cell lung cancer. These medicines demonstrated relevant survival benefits (similar to that of cytotoxic chemotherapy) and offer better toxicity profiles and improved quality of life compared to chemotherapy.

Prostate cancer: abiraterone for the treatment of patients with metastatic castration-resistant prostate cancer. Abiraterone demonstrated relevant survival benefits for patients and an

acceptable safety profile. It is associated with potential advantages in terms of emerging dosing strategies, lower pill burden and availability of generics, which would be associated with cost-savings compared to similarly effective enzalutamide. Enzalutamide was not recommended for listing on the EML.

Leukaemias (EML and EMLc): arsenic (oral and IV formulations) for use in the treatment of patients with acute promyelocytic leukaemia. Arsenic-containing regimens were associated with less toxicity, high response rates and greater survival benefits compared to standard regimens. Pegaspargase was recommended for treatment of patients with acute lymphoblastic leukaemia as it is associated with less immunogenicity and antibody development compared to asparaginase.

The listings of some cancer medicines currently on the EML were recommended to be extended to include new indications of cervical cancer and multiple myeloma. Additionally, listing of 10 medicines currently included on the EML were recommended to be extended to the EMLc and additional indications were recommended for 11 cancer medicines currently included on the EMLc to improve access to these medicines for children. Refer to Table 1 for details.

The applications for cancer medicines that were not recommended for listing on the EML were:

- nivolumab, pembrolizumab and atezolizumab for the treatment of non-small cell lung cancer, as the Committee considered that their place in therapy for this condition is still evolving and that more data with longer follow-up are needed to better demonstrate estimates of their actual magnitude of benefit;
- pertuzumab for human epidermal growth factor receptor 2 (HER2)-positive breast cancer, as the evidence did not demonstrate a clinically meaningful survival benefit in early stage disease. A large overall survival benefit has been demonstrated in a single trial in metastatic disease, but similar results have not been seen in other trials. The Committee recommended further independent analysis of data from existing and ongoing trials be undertaken to inform future consideration for EML listing.
- Trastuzumab emtansine for HER2 positive breast cancer, because while it demonstrates a relevant survival benefit, its use as second-line treatment of metastatic disease was considered not to be a priority in the context of treatment of breast cancer, and alternative EML-listed options are available.
- Subcutaneous formulations of rituximab and trastuzumab, as the Committee was concerned that listing of these formulations, for which biosimilars are not yet available, could limit competition and therefore limit access for patients.

## EML Cancer Medicines Working Group

The Expert Committee acknowledged the work of the EML Cancer Medicines Working Group and endorsed the Working Group recommendations that WHO adopt a threshold for benefit of at least four to six months survival gain to be considered as candidates for EML inclusion. The Committee acknowledged the role of the European Society For Medical Oncology (ESMO) Magnitude of

Clinical Benefit Scale[6] (ESMO–MCBS) as a screening tool to identify cancer treatments that have potential therapeutic value that warrants full evaluation for EML listing. Potential new EML cancer medicines, in general, should have a score on the ESMO-MCBS of A or B in the curative setting and of 4 or 5 in the non-curative setting. These scores would support a medicine being evaluated by the Expert Committee for inclusion in the EML through a full application.

The Committee recommended the continuation and further expansion of the activities of the Working Group. This should include the updated revision of treatment protocols for cancers previously considered by the Committee and identification of new cancer medicines that meet the above-mentioned criteria to be candidates for consideration of inclusion on the EML.

The Working Group should also review the issues being experienced at country level in relation to implementation of EML cancer medicine recommendations and access to cancer medicines. The Committee recommended the need for consolidation of cancer medicine recommendations and EML listings through a broader technical advisory group meeting, with country engagement to support implementation within a UHC perspective.

## Section 10: Medicines affecting the blood

### Section 10.2: Medicines affecting coagulation

The Committee recommended the addition of dabigatran to the core list of the EML, with a square box (representative of the direct oral anticoagulants including apixaban, edoxaban and rivaroxaban) for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, and for the treatment of venous thromboembolism. These medicines have a similar overall benefit-risk profile compared to warfarin, are associated with a lower risk of major bleeding, and may be particularly beneficial in settings where warfarin monitoring is not available.

## Section 12: Cardiovascular medicines

### Section 12.3: Antihypertensive medicines

The Committee recommended the addition of four, two-drug fixed-dose combination formulations to the core list of the EML for the treatment of hypertension: lisinopril + amlodipine, lisinopril + hydrochlorothiazide, telmisartan + amlodipine and telmisartan + hydrochlorothiazide. Each component is listed with a square box as representative of the relevant pharmacological classes. The Committee accepted that fixed-dose combinations may confer advantages for patients over single medicines given concomitantly in terms of better adherence and reduced pill burden. However, the Committee considered that the ongoing availability of single agent antihypertensive medicines remains critical to allow treatment modification where necessary.

[6] For European Society For Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale (ESMO–MCBS), see: https://www.esmo.org/score/cards.

### Section 12.5.2: Thrombolytic medicines

The Committee recommended the addition of alteplase to the complementary list of the EML for use in patients diagnosed with acute ischaemic stroke. The Committee noted that alteplase thrombolysis is associated with reductions in death and dependence when administered within 4.5 hours of the onset of stroke symptoms. Optimal use will require timely and highly organized care pathways, in facilities equipped and capable of managing stroke patients.

## Section 17: Gastrointestinal medicines

### Section 17.2: Antiemetic medicines

The Committee recommended the addition of aprepitant to the complementary list of the EML and EMLc for management of chemotherapy-induced nausea and vomiting in patients undergoing moderately- to highly-emetogenic chemotherapy, as it has been shown to be more effective than standard antiemetics. The Committee also recommended the addition of a square box to the current listings of ondansetron on the EML and EMLc, indicating therapeutic equivalence among 5HT3 receptor antagonists.

### Section 17.5: Medicines used in diarrhoea

The Expert Committee recommended listing on the core list of the EMLc of a co-packaged presentation of oral rehydration salts and zinc sulfate tablets, noting the recommendations for co-administration of the two components in the management of diarrhoea in children. The co-packaged product was considered practical, and likely to support better adherence to treatment.

## Section 18: Medicines for endocrine disorders (Re-named)

This section has been updated and amended to include only medicines for endocrine disorders in revised sub-sections as follows:

- **18.1: Adrenal hormones and synthetic substitutes**
- **18.2: Androgens**
- **18.3: Estrogens**
- **18.4: Progestogens**
- **18.5: Medicines for diabetes**
- **18.6: Medicines for hypoglycaemia**
- **18.7: Thyroid hormones and antithyroid medicines**

Contraceptives and other medicines for reproductive health have been transferred to Section 22 (see below).

### Section 18.5: Medicines for diabetes

The Committee acknowledged that insulin is a life-saving essential medicine for which a compelling public health need exists. Yet, despite being available for almost 100 years, achieving

reliable, equitable and affordable access to insulin remains a public health challenge in many countries. The Committee recognized the need for a wider understanding of the complexities of access to insulin and the current insulin market and recommended WHO to prioritize the coordination of a series of actions to address the issues of insulin access and affordability.

This WHO coordinated approach should aim at tackling the different aspects of the current situation of sub-optimal access to insulin in many countries. This includes:

- establishment of a WHO technical working group on access to insulin;
- consultation with Member States and other stakeholders to identify/clarify barriers to access at country level;
- strategies to address current regulatory barriers for biosimilar insulins, including the expansion of the WHO Prequalification Programme;
- development of a comprehensive approach to address insulin prices, including new mechanisms for pooled procurement through UN supply agencies (e.g. UNICEF and UNDP) and through providing support for countries;
- identification of evidence and research gaps regarding insulin use and supply, including setting-specific differences in clinical practice and health systems.

The Committee did not recommend the addition of insulin analogues to the EML, reiterating the conclusion of the 2017 Expert Committee, that while long-acting insulin analogues are an effective treatment for type 1 diabetes, the available evidence shows efficacy and safety advantages of analogues compared to human insulin which are insufficiently large to justify the cost differential that continues to exist. In the absence of other coordinated actions, the Committee considered that the inclusion of insulin analogues for adults on the EML would be inadequate to address the underlying issues of poor access and affordability of insulins. The Committee would therefore welcome a report that comprehensively describes the actions that are undertaken over the next two years and an application that reviews in greater depth the current challenges for optimal global access and the role of insulin analogues in children.

## Section 18.6: Medicines for hypoglycaemia

The Committee recommended addition of diazoxide on the complementary list of the EMLc for the management of hypoglycaemia secondary to prolonged hyperinsulinism, based on a positive benefit-to-risk ratio and for its impact on reducing the serious neurological consequences of untreated hyperinsulinism in newborns.

## Section 18.7: Thyroid hormones and antithyroid medicines

The Committee recommended the addition of methimazole with a square box to the core list of the EML and to the complementary list of the EMLc for the treatment of primary hyperthyroidism. Carbimazole is a therapeutically equivalent alternative. The Committee also recommended that the square box be removed from the listing of propylthiouracil on the EML. Propylthiouracil remains the recommended first-line treatment for women in the first trimester of pregnancy, and in patients for whom first-line treatment with methimazole (or carbimazole) is not appropriate

or available. Propylthiouracil remains listed on the complementary list of the EMLc for use in patients for whom alternative first-line treatment is not appropriate or available.

## Section 19: Immunologicals

### Section 19.3: Vaccines

This section was updated by the Secretariat for consistency and alignment with the most recent WHO immunization policy recommendations and vaccine position papers. Dengue vaccine was added to the EML and EMLc for use in some high-risk populations, in line with the September 2018 dengue vaccine WHO position paper.[7]

## Section 22: Medicines for reproductive health and perinatal care (Re-named)

This section has been updated and amended to include contraceptives and other medicines for reproductive health, maternal and neonatal care (from Sections 18, 22 and 29).

### Section 22.3: Uterotonics

The Committee recommended the addition of heat-stable carbetocin injection to the core list of the EML for the prevention of postpartum haemorrhage based on similar effects compared to oxytocin for efficacy and safety outcomes. The Committee agreed that heat-stable carbetocin may offer advantages over oxytocin in some settings as it does not require cold chain transport or refrigerated storage.

The Committee did not recommend deletion of the indication of prevention of post-partum haemorrhage for misoprostol, noting that misoprostol is recommended in WHO guidelines as an alternative to oxytocin in settings where injectable uterotonics are not available or cannot be safely administered.

The Committee recommended the transfer of mifepristone – misoprostol from the complementary to the core list of the EML, and removal of the note accompanying the listing stating, "Requires close medical supervision", based on the evidence presented that close medical supervision is not required for its safe and effective use. The Committee also recommended the addition of a co-packaged presentation of mifepristone and misoprostol to the core list of the EML.

Recalling that their role and responsibility is to provide WHO with technical guidance in relation to the selection and use of essential medicines, the Committee noted that its mandate did not extend to providing advice regarding the statement "Where permitted under national law and where culturally appropriate". Subsequent to the Committee meeting, the Director-General, in consultation with the Department of Essential Medicines and Health Products, decided that no change to the statement be made.

[7] Dengue vaccine: WHO position paper (2018). See: https://apps.who.int/iris/bitstream/handle/10665/274315/WER9336.pdf?ua=1.

### Section 22.6: Other medicines administered to the mother

The Committee recommended the addition of tranexamic acid to the core list of the EML for the new indication of treatment of postpartum haemorrhage (PPH), to be used as part of the standard PPH treatment package, including fluid replacement, uterotonics surgical and non-surgical interventions, in accordance with WHO guidelines.

## Section 24: Medicines for mental and behavioural disorders

The Committee did not recommend inclusion of methylphenidate on the Model Lists for the treatment of attention-deficit hyperactivity disorder (ADHD) due to uncertainties in the estimates of benefit, and concerns regarding the quality and limitations of the available evidence for both benefit and harm.

### Section 24.2.1: Medicines used in depressive disorders

The Committee recommended the addition of a square box to the listing of fluoxetine on the core list of the EML for the treatment of depressive disorders. The Committee noted that medicines within the pharmacological class of selective serotonin reuptake inhibitors (SSRI) have demonstrated efficacy, but can differ in terms of pharmacokinetics, adverse events and drug-interaction profiles. The availability of different SSRIs as essential medicines may be beneficial at the country level to expand therapeutic alternatives for patients and support better procurement. The Committee considered that it was not necessary to add escitalopram to the EML, as the addition of the square box to fluoxetine would allow the selection of escitalopram at national level.

## Section 25: Medicines acting on the respiratory tract

The Committee recommended the addition of tiotropium to the core list of the EML, with a square box as representative of the pharmacological class of long-acting muscarinic antagonists (LAMA) for the treatment of chronic obstructive pulmonary disease (COPD), based on evidence of effectiveness in controlling COPD symptoms and reducing exacerbations, and acceptable safety.

## Section 27: Vitamins and minerals

The Committee recommended a correction to the listed strength of iodine capsules to 190 mg, to accurately reflect the quantitative composition of this product.

The Committee recommended the addition of multiple micronutrient powders to the core list of the EMLc for the prevention of anaemia in infants and children, noting that a standardized product monograph is to be included in the United States Pharmacopoeia.

## Section 29: Medicines for diseases of joints

Formerly Section 30. Re-numbered following the transfer of medicines specific for neonatal care to Section 22. The former Section 30 has been deleted.

## Follow up decisions from the 2017 Expert Committee meeting

### Oseltamivir

The Committee noted the advice from the WHO Secretariat that the WHO Guidelines for clinical management of influenza are in the process of being updated, but the recommendations of the guideline development group were not yet available. The Committee recommended that no change be made to the current listing for oseltamivir on the Model Lists until the updated guidelines and supporting evidence can be reviewed.

### Ready-to-use therapeutic food

The Committee did not recommend the addition of ready-to-use therapeutic food (RUTF) to the Model Lists for the treatment of severe acute malnutrition, but again acknowledged the effectiveness of this product for this condition. The Committee considered that the comprehensive report prepared by the WHO Department of Nutrition in response to the request of the previous Expert Committee, highlighted the divided opinions and ongoing uncertainty of the implications at country level of listing RUTF as a medicine on the Model List.

### Working Group on Transparency and Access to Clinical Trial Data

The Committee reiterated its recommendation from 2017 to establish a working group on transparency and timely public disclosure of all clinical trial results and available data. The Working Group should identify strategic actions to address factors known to impact the availability of reliable data informing applications for the inclusion or removal of medicines on the Model Lists. Such factors include selective outcome reporting, publication bias and open access to clinical trial results. This Working Group could also action the recommendation made by the Expert Committee for further independent analysis of data for pertuzumab in breast cancer.

## Improving access to and affordability of essential medicines

Throughout the meeting, the Committee repeatedly noted and discussed the issue of improving access to high-priced essential medicines (e.g. insulin, immunomodulators and new cancer medicines) and the issue of affordability for health systems and patients.

The Committee acknowledged the limited role of WHO in price-setting at the country level, but identified several different actions that could contribute to making some of the recently listed essential medicines more affordable at the country level:

1. A wider adoption of biosimilars.
2. Expanding the remit of the Medicines Patent Pool.
3. The role of pooled procurement/tendering.
4. Use of flexibilities enshrined in the WHO TRIPS agreement.
5. Other existing instruments.

## 1. Biosimilars

With the addition of new biological medicines to the Model Lists in 2019, the Committee recognized that biologicals, including biosimilars, are associated with a significant budget impact to health systems. However, the availability of several therapeutically equivalent alternatives and the increasing availability of biosimilar products could lead to greater market competition, improved patient access and reduced costs. Access to biosimilars is critical for achieving affordable access to many biological medicines including new cancer treatments and immunomodulators for chronic inflammatory conditions such as rheumatoid arthritis. The Committee noted, with concern, the limited progress to date with access to biosimilars of some essential medicines (e.g. rituximab).

The Committee recommended that WHO expand its Prequalification Programme to include biosimilars of medicines listed on the EML, such that they are routinely evaluated along with the reference product, to ensure accessibility and affordability to quality-assured products.

The Expert Committee considered the issue of interchangeability of biosimilar products as a very important one for wider access and a crucial aspect to foster competition. The Committee recommended that the EML Secretariat develops a concept note to summarize all the issues and barriers to full interchangeability for wider access to affordable biosimilars for consideration by the Expert Committee in 2021.

Finally, the Committee considered that where biosimilars of listed essential medicines exist, these are considered therapeutically equivalent also for procurement purposes.

## 2. The expanded role of the Medicines Patent Pool

The Medicines Patent Pool (MPP), a public health organization funded by Unitaid, has played a significant role in facilitating affordable access to essential medicines in the field of HIV and hepatitis C virus (HCV) through its public health-oriented licences with originator companies. To date, the MPP has licences on 14 medicines on the WHO EML. Licensing through the MPP of patented essential medicines for the treatment of tuberculosis (e.g. bedaquiline) would also be a welcome contribution to improving access.

The recent expansion of the MPP to other patented essential medicines beyond HIV, hepatitis C and tuberculosis represents a real opportunity to facilitate affordable access to some of the new medicines that have been added to the list this year in low and middle-income countries (LMICs). Licensing through the MPP could, for example, contribute to facilitating access to some of the cancer medicines, the novel oral anticoagulants, the new antibiotics and the heat-stable formulation of carbetocin. In the case of cancer, it would be important that the MPP also explore the application of its model to biotherapeutics so as to facilitate early entry of biosimilars through voluntary licensing agreements in LMICs.

## 3. The role of pooled procurement and tendering

The square box symbol (□) is primarily intended to indicate similar clinical performance within a pharmacological class of medicines on the EML. The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. Examples of pharmacological classes with established therapeutic equivalence include proton pump inhibitors, ACE inhibitors and erythropoietins.

More recently, the square box has been selectively applied to some listings, indicating specific acceptable alternative options such as for morphine and enoxaparin. A square box was applied to three pangenotypic regimens for hepatitis C, to indicate similar clinical performance across the combination regimens.

When there are multiple options within the same pharmacological class or in the same therapeutic area there can be substantial market competition that can allow for price reductions. Large price reductions can be the result of tendering processes at the country or local level. Applying the square box concept can improve outcomes in pooled procurement activities at national or sub-national levels, and has the advantage of improving transparent governance.

The Committee recommended a comprehensive review of medicines listed with a square box on the Model Lists be undertaken for consideration at its next meeting. The review will provide greater clarity for countries regarding application of the square box concept for national essential medicines lists selection and procurement.

## 4. Use of TRIPS flexibilities in line with the Doha Declaration on TRIPS and Public Health

Application and management of intellectual property should contribute to innovation and promotion of public health, in line with *WHO Global strategy and plan of action on public health, innovation and intellectual property*.

Member States have the possibility to make use of the provisions that provide public health flexibilities contained in the *Agreement on Trade-Related Aspects of Intellectual Property Rights*, including the public health flexibilities recognized by the *Doha Ministerial Declaration on the TRIPS Agreement and Public Health* in order to promote access to essential medicines.

## 5. Other existing instruments

Countries can define different pricing policies on how prices are set and negotiated at the national level. However, medicines prices are the end result of a number of measures, actions and contextual factors (such as market size and cost structures) acting at a country level. These can involve different stakeholders that include regulators, reimbursement systems/third-party payers, and competition authorities.

Competition law and policies are also instruments available to governments in addressing public health concerns, competition policy has an important role to play in ensuring access to medical technology and fostering innovation in the pharmaceutical sector.[8]

All applications and documents reviewed by the Expert Committee are available on the WHO website at: https://www.who.int/selection_medicines/committees/expert/22/en/.

Table 1
**Recommended additions, changes and deletions on the 2019 EML and EMLc**

| **EML – New medicines added** | | **EMLc – New medicines added** | |
|---|---|---|---|
| **Medicine** | **Indication** | **Medicine** | **Indication** |
| Abiraterone | Prostate cancer | ☐ Adalimumab | Chronic systemic inflammatory conditions |
| ☐ Adalimumab | Chronic systemic inflammatory conditions | All-trans retinoid acid (ATRA) | Acute promyelocytic leukaemia |
| Alteplase | Thrombolytic | Aprepitant | Nausea and vomiting |
| Aprepitant | Nausea and vomiting | Arsenic trioxide | Acute promyelocytic leukaemia |
| Arsenic trioxide | Acute promyelocytic leukaemia | Bedaquiline | Tuberculosis |
| Bortezomib | Multiple myeloma | Ceftazidime + avibactam | Reserve antibiotic |
| Carbetocin | Post-partum haemorrhage | Cefuroxime | Surgical prophylaxis |
| Ceftazidime + avibactam | Reserve antibiotic | Dasatinib | Imatinib-resistant chronic myeloid leukaemia (CML) |
| Cefuroxime | Surgical prophylaxis | Dengue vaccine | Vaccine |
| ☐ Dabigatran | Anticoagulant | Diazoxide | Hypoglycaemia |
| Dengue vaccine | Vaccine | Dolutegravir | HIV |
| Dolutegravir + lamivudine + tenofovir | HIV | ☐ Enoxaparin | Anticoagulant |
| ☐ Erlotinib | Lung cancer | Fexinidazole | Human African trypanosomiasis |

[8] Promoting access to medical technologies and innovation: intersections between public health, intellectual property and trade. See: http://www.who.int/iris/handle/10665/78069.

Table 1 *continued*

| EML – New medicines added | | EMLc – New medicines added | |
|---|---|---|---|
| **Medicine** | **Indication** | **Medicine** | **Indication** |
| Fexinidazole | Human African trypanosomiasis | Fluorouracil | Nasopharyngeal cancer, metastatic colorectal cancer, early colon cancer, early rectal cancer |
| Glecaprevir + pibrentasvir | Hepatitis C | Imatinib | Chronic myeloid leukaemia, gastrointestinal stromal tumour |
| Lenalidomide | Multiple myeloma | Irinotecan | Metastatic colorectal cancer |
| ☐ Lisinopril + ☐ amlodipine | Hypertension | ☐ Methimazole | Hyperthyroidism |
| ☐ Lisinopril + ☐ hydrochlorothiazide | Hypertension | Multiple micronutrient powders | Prevention of anaemia |
| Melphalan | Multiple myeloma | Nilotinib | Imatinib-resistant CML |
| Meropenem + vaborbactam | Reserve antibiotic | Oxaliplatin | Metastatic colorectal cancer, early colon cancer |
| ☐ Methimazole | Hyperthyroidism | Pegaspargase | Acute lymphoblastic leukaemia |
| ☐ Nivolumab | Metastatic melanoma | Procarbazine | Hodgkin lymphoma |
| Pegaspargase | Acute lymphoblastic leukaemia | RIF oral arsenic formulation | Acute promyelocytic leukaemia |
| Plazomicin | Reserve antibiotic | Rituximab | Diffuse large B-cell lymphoma |
| RIF oral arsenic formulation | Acute promyelocytic leukaemia | | |
| ☐ Telmisartan + ☐ amlodipine | Hypertension | | |
| ☐ Telmisartan + ☐ hydrochlorothiazide | Hypertension | | |
| Thalidomide | Multiple myeloma | | |
| ☐ Tiotropium | COPD | | |

| EML - New/changed indications | | EMLc - New/changed indications | |
|---|---|---|---|
| **Medicine** | **Indication** | **Medicine** | **Indication** |
| Amoxicillin | Dental abscess | Amoxicillin | Dental abscess |
| Amoxicillin + clavulanic acid | Surgical prophylaxis, MDR-TB | Amoxicillin + clavulanic acid | Surgical prophylaxis, MDR-TB |
| Azithromycin | Enteric fever | Azithromycin | Enteric fever |
| Carboplatin | Cervical cancer | Bleomycin | Kaposi sarcoma |
| Cefazolin | Surgical prophylaxis | Cefazolin | Surgical prophylaxis |
| Ceftriaxone | Enteric fever | Ceftriaxone | Enteric fever |
| Ciprofloxacin | Enteric fever | Ciprofloxacin | Enteric fever |
| Cisplatin | Cervical cancer | Cisplatin | Nasopharyngeal cancer |
| Cyclophosphamide | Multiple myeloma | Cyclophosphamide | Diffuse large B cell lymphoma |
| Dexamethasone | Multiple myeloma | Cytarabine | Acute myeloid leukaemia, acute promyelocytic leukaemia |
| Doxorubicin | Multiple myeloma | Daunorubicin | Acute promyelocytic leukaemia |
| Gentamicin | Surgical prophylaxis | Doxorubicin | Diffuse large B cell lymphoma, Kaposi sarcoma |
| Ivermectin | Scabies | Gentamicin | Surgical prophylaxis |
| Meropenem | MDR-TB | Hydroxycarbamide | Chronic myeloid leukaemia |
| Metronidazole | Surgical prophylaxis | Ivermectin | Scabies |
| Phenoxymethyl-penicillin | Dental abscess | Mercaptopurine | Acute promyelocytic leukaemia |
| Prednisolone | Multiple myeloma, prostate cancer | Meropenem | MDR-TB |
| Sulfadoxine + pyrimethamine | Malaria - Intermittent preventive treatment in pregnancy | Methotrexate | Acute promyelocytic leukaemia |
| Tranexamic acid | Post-partum haemorrhage | Metronidazole | Surgical prophylaxis |
| | | Phenoxymethyl-penicillin | Dental abscess |

Table 1 *continued*

| **EML - New/changed indications** | | **EMLc - New/changed indications** | |
|---|---|---|---|
| **Medicine** | **Indication** | **Medicine** | **Indication** |
| | | Prednisolone | Diffuse large B-cell lymphoma |
| | | Sulfadoxine + pyrimethamine | Malaria – intermittent preventive treatment in infancy |
| | | Vincristine | Diffuse large B-cell lymphoma, Kaposi sarcoma |

| **EML – New formulation/strength** | | **EMLc – New formulation/strength** | |
|---|---|---|---|
| **Medicine** | **Indication** | **Medicine** | **Indication** |
| Calcium folinate | Tablet 5 mg and 25 mg | Amodiaquine with sulfadoxine + pyrimethamine | Co-package |
| Cyclophosphamide | Tablet 50 mg | Calcium folinate | Tablet 5 mg and 25 mg |
| Etoposide | Capsule 50 mg | Cyclophosphamide | Tablet 50 mg |
| Mifepristone-misoprostol | Co-package | Cycloserine | Solid oral dosage form 125 mg |
| Raltegravir | Granules 100 mg | Ethambutol | Dispersible tablet 100 mg |
| Ritonavir | Oral powder 100 mg | Ethionamide | Dispersible tablet 125 mg |
| | | Etoposide | Capsule 50 mg |
| | | Isoniazid | Dispersible tablet 100 mg |
| | | Levofloxacin | Dispersible tablet 100 mg |
| | | Linezolid | Dispersible tablet 150 mg |
| | | Lopinavir + ritonavir | Granules 40 mg + 10 mg |
| | | Moxifloxacin | Dispersible tablet 100 mg |
| | | ORS + zinc sulfate | Co-package |
| | | Raltegravir | Granules 100 mg |
| | | Ritonavir | Oral powder 100 mg |

| EML – Medicines/formulations deleted | | EMLc – Medicines/formulations deleted | |
|---|---|---|---|
| **Medicine** | **Indication** | **Medicine** | **Indication** |
| Abacavir + lamivudine | Dispersible tablet 60 mg + 30 mg | Abacavir + lamivudine | Dispersible tablet 60 mg + 30 mg |
| Aztreonam | Powder for injection 1 g; 2 g | Aztreonam | Powder for injection 1 g; 2 g |
| Capreomycin | Powder for injection 1 g | Capreomycin | Powder for injection 1 g |
| Daptomycin | Powder for injection 350 mg, 500 mg | Daptomycin | Powder for injection 350 mg, 500 mg |
| Ethambutol + isoniazid | Tablet 400 mg + 150 mg | Fifth-generation cephalosporins: e.g., ceftaroline | Powder for injection 400 mg; 600 mg |
| Fifth-generation cephalosporins: e.g., ceftaroline | Powder for injection 400 mg; 600 mg | Fourth-generation cephalosporins: e.g., cefepime | Powder for injection 500 mg; 1 g; 2 g |
| Fourth-generation cephalosporins: e.g., cefepime | Powder for injection 500 mg; 1 g; 2 g | Kanamycin | Powder for injection 1 g |
| Isoniazid + pyrazinamide + rifampicin | Tablet 150 mg + 500 mg + 150 mg | Tigecycline | Powder for injection 50 mg |
| Isoniazid + rifampicin | Tablet 60 mg + 60 mg; 150 mg + 150 mg | Zidovudine | Dispersible tablet 60 mg |
| Kanamycin | Powder for injection 1 g | | |
| Simeprevir | Capsule 150 mg | | |
| Tigecycline | Powder for injection 50 mg | | |
| Zidovudine | Dispersible tablet 60 mg | | |

| Other changes to listings | | |
|---|---|---|
| Clofazimine | Replace 'capsule' with 'solid oral dosage form' | EML and EMLc |
| Rifabutin | Replace 'capsule' with 'solid oral dosage form' | EML |
| Propylthiouracil | Remove square box, add note "for use when alternative first-line treatment is not appropriate or available; and in patients during the first trimester of pregnancy" | EML |

Table 1 *continued*

| **Other changes to listings** | | |
|---|---|---|
| Propylthiouracil | Add note "for use when alternative first-line treatment is not appropriate or available" | EMLc |
| Fluoxetine | Add square box | EML |
| Iodine capsules | Amend strength from 200 mg to 190 mg | EML and EMLc |
| Ondansetron | Add square box | EML and EMLc |
| Mifepristone-misoprostol | Transfer from complementary to core list, remove note regarding requirement for close medical supervision | EML |

| **Changes to terminology of indications** | | |
|---|---|---|
| | **2017** | **2019** |
| Infections | Chlamydia trachomatis | Sexually transmitted infection due to Chlamydia trachomatis |
| | Neisseria gonorrhoeae | Gonorrhoea |
| | Trichomonas vaginalis | Trichomoniasis |
| Cancers | Acute myelogenous leukaemia | Acute myeloid leukaemia |
| | Wilms tumour | Nephroblastoma (Wilms tumour) |

| **Changes to sections and sub-sections of the Model Lists** | |
|---|---|
| **2017** | **2019** |
| Section 6.2: Antibacterials | |
| 6.2.1 Beta-lactam medicines | 6.2.1 Access group antibiotics |
| 6.2.2 Other antibacterials | 6.2.2 Watch group antibiotics |
| 6.2.3 Antileprosy medicines | 6.2.3 Reserve group antibiotics |
| 6.2.4 Antituberculosis medicines | 6.2.4 Antileprosy medicines |
| | 6.2.5 Antituberculosis medicines |
| | 6.6 Medicines for ectoparasitic infections |
| Section 6.4.4.2: Medicines for hepatitis C | |
| 6.4.4.2.1 Nucleotide polymerase inhibitors | 6.4.4.2.1 ☐ Pangenotypic direct-acting antiviral combinations |

Table 1 *continued*

| Changes to sections and sub-sections of the Model Lists | |
|---|---|
| **2017** | **2019** |
| 6.4.4.2.2 Protease inhibitors | 6.4.4.2.2 Non-pangenotypic direct-acting antiviral combinations |
| 6.4.4.2.3 NS5A inhibitors | 6.4.4.2.3 Other antivirals for hepatitis C |
| 6.4.4.2.4 Non-nucleoside polymerase inhibitors | **6.4.4.2.4 Deleted** |
| 6.4.4.2.5 Other antivirals | **6.4.4.2.5 Deleted** |
| Section 8: RENAMED - Immunomodulators and antineoplastics (was Antineoplastics and immunosuppressives) | |
| 8.1 Immunosuppressive medicines | 8.1 Immunomodulators for non-malignant disease |
| 8.2 Cytotoxic and adjuvant medicines | 8.2 Antineoplastics and supportive medicines |
| | 8.2.1 Cytotoxic medicines |
| | 8.2.2 Targeted therapies |
| | 8.2.3 Immunomodulators |
| | 8.2.4 Hormones and antihormones |
| | 8.2.5 Supportive medicines |
| 8.3 Hormones and antihormones | **8.3 Deleted** |
| Section 18: RENAMED - Medicines for endocrine disorders (formerly Hormones, other endocrine medicines and contraceptives) | |
| 18.1 Adrenal hormones and synthetic substitutes | 18.1 Adrenal hormones and synthetic substitutes |
| 18.2 Androgens | 18.2 Androgens |
| 18.3 Contraceptives | 18.3 Estrogens |
| 18.4 Estrogens | 18.4 Progestogens |
| 18.5 Insulins and other medicines used for diabetes | 18.5 Medicines for diabetes |
| 18.6 Ovulation inducers | 18.6 Medicines for hypoglycaemia |
| 18.7 Progestogens | 18.7 Thyroid hormones and antithyroid medicines |
| 18.8 Thyroid hormones and antithyroid medicines | **18.8 Deleted** |

Table 1 *continued*

| **Changes to sections and sub-sections of the Model Lists** | |
|---|---|
| **2017** | **2019** |
| Section 22: RENAMED - Medicines for reproductive health and perinatal care (formerly Oxytocics and antioxytocics) | |
| 22.1 Oxytocics | 22.1 Contraceptives |
| 22.2 Antioxytocics (tocolytics) | 22.2 Ovulation inducers |
| | 22.3 Uterotonics |
| | 22.4 Antioxytocics (tocolytics) |
| | 22.5 Other medicines administered to the mother |
| | 22.6 Medicines administered to the neonate |
| Section 29: RENAMED – Medicines for diseases of joints (formerly Specific medicines for neonatal care) | |
| 29.1 Medicines administered to the neonate | 29.1 Medicines used to treat gout |
| 29.2 Medicines administered to the mother | 29.2 Disease modifying agents used in rheumatoid disorders (DMARDs) |
| | 29.3 Juvenile joint diseases |
| Section 30: DELETED (formerly Medicines for diseases of joints) | |
| 30.1 Medicines used to treat gout | **30.1 Deleted** |
| 30.2 Disease-modifying agents used in rheumatoid disorders (DMARDs) | **30.2 Deleted** |
| 30.3 Juvenile joint diseases | **30.3 Deleted** |

Table 2
**Applications and medicines not recommended for 2019 EML and EMLc**

| | |
|---|---|
| **ADDITIONAL MEDICINES** | |
| Addition of anti-PD-1 immune checkpoint inhibitors for treatment of non-small cell lung cancer **(atezolizumab, nivolumab, pembrolizumab)** | EML |
| Addition of newly registered antibiotics for treatment of infections due to multi-drug resistant organisms (including AWaRe classification) **(ceftolozane + tazobactam, delafloxacin, eravacycline, omadacycline)** | EML |
| Addition of medicines for treatment of multiple sclerosis **(fingolimod, glatiramer acetate, ocrelizumab)** | EML & EMLc |
| Addition of long-acting insulin analogues for treatment of type 1 diabetes **(insulin detemir, insulin glargine, insulin degludec)** | EML |
| Addition of **enzalutamide** for treatment of metastatic castration-resistant prostate cancer | EML |
| Addition of **escitalopram** for treatment of major depressive disorder | EML |
| Addition of **methylphenidate** for treatment of attention-deficit hyperactivity disorder | EML & EMLc |
| Addition of **pertuzumab** for use in the treatment of breast cancer | EML |
| Addition of **sumatriptan** for treatment of migraine | EML |
| Addition of **trastuzumab emtansine** (TDM-1) for use in the treatment of breast cancer. | EML |
| **ADDITIONAL FORMULATIONS/STRENGTHS** | |
| New injectable formulation of **ethambutol** for treatment of drug-susceptible tuberculosis | EML & EMLc |
| New injectable formulation of **isoniazid** for treatment of drug-susceptible tuberculosis | EML & EMLc |
| New strength of **isoniazid** oral liquid for treatment of drug-susceptible tuberculosis | EMLc |
| New injectable formulation of **p-aminosalicylic acid** for treatment of drug-susceptible tuberculosis | EML & EMLc |
| New injectable formulation of **rifampicin** for treatment of drug-susceptible tuberculosis | EML & EMLc |
| New subcutaneous formulation of **rituximab** for use in the treatment of lymphoma and leukaemia | EML |
| New subcutaneous formulation of **trastuzumab** for use in the treatment of breast cancer. | EML |

Table 2 *continued*

| | |
|---|---|
| **NEW INDICATIONS** | |
| New indication for **5-fluorouracil** for treatment of cervical cancer in the curative setting. | EML |
| **DELETIONS** | |
| Deletion of **misoprostol** for the indication for prevention of postpartum haemorrhage | EML |
| Deletion of antiretroviral formulations for treatment of HIV infection (**raltegravir** 100 mg tablets, **ritonavir** 400 mg/5 mL oral liquid) | EML & EMLc |
| **AGE RESTRICTIONS** | |
| Change to age restriction for use of **delamanid** in children with multi-drug resistant tuberculosis | EMLc |

# List of participants

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**Armando Genazzani**, Professor of Pharmacology, Università del Piemonte Orientale, Italy

**Gregory Kearns**, Paediatric clinical pharmacologist and Professor of Paediatrics at the University of Arkansas for Medical Sciences, Arkansas, United States

**Gabriela Prutsky Lopez**, Senior associate consultant in pediatrics at the Mayo Clinic Health System; and Founder of Unidad de Conocimiento y Evidencia (CONEVID), Universidad Peruana Cayetano Heredia, Lima, Peru

**Nizal Sarrafzadegan**, Professor of Internal Medicine & Cardiology, Isfahan University, Iran and Affiliate Professor of the Faculty of Medicine, School of Population and Public Health in the University of British Columbia in Vancouver, Canada

**Mike Sharland**, Professor of Paediatric Infectious Diseases; Lead Consultant Paediatrician, Paediatric Infectious Diseases Unit, St George's University Hospitals NHS Foundation Trust, London, United Kingdom

**Shalini Sri Ranganathan**, Professor in Pharmacology and Specialist in Paediatrics, University of Colombo, Colombo, Sri Lanka (*Vice-Chair*)

**Fatima Suleman**, Professor in the Discipline of Pharmaceutical Sciences at the University of KwaZulu-Natal, South Africa (*Rapporteur*)

**Worasuda Yoongthong**, Director of Regional and Local Consumer Health Product Protection and Promotion Division, and Director of the Health Products Entrepreneurship Promotion Division, Food and Drug Administration of Thailand, Nonthaburi, Thailand

**Mei Zeng**, Professor and Director, Department of Infectious Diseases and Chief, Infectious Diseases Unit, Children's Hospital of Fudan University, Shanghai, China

## Temporary Advisers

**Andrea Biondi**, Professor of Paediatrics, Department of Paediatrics, University of Milano-Bicocca, Italy

**Elisabeth de Vries**, Professor of Medical Oncology at the University Medical Center, Groningen, the Netherlands

**Monica Imi**, Medical internist, practicing clinician and technical adviser to the Ministry of Health, Kampala, Uganda

**Gilbert Kokwaro**, Pharmacist and health systems specialist; Director of Institute of Healthcare Management and Professor of Health Systems Research at Strathmore University, Kenya; Professor of Pharmaceutics, Nairobi University, Kenya

## Apologies - Temporary Advisers

**Maria Auxilliadora Oliveira**, Senior Professor and Researcher, National School of Public Health, Oswaldo Cruz Foundation, Ministry of Health, Brazil

## UN Agencies

*United Nations Population Fund (UNFPA)*

**Alfonso Barragues**, Deputy Director, UNFPA Geneva Office, Geneva, Switzerland

*United Nations Children's Fund (UNICEF)*

**Akthem Fourati**, Chief, Medicine & Nutrition Centre, UNICEF Supply Division, Copenhagen, Denmark

## WHO Regions

*WHO Regional Office for Africa*

**Jean-Baptiste Nikiema**, Acting HTI Team Leader, Health Technologies and Innovations, Brazzaville, Republic of the Congo

*WHO Regional Office for the Americas/Pan American Health Organization*

**Alexandra Guta**, Specialist in Medicines and Technologies, Washington DC, United States

*WHO Regional Office for Europe*

**Hanne Bak Pedersen**, Programme Manager, Health Technologies and Pharmaceuticals, Copenhagen, Denmark

## WHO Headquarters Geneva - Secretariat

**Nicola Magrini**, Secretary of the Expert Committee on Selection and Use of Essential Medicines; Innovation, Access and Use, Department of Essential Medicines and Health Products

**Bernadette Cappello**, Technical Officer, EML Secretariat, Innovation, Access and Use, Department of Essential Medicines and Health Products

**Benedikt Huttner**, Consultant, EML Secretariat, Innovation, Access and Use, Department of Essential Medicines and Health Products

**Lorenzo Moja**, Technical Officer, EML Secretariat, Innovation, Access and Use, Department of Essential Medicines and Health Products

**Clive Ondari**, Director a.i., Department of Essential Medicines and Health Products

# Declaration of interests for Expert Committee Members and Temporary Advisers

Declaration of Interest, and management of any disclosures, is an important process governed by the WHO Guidelines for Declaration of Interests (WHO Experts). The WHO Essential Medicines Secretariat identified and screened a number of individuals, considered for participation at the 22nd Expert Committee on the Selection and Use of Essential Medicines, in different capacities – as Members and Temporary Advisers.

The screening process required a close and detailed review of all the potential Members and Temporary Advisers and their disclosures prior to confirming participation. In this regard, the WHO Essential Medicine Secretariat rigorously examined each potential participant. Guidance from the Office of Compliance, Risk Management and Ethics was additionally sought.

The declaration of interest process, resulted in the participation of Expert Committee Members and Temporary Advisers as reported in the list of participants.

Expert Committee Members and Temporary Advisers who declared having no conflicts of interests were: Zeba Aziz, Andrea Biondi, Sumanth Gandra, Armando Genazzani, Monica Imi, Maria Auxiliadora Oliveira; Gabriela Prutsky-Lopez, Nizal Sarrafzadegan, Fatima Suleman, Worasuda Yoongthong and Mei Zeng.

The following Expert Committee Members declared interests that were determined not to represent a conflict of interest:

Dr Franco Cavalli disclosed being a President of the World Oncology Forum, The World Oncology Forum is funded exclusively from independent, non-commercial sources. This is an unpaid activity.

Dr Graham Cooke disclosed having chaired the Lancet Gastroenterology & Hepatology Commission on Accelerating the Elimination of Viral Hepatitis, for which he is unpaid. Dr Cooke also declared having received minimal honoraria for a speaking engagement in 2017 from Merck and Gilead Sciences Inc. respectively on subjects not related to the work of the Essential Medicine Secretariat. He has additionally received a minimal honoraria from Edixomed Ltd to provide advice on study designs to test nitric oxide, a treatment not related to any application under evaluation at this meeting. Conflicts of interests declared by Dr Cooke were considered minor and did not require further management.

Dr Gregory Kearns disclosed a consultancy contract as a paediatric pharmacology adviser with Boehringer Ingelheim that will commence after the Expert Committee meeting. This is a paid activity at a level of remuneration below the threshold of US$ 5 000. This was considered not to represent a conflict.

Dr Mike Sharland disclosed being the chair of the Department of Health's Expert Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare Associated Infection (APRHAI); leading the NeoAMR Project, an initiative to address neonatal sepsis launched by the Global Antibiotic Research and Development Partnership (GARDP), a joint programme of WHO and the Drugs for Neglected Diseases initiative (DNDi) in support of the Global Action Plan for Antimicrobial

Resistance. All positions are unpaid. Dr Sharland also declared that his institution, St George's University London, has received research funding from GARDP to support the development of academic activities, including observational cohort studies, on antibiotic use in children. GARDP is funded exclusively from independent, non-commercial sources. As a GARDP advisor, Dr Sharland was involved in discussion on several antibiotics, particularly fosfomycin and polymyxin B, antibiotics included in AWaRe and under discussion at this meeting. As the mandate of GARDP largely coincides with WHO – to drive the global response to antimicrobial resistance and set health priorities – and all R&D activities are limited to neglected diseases to deliver not-for-profit, needs-driven R&D, Dr Sharland declaration was considered not to represent a conflict.

Professor Shalini Sri Ranaganathan declared that she has received research funding from Colombo University, where she is employed, to conduct a survey on availability and affordability of essential medicines for children in Sri Lanka. This was determined not to represent a conflict.

## Temporary Advisers

Dr Elisabeth de Vries participated as a Temporary Adviser and disclosed having served as an expert member of Data Safety Monitoring Committees for trials promoted by a non-profit research programme (National Surgical Adjuvant Breast and Colon Project) and for-profit companies (Daiichi Sankyo, Merck, Synthon, Sanofi and Pfizer). The matters under consideration by the Data Safety Monitoring Committees are not related to medicines under evaluation or the work of the 22nd Expert Committee on the Selection and Use of Essential Medicines. Dr de Vries chairs the Magnitude of Clinical Benefit Scale Working Group of the European Society for Medical Oncology (ESMO-MCBS), the Cancer Medicines Working Group of ESMO, and the Response Evaluation Criteria in Solid Tumours (RECIST) Working Group. It is noted that ESMO is a non-governmental organization in official relations with WHO. All positions are unpaid. Through her involvement in the above mentioned ESMO and RECIST panels, Dr de Vries was involved in the evaluation of medicines to be considered by this Expert Committee (abiraterone, atezolizumab, enzalutamide, nivolumab, pembrolizumab, pertuzumab, trastuzumab emtansine).

Her institution (University of Groningen) is involved in early phase clinical trials to explore the therapeutic and diagnostic/prognostic roles of cancer medicines and biomarkers receiving institutional funding from Amgen, Astra Zeneca, Bayer, Chugai, CytomX, Genentech, G1 Therapeutics, Nordic Nanovector, Radius Health, Roche, Synthon. These trials are not directly related to medicines for which applications are to be evaluated at this meeting. After reviewing Dr de Vries declarations, it was determined she could participate as a Temporary Adviser.

Dr Gilbert Kokwaro disclosed an appointment as Chair of the Universal Health Coverage Advisory Panel for Kenya. The Advisory Panel will develop a package of essential medicines that will form the benefits package to be provided under the UHC programme in Kenya. This was considered not to represent a conflict and it was determined that he could participate as a Temporary Adviser. It is noted that the names and brief biographies of all the Committee Members and Temporary Advisers were made publicly available for comment ahead of the meeting.

# 1. Introduction

The 22nd meeting of the World Health Organization (WHO) Expert Committee on the Selection and Use of Essential Medicines was held from 1 to 5 April 2019, in Geneva, Switzerland.

The meeting agenda included 65 applications involving over 100 medicines for addition, deletion, amendment and review in order to update the *WHO Model List of Essential Medicines* (EML) and *WHO Model List of Essential Medicines for Children* (EMLc). In addition, reports and recommendations made by two EML Working Groups were also submitted for consideration.

The meeting was opened by Mariângela Simão, Assistant Director-General, Medicines, Vaccines and Pharmaceuticals, on behalf of WHO Director-General, Dr Tedros Adhanom Ghebreyesus. Dr Simão welcomed Committee Members and Temporary Advisers, representatives from WHO regional offices, nongovernmental organizations (NGOs) and other participants.

In her opening remarks Dr Simão described the importance of the Model Lists of Essential Medicines to Member States as a standard reference for medicines, and a valuable tool for policy-makers to optimize selection and use of medicines at the national level to ensure access in the context of universal health coverage (UHC). She highlighted the roles of the Model Lists in priority-setting and informing reimbursement policies, both as an intrinsically positive list, and also by looking at medicines that have been assessed and not recommended for listing on the basis of uncertain benefit or safety. Furthermore, she highlighted the functions of the Model Lists as a guide for better procurement and competition among similar treatments, as a guide for expanding the mandate of the WHO Prequalification Programme and the Medicines Patent Pool, and as a tool for UHC and health financing.

With reference to the meeting agenda, Dr Simão highlighted some of the key topics to be considered by the Expert Committee including applications for new cancer medicines, the review of the Access, Watch and Reserve (AWaRe) classification of antibiotics, medicines for multiple sclerosis, and policy-oriented discussions around biosimilars and medicines affordability and availability. In particular, the ongoing challenges and complexities of access to insulin were highlighted as important factors in the Committee's consideration of the application for inclusion of insulin analogues.

Dr Simão acknowledged the work already undertaken by Committee Members and Temporary Advisers in reviewing applications and thanked them for their preparation. She reminded them of their obligations to provide advice to the Organization in their individual capacities as experts, and not as representatives of their governments, institutions or organizations. On behalf of the Director-General, she offered special thanks to the Committee for dedicating their time to this valuable work.

## 2. Open session

The open session of the meeting was chaired by Mariângela Simão, Assistant Director-General, Access to Medicines, Vaccines and Pharmaceuticals, on behalf of the Director-General, and was attended by a variety of interested parties, representatives of non-governmental organizations and representatives of WHO Member States.

Nicola Magrini, Secretary of the Expert Committee delivered an update on current activities of the EML Secretariat, methodology for the Model List update, and the impact and implementation of recommendations made by the previous Expert Committee.

Manica Balasegaram, Executive Director of the Global Antibiotic Research and Development Partnership (GARDP) presented the work being undertaken by GARDP, in collaboration with WHO and the Drugs for Neglected Diseases initiative (DNDi), on antimicrobial resistance and antibiotic research and development (R&D).

Nav Persaud, Assistant Professor at the University of Toronto, presented details of a global database of national essential medicine lists from 137 countries, which allows comparison and benchmarking with the Model List and comparison between countries.

Additional presentations and/or statements of relevance to the agenda of the Expert Committee were made by the following participants:

- Rosa Guiliani, European Society for Medical Oncology
- Hans Hogerzeil, Health Action International and the Lancet Commission on Essential Medicines
- Greg Perry, International Federation of Pharmaceutical Manufactures & Associates
- Thiru Balasubramanian, Knowledge Ecology International
- Esteban Burrone, Medicines Patent Pool
- Myriam Henkens, Medicins Sans Frontières
- Patrick Durisch, Public Eye
- Tom Frieden, Resolve to Save Lives

Copies of the presentations and statements are available on the WHO website.[9]

[9] Available at: https://www.who.int/selection_medicines/committees/expert/22/en/.

# 3. Follow-up items and EML Working Groups

## Follow-up items from the 2017 Expert Committee meeting

### Ready-to-use therapeutic food

The Expert Committee considered the comprehensive report prepared by the WHO Department of Nutrition in response to the request of the previous Expert Committee for the proposal to include ready-to-use therapeutic food (RUTF) on the Model List.[10]

The Expert Committee acknowledged once again the efficacy of RUTF for the dietary management of uncomplicated severe acute malnutrition in children under 5 years of age, many in non-hospitalized settings. However, the report highlighted the divided opinions and ongoing uncertainty of the country level implications of including RUTF as a medicine on the Model List. The Committee felt that the report did not fully address the concerns held by the 2017 Expert Committee. The Committee recognized that the report highlighted that adding RUTF to the Model List could have unknown or unintended consequences such as more restricted access, increased costs and could potentially hamper local production. The Committee recommended that a comprehensive risk-mitigation plan for these potential consequences would be highly relevant for any future consideration of the inclusion of RUTF on the Model List. The Committee noted that there is work currently underway to establish standards and guidelines for RUTF under the *Codex alimentarius*, regarding production, nutritional aspects and labelling in order to facilitate harmonization for the requirements of RUTF at an international level.

In the absence of such standards, and without a clear indication of the potential consequences and implications at country level of including RUTF on the Model List, and without the reassurance of a risk-mitigation plan to address any consequences, the Expert Committee did not recommend the addition of RUTF to the core list of the EMLc.

With regard to questions around the eligibility of RUTF to be added to the EML as a food/nutritional product rather than a medicine, the Committee noted that the Model Lists already include non-medicine products when they form part of a comprehensive WHO policy or strategy (e.g. condoms) and that RUTF would be eligible for future consideration for inclusion on the Model Lists, provided the concerns around the potential consequences of listing on access can be addressed.

[10] Available at: https://www.who.int/selection_medicines/committees/expert/22/applications/rutf_nhd-report/en/.

### Oseltamivir

The Expert Committee recalled the recommendation of the 2017 Expert Committee that oseltamivir be considered for deletion in 2019 unless new information supporting its use in seasonal and pandemic outbreaks is provided. The Committee noted the advice from the WHO Secretariat that the WHO *Guidelines for clinical management of influenza* are in the process of being updated and a meeting of the Guideline Development Group (GDG) was held in March 2019, but the recommendations of the GDG were not yet available. As part of the guideline development process, a systematic review (SR) of the effect of antiviral treatments for influenza was conducted, but the results were not yet available. This review, yet to be published or presented to the GDG, updated previous SRs and considered non-randomized studies.

The Expert Committee accepted that the updated recommendations and SR would represent new information relevant to any decision regarding the inclusion or deletion of oseltamivir for treatment of influenza on the Model Lists. The Committee therefore decided that any decision regarding the potential deletion of oseltamivir from the Model List should take into consideration this new evidence, and that the current listing for oseltamivir should be maintained until such time that this evidence can be reviewed.

## EML Cancer Medicines Working Group

Following the recommendation of the 2017 Expert Committee, the EML Cancer Medicines Working Group was established in March 2018 to support the work of the Committee by identifying cancer medicines for potential inclusion on the Model Lists and by establishing clear principles that can serve as a guide for selection of optimal treatments. The Working Group was mandated to propose clear principles that can serve as a guide for selection of optimal cancer medicines for EML inclusion through a review of the available tools for assessing the magnitude of clinical benefit, and meaningful thresholds for clinical and public health relevance of cancer medicines. A meeting of the Working Group was held in March 2018 in Geneva. The report of the Working Group meeting,[11] together with two commissioned reports outlining: 1) temporal trends in oncology trials;[12] and 2) how to prioritize the selection of essential cancer medicines[13] were presented to the 2019 Expert Committee for consideration.

[11] Available at: https://www.who.int/selection_medicines/committees/expert/22/applications/CMWG_meeting_report.pdf?ua=1.

[12] Available at: https://www.who.int/selection_medicines/committees/expert/22/applications/CMWG_temporal_trends_report-rev1.pdf?ua=1.

[13] Available at: https://www.who.int/selection_medicines/committees/expert/22/CMWG_Report_Fojo.pdf?ua=1.

The Expert Committee endorsed the Working Group's recommendations that WHO adopts in general, a threshold for benefit of at least four to six months survival gain for new cancer medicines to be considered as candidates for EML inclusion. A range was preferred over a specific threshold (e.g. four months) given the uncertainty associated with how clinical trial data relates to real-world benefits, and may differ between different cancers.

The Expert Committee endorsed the role of the European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale[14] (ESMO–MCBS) as a screening tool to identify cancer treatments that have potential therapeutic value that warrants full evaluation for EML inclusion. Potential new EML cancer medicines, in general, should have a score on the ESMO-MCBS of A or B in the curative setting and of 4 or 5 in the non-curative setting. These scores would support a medicine being evaluated by the Expert Committee for inclusion in the EML through a full application.

With regard to other attributes of new cancer medicines and clinical evidence requirements to support their inclusion on the EML, the Expert Committee recommended the following general principles:

- Clinical data from more than one trial is usually required.
- Data from high quality randomized trials is considered most important, and must be mature in order to assess the impact of the medicine on overall survival, and to show consistent results across different trials.
- Randomized trials should compare efficacy of new regimens to current best standard of care (e.g. regimen, dose) rather than to available but sub-optimal comparators.
- Additional information to inform the deployment of cancer regimens in countries with varying resources and capacity would be useful.
- Trials that define the need for maintenance therapy and the length of maintenance. Shorter treatment durations that compromise efficacy only marginally (or not at all) might substantially reduce outlays and allow more patients to access treatment.
- Trials that demonstrate superiority are preferred to non-inferiority trials for new drugs, rather than an absence of inferiority to the relevant comparator(s). However, non-inferiority trials can be informative in some circumstances, eg, comparison of different dosing regimens or treatment durations;

[14] Available at: https://www.esmo.org/Guidelines/ESMO-MCBS.

- Consideration should be given to disease stage and line of therapy: efficacy of cancer medicines is usually less in more advanced stages of disease, and when used in advanced lines of treatment; therefore, medicines that are effective in the first-line treatment setting are more clinically meaningful and therefore highly desirable.
- The inclusion of a cancer medicine on the EML for a given indication does not imply that the medicine should be considered essential for other indications.

The Expert Committee acknowledged the valuable work of the Working Group and recommended the continuation and further expansion of the Working Group's activities. Activities over the next biennium should include the update of treatment regimens for cancers previously considered by the Expert Committee and the identification of new cancer medicines that meet the above criteria.

The Working Group should also review the issues being experienced at country level in relation to the implementation of EML cancer medicine recommendations and access to cancer medicines.

The Expert Committee also recommended the need for consolidation of cancer medicine recommendations and EML listings through a broader technical advisory group meeting in 2020, with country engagement to support implementation within a UHC perspective. This meeting should also be aimed at sharing these approaches with a larger group of cancer experts and important stakeholders and engage with countries in their implementation capacity.

## EML Antibiotics Working Group

Two meetings of the EML Antibiotics Working Group were held during the intervening period since the last Expert Committee meeting: in September 2017 and August 2018. The Working Group submitted three reports for consideration by the Expert Committee: 1) a review of the AWaRe classification of antibiotics and proposed amendments and expansion; 2) guidance on paediatric dosing regimens for EML Access antibiotics in children;[15] and 3) optimal duration of antibiotic therapy.[16]

### Review of the AWaRe classification and EML listings of antibiotics

The Expert Committee noted the adoption and utilization of the Access, Watch and Reserve (AWaRe) classification of antibiotics on the EML by several Member

[15] Available at: https://www.who.int/selection_medicines/committees/expert/22/applications/ABWG_paediatric_dosing_AB.pdf.

[16] Available at: https://www.who.int/selection_medicines/committees/expert/22/applications/ABWG_optimal_duration_AB.pdf.

States including the endorsement of AWaRe by the G20 Health Ministers in 2018.[17] A new target indicator based on AWaRe was also adopted by WHO under its *13th General programme of work*.[18] It specifies a country level target of at least 60% of antibiotic consumption being from the Access group. This indicator is intended to monitor access to essential medicines and progress towards UHC. The Committee recognized the emerging role of the AWaRe groups for stewardship and quality improvement programmes, complementary to the specific listing of antibiotics as essential medicines.

The Expert Committee recommended that specific listing of antibiotics in the EML and the classification of antibiotics into the different AWaRe groups should be distinguished from each other, recognizing their distinct, albeit complementary, purposes. The Committee acknowledged that EML-listed antibiotics represent a parsimonious, evidence-based selection of essential narrow spectrum antibiotics for first- and second-choice empiric treatment of most common bacterial infections and a tool for stewardship. The Committee noted that the existing AWaRe groupings did not include a range of antibiotics used internationally and this impeded data collection and use. The Committee therefore recommended that the AWaRe classification should extend beyond the EML to all commonly used antibiotics globally, to better support antibiotic monitoring and stewardship activities. The Expert Committee recommended the development of an AWaRe classification database as a searchable tool for countries.

The Committee also recommended, based on the advice of the Working Group, that WHO consider creating an additional group in the AWaRe classification database for antibiotics whose use is not evidence-based, nor recommended in high-quality international guidelines, particularly fixed-dose combinations of multiple broad-spectrum antibiotics. Antibiotics in this group are not included on the Model Lists.

The Committee considered the proposals by the Working Group for amendments to the AWaRe classification of antibiotics to expand the AWaRe classification to include antibiotics and antibiotic classes not included in the 2017 iteration. Furthermore, the Committee agreed that fourth-generation cephalosporins should be re-classified as Watch group, as they did not meet the criteria for classification as Reserve. The Committee also recommended the re-classification of faropenem from Watch to Reserve due to its high potential for inappropriate use. It is an orally available formulation with broad-spectrum activity, inappropriate use of which may further the spread of carbapenemase-producing *Enterobacteriaceae*.

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[17] Available at: http://www.g20.utoronto.ca/2018/2018-10-04-health.pdf.

[18] Available at: http://apps.who.int/gb/ebwha/pdf_files/EB144/B144_7-en.pdf.

With regard to the EML listing of antibiotics, the Committee endorsed revised criteria for the inclusion of Reserve group antibiotics on the Model List. Namely, Reserve group antibiotics should be included individually on the Model List when they have a favourable benefit–risk profile and proven activity against "Critical Priority" or "High Priority" pathogens as identified by the WHO priority pathogens list, most notably carbapenem-resistant *Enterobacteriaceae*. Subsequently, the Committee recommended the removal of aztreonam, fourth- and fifth-generation cephalosporins (as classes), tigecycline and daptomycin from the EML and EMLc as these antibiotics did not meet the revised criteria for inclusion on the Model Lists as individual Reserve group agents.

In summary, 19 Access group antibiotics and 11 Watch group antibiotics are now included individually on the 2019 Model Lists as first or second choice empiric treatment options for infectious syndromes reviewed by the Expert Committee. Seven Reserve group antibiotics are listed individually as last-resort treatment options for infections due to multidrug-resistant organisms. The Committee recommended the re-structuring of Section 6.2 by AWaRe groups, such that antibiotics on the Model Lists are listed in revised sub-sections accordingly, replacing the existing sub-sections based on chemical structure.

The revised EML AWaRe listing of antibiotics is summarized in Table 1.

The antibiotics classified into AWaRe groups has been revised and expanded in 2019 to include 177 specific, commonly used antibiotics. A general summary of the antibiotics and antibiotic classes classified is presented in Table 2. The full AWaRe classification database of antibiotics is available as an online appendix to this report.[19]



[19] Available at: https://apps.who.int/iris/bitstream/handle/10665/327957/WHO-EMP-IAU-2019.11-eng.xlsx.

Table 1
**Antibiotics included on the 2019 Model Lists of Essential Medicines by AWaRe groups**

| 6.2.1 Access group antibiotics | 6.2.2 Watch group antibiotics | 6.2.3 Reserve group antibiotics |
|---|---|---|
| Amikacin | Azithromycin | *Ceftazidime + avibactam* |
| Amoxicillin | Cefixime | *Colistin* |
| Amoxicillin + clavulanic acid | Cefotaxime | *Fosfomycin (intravenous)* |
| Ampicillin | *Ceftazidime* | *Linezolid* |
| Benzathine benzylpenicillin | Ceftriaxone | *Meropenem + vaborbactam* |
| Benzylpenicillin | Cefuroxime | *Plazomicin* |
| Cefalexin | Ciprofloxacin | *Polymyxin B* |
| Cefazolin | Clarithromycin | |
| Chloramphenicol | *Meropenem* | |
| Clindamycin | Piperacillin + tazobactam | |
| Cloxacillin | Vancomycin (oral) | |
| Doxycycline | *Vancomycin (intravenous)* | |
| Gentamicin | | |
| Metronidazole | | |
| Nitrofurantoin | | |
| Phenoxymethylpenicillin | | |
| Procaine benzylpenicillin | | |
| Spectinomycin | | |
| Sulfamethoxazole + trimethoprim | | |

Italic font indicates listing on the complementary list.

Table 2
**Summary of AWaRe classification of antibiotics**

| | |
|---|---|
| **Access group** | Aminoglycosides (unless included in Watch or Reserve)<br>Amphenicols<br>Beta-lactams with beta-lactamase inhibitors<br>First-generation cephalosporins<br>Penicillins (unless included in Watch)<br>Tetracyclines (unless included in Watch or Reserve)<br>Trimethoprim, alone or in combination with sulfonamides<br>Clindamycin<br>Metronidazole<br>Nitrofurantoin<br>Spectinomycin |
| **Watch group** | Aminoglycosides (unless included in Access or Reserve)<br>Anti-pseudomonal penicillins with beta-lactamase inhibitors<br>Carbapenems (unless included in Reserve) |
| **Watch group** | Carboxypenicillins<br>Fluoroquinolones<br>Glycopeptides (unless included in Reserve)<br>Macrolides (unless included in Reserve)<br>Penicillins (unless included in Access)<br>Tetracyclines (unless included in Access or Reserve)<br>Second generation cephalosporins<br>Third generation cephalosporins (unless included in Reserve)<br>Fourth generation cephalosporins<br>Rifamycins<br>Clofoctol<br>Fosfomycin (oral formulation)<br>Fusidic acid |
| **Reserve group** | Carbapenems (unless included in Watch)<br>Monobactams<br>Third generation cephalosporins (unless included in Watch)<br>Polymyxins<br>Glycopeptides (unless included in Watch)<br>Macrolides (unless included in Watch)<br>Oxazolidinones<br>Tetracyclines (unless included in Access or Watch)<br>Daptomycin<br>Faropenem<br>Fosfomycin (IV formulation)<br>Tigecycline |

### Dosing and duration reports

The Expert Committee noted the reports presented on paediatric dosing regimens for Access antibiotics and on optimal duration of antibiotic therapy. The Committee considered that these reports were valuable work that could be further expanded to inform the development of antibiotic guidance tools for countries.

To this end, the Committee recommended the development of clinical guidance summaries for each infectious syndrome, for both adults and children, as a useful tool for countries to implement EML recommendations and stewardship interventions using AWaRe. These summaries should include information on choice of antibiotic, recommended daily dose, optimal dosing frequency, and optimal duration of therapy. Guidance on when not to prescribe or use antibiotics should also be incorporated. Management and treatment algorithms for infectious syndromes could also be included.

The Expert Committee acknowledged the valuable work of the Working Group and recommended the continuation and expansion of the Working Group's activities. Activities over the next biennium should include:

- continued evaluation and review of the AWaRe classification of antibiotics, including potential inclusion on the Model Lists;
- review of new infectious syndromes for which antibiotics could be considered for inclusion on the Model Lists by the Expert Committee;
- development of clinical guidance on optimal antibiotic dosing and dosing frequency for adults and children to inform the clinical guidance summaries;
- development of clinical guidance on optimal antibiotic treatment duration for clinical infection syndromes reviewed by the Expert Committee, to inform the clinical guidance summaries.
- development, in collaboration with key relevant stakeholders, of the clinical guidance summaries and management and treatment algorithms as educational tools for optimal use;
- development of potential models of stewardship tools and processes using AWaRe, including metrics of optimal prescribing.

## EML Working Group on Transparency and Access to Clinical Trial Data

The Expert Committee reiterated its recommendation from 2017 to establish a Working Group on transparency and timely public disclosure of all clinical trial results and available data. The Working Group should identify strategic actions to address factors known to impact the availability of reliable data informing

applications for the inclusion or removal of medicines on the Model Lists. Such factors include selective outcome reporting, publication bias and open access to clinical trial results. This Working Group could also action the recommendation made by the Expert Committee for further independent analysis of data for pertuzumab in breast cancer.

# 4. Summary of changes

## Changes to sections of the Model Lists

Refer to Table 1 of the Executive summary for details of changes to sections and sub-sections of the Model Lists.

## Additions to Model Lists

Section 6.2.2: Cefuroxime was added to the core list of the EML and EMLc as a Watch group antibiotic for surgical prophylaxis.

Section 6.2.3: Ceftazidime + avibactam, meropenem + vaborbactam and plazomicin were added to the complementary list of the EML as Reserve group antibiotics for treatment of infections due to multidrug-resistant organisms. Ceftazidime + avibactam was added to the complementary list of the EMLc.

Section 6.2.4: Bedaquiline was added to the complementary list of the EMLc for the treatment of multidrug-resistant tuberculosis in children aged 6 years and older.

Section 6.4.2: For treatment of HIV infection, a fixed-dose combination of dolutegravir + lamivudine + tenofovir was added to the core list of the EML, and single-agent dolutegravir was added to the core list of the EMLc.

Section 6.4.4.2.1: Fixed-dose combination of glecaprevir + pibrentasvir was added to the core list of the EML as a pan-genotypic treatment for adult patients with chronic hepatitis C virus infection.

Section 6.5.5.1: Fexinidazole was added to the core list of the EML and EMLc for the treatment of human African trypanosomiasis.

Section 8.1: Adalimumab with a square box, representative of the class of anti-tumour necrosis factor alpha (TNF-α) biologics, was added to the complementary list of the EML and EMLc for use in the treatment of chronic inflammatory autoimmune disorders (rheumatoid arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and Crohn disease). Alternatives are limited to etanercept and infliximab on the EMLc and to etanercept, infliximab, certolizumab pegol and golimumab on the EML.

Section 8.2.1: Arsenic trioxide, pegaspargase and realgar-Indigo naturalis formulation (RIF) were added to the complementary list of the EML and EMLc for treatment of leukaemias. Melphalan was added to the complementary list of the EML for treatment of multiple myeloma. Fluorouracil, irinotecan, oxaliplatin and procarbazine were added to the complementary list of the EMLc for selected indications for which they are already included on the EML.

Section 8.2.2: Bortezomib was added to the complementary list of the EML for the treatment of multiple myeloma. Erlotinib with a square box (gefitinib and afatinib are alternatives) was added to the complementary list of the EML for the treatment of epidermal growth factor receptor (EGFR) mutation-positive advanced non-small lung cancer. All-trans retinoid acid, dasatinib, imatinib, nilotinib and rituximab were added to the complementary list of the EMLc for selected indications for which they are already included on the EML.

Section 8.2.3: Lenalidomide and thalidomide were added to the complementary list of the EML for the treatment of multiple myeloma. Nivolumab with a square box (pembrolizumab as an alternative) was added to the complementary list of the EML for the treatment of metastatic melanoma.

Section 8.2.4: Abiraterone was added to the complementary list of the EML for the treatment of metastatic castration-resistant prostate cancer.

Section 10.2: Dabigatran with a square box (apixaban, edoxaban and rivaroxaban are alternatives) was added to the core list of the EML for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, and for treatment of venous thromboembolism. Enoxaparin with a square box (nadroparin and dalteparin as alternatives) was added to the core list of the EMLc.

Section 12.3: Four fixed-dose combination formulations were added to the core list of the EML for treatment of hypertension: lisinopril + amlodipine, lisinopril + hydrochlorothiazide, telmisartan + amlodipine and telmisartan + hydrochlorothiazide. Each component is listed with a square box as representative of the relevant pharmacological classes.

Section 12.5.2: Alteplase was added to the complementary list of the EML for use as a thrombolytic in patients diagnosed with acute ischaemic stroke.

Section 17.2: Aprepitant was added to the complementary list of the EML and EMLc for management of chemotherapy-induced nausea and vomiting in patients undergoing moderately- to highly-emetogenic chemotherapy.

Section 18.6: Diazoxide was added to the complementary list of the EMLc for the management of hypoglycaemia secondary to prolonged hyperinsulinism.

Section 18.7: Methimazole with a square box (carbimazole as an alternative) was added to the core list of the EML and the complementary list of the EMLc for the treatment of primary hyperthyroidism.

Section 19.3: Dengue vaccine was added to the EML and EMLc for use in some high-risk population in line with the recommendations in the *Dengue vaccine: WHO position paper – September 2018*.

Section 22.3: A heat-stable formulation of carbetocin was added to the core list of the EML for the prevention of postpartum haemorrhage.

Section 25: Tiotropium with a square box, representative of long-acting muscarinic antagonists (LAMAs), was added to the core list of the EML for the treatment of chronic obstructive pulmonary disease (COPD).

Section 27: Multiple micronutrient powders were added to the core list of the EMLc for the prevention of anaemia in infants and children.

## Deletions from Model Lists

Section 6.2.3: Aztreonam, daptomycin, fourth- and fifth-generation cephalosporins, and tigecycline were deleted from the EML and EMLc.

Section 6.2.4: Capreomycin and kanamycin were deleted from the EML and EMLc. Ethambutol + isoniazid tablet 400 mg + 150 mg, isoniazid + pyrazinamide + rifampicin tablet 150 mg + 500 mg + 150 mg, and isoniazid + rifampicin tablets 60 mg + 60 mg and 150 mg + 150 mg were deleted from the EML.

Section 6.4.2: Abacavir + lamivudine dispersible tablet 60 mg + 30 mg, and zidovudine dispersible tablet 60 mg were deleted from the EML and EMLc.

Section 6.4.4.2: Simeprevir was deleted from the EML.

## New indications

Section 6.2.1: The new indication of treatment for progressive apical dental abscess was added for amoxicillin and phenoxymethylpenicillin on the EML and EMLc. The new indication of surgical prophylaxis was added for amoxicillin + clavulanic acid, cefazolin, gentamicin and metronidazole on the EML and EMLc.

Section 6.2.2: The new indication of treatment for enteric fever was added for azithromycin, ceftriaxone and ciprofloxacin on the EML and EMLc.

Section 6.2.5: Amoxicillin + clavulanic acid and meropenem were included on the complementary list of the EML and EMLc for the new indication of treatment of multidrug-resistant tuberculosis (MDR-TB).

Section 6.6: Ivermectin was included on the core list of the EML and EMLc for the new indication of treatment of scabies.

Section 6.5.3.2: New indications of intermittent preventive treatment in pregnancy (IPTp) and intermittent preventive treatment in infants (IPTi) were included for sulfadoxine + pyrimethamine in malaria.

Section 8.2: Additional indications for multiple cancer medicines were included the complementary list of the EML and EMLc as follows:

- Cervical cancer (EML): carboplatin, cisplatin
- Multiple myeloma (EML): cyclophosphamide, doxorubicin, dexamethasone, prednisolone
- Prostate cancer (EML): prednisolone
- Kaposi sarcoma (EMLc): bleomycin, doxorubicin, vincristine
- Nasopharyngeal cancer (EMLc): cisplatin
- Diffuse large B-cell lymphoma (EMLc): cyclophosphamide, doxorubicin, vincristine, prednisolone
- Acute myeloid leukaemia (EMLc): cytarabine
- Acute promyelocytic leukaemia (EMLc): cytarabine, daunorubicin, mercaptopurine, methotrexate
- Chronic myeloid leukaemia (EMLc): hydroxycarbamide

Section 22.5: Tranexamic acid was included in the core list of the EML for the new indication of treatment of postpartum haemorrhage.

## New formulation and/or strength

Section 6.2.5: Additional formulations and/or strengths of medicines for treatment of tuberculosis were included in the EMLc as follows:

- Cycloserine: solid oral dosage form 125 mg
- Ethambutol: dispersible tablet 100 mg
- Ethionamide: dispersible tablet 125 mg
- Isoniazid: dispersible tablet 100 mg
- Levofloxacin: dispersible tablet 100 mg
- Linezolid: dispersible tablet 150 mg
- Moxifloxacin: dispersible tablet 100 mg

Section 6.4.2: Additional formulations and/or strengths of medicines for HIV infection were included in the EML and EMLc as follows:

- Lopinavir + ritonavir (EMLc): granules 40 mg + 10 mg (listed as "solid oral dosage form")
- Raltegravir (EML and EMLc): granules for oral suspension 100 mg
- Ritonavir (EML and EMLc): oral powder 100 mg

Section 6.5.3.2: Co-packaged presentations of amodiaquine and sulfadoxine + pyrimethamine dispersible tablets were included on the EMLc for seasonal malaria chemoprevention in children.

Section 8.2: Additional formulations and/or strengths of multiple cancer medicines were included the complementary list of the EML and EMLc as follows:

- Calcium folinate (EML and EMLc): tablet 5 mg and 25 mg
- Cyclophosphamide (EML and EMLc): tablet 50 mg
- Etoposide (EML and EMLc): tablet 50 mg

Section 17.5: A co-packaged presentation of oral rehydration salts (ORS) and zinc sulfate tablets was included on the core list of the EMLc.

Section 22.3: A co-packaged presentation of mifepristone and misoprostol was included on the core list of the EML.

## Other changes to listings

Sections 2.3 and 17.2: addition of a square box to the listing of ondansetron on the EML and EMLc.

Section 6.2.5: replaced "capsule" with "solid oral dosage form" in the listings for clofazimine and rifabutin.

Section 18.7: removal of the square box on the EML listing for propylthiouracil and addition of notes on the EML and EMLc regarding use when alternative first-line treatment is not appropriate or available.

Section 22.3: transfer the listing of mifepristone-misoprostol from the complementary to the core list of the EML and removal of the note regarding the requirement for close medical supervision.

Section 24.2.1: addition of a square box to the listing of fluoxetine on the EML.

Section 27: amendment to the strength of iodine capsules from 200 mg to 190 mg on the EML and EMLc from 200 mg to 190 mg.

## Applications not recommended

Section 6.2.3: addition of ceftolozane + tazobactam, delafloxacin, eravacycline and omadacycline for treatment of infections due to multidrug-resistant organisms.

Section 6.2.4: addition of injectable formulations of ethambutol, isoniazid, p-aminosalicylic acid and rifampicin; new strength formulation of isoniazid oral

liquid; change to the age restriction associated with the listing of delamanid for the treatment of tuberculosis.

Section 6.4.2: deletion of raltegravir 100 mg tablets and ritonavir 400 mg/5 mL oral liquid formulations for treatment of HIV infection.

Section 7.1: addition of sumatriptan for treatment of acute migraine.

Section 8.1: addition of fingolimod, glatiramer acetate and ocrelizumab for the treatment of multiple sclerosis.

Section 8.2: addition of nivolumab, pembrolizumab and atezolizumab for the treatment of non-small cell lung cancer; pertuzumab and trastuzumab emtansine for treatment of HER-2 positive breast cancer; enzalutamide for treatment of metastatic castration-resistant prostate cancer; subcutaneous formulations of rituximab and trastuzumab; extension of indications for fluorouracil to include treatment of cervical cancer in the curative setting.

Section 18.5.1: addition of long-acting insulin analogues for treatment of type 1 diabetes.

Section 22.3: deletion of the indication of prevention of post-partum haemorrhage for misoprostol.

Section 24: addition of methylphenidate for treatment of attention-deficit hyperactivity disorder (ADHD); addition of escitalopram for the treatment of depressive disorders.

Refer to the individual application summaries in this Report for full details of the Expert Committee's recommendations.

# 5. Applications for the 21st Model List of Essential Medicines and the 7th Model List of Essential Medicines for Children

## Section 6: ANTI-INFECTIVE MEDICINES

## 6.2 Antibacterials

*Antibiotics for typhoid fever*

### Typhoid and paratyphoid (enteric) fever

**Applicant(s)**

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**Introduction**

Enteric fever, a bloodstream infection caused by *Salmonella enterica* serovars Typhi and Paratyphi, causes a major public health burden, especially in children and young adults in resource-limited settings. Recent estimates put the burden of enteric fever at 16 million cases and an estimated 150 000 deaths per year (*1*). Resistance to first-line treatments (multidrug resistance (MDR) defined as resistance against chloramphenicol, ampicillin and trimethoprim/sulfamethoxazole) and to fluoroquinolone antibiotics is now ubiquitous at the global level (*2*). Resistant infections cause high clinical failure rates and prolonged carriage, increasing the risk of complications (intestinal haemorrhage, gut perforation and encephalopathy) in the individual patient, and lead to continued transmission in families and their communities (*3*). There are now very few effective treatment options. Worryingly, extensively drug-resistant (XDR) *S. Typhi* strains, combining MDR, resistance to fluoroquinolones and third-generation cephalosporins, have recently been reported in Pakistan (*4*). The most recent WHO *Guidelines for the diagnosis, treatment and prevention of typhoid* were published in 2003, and are now outdated particularly in an era of widespread drug resistance (*5*).

Antibiotic treatment and sanitation have been the only widely used intervention aimed at reducing the burden of enteric fever. Vaccines have been underutilized. The recent decision of Gavi, the Vaccine Alliance, to support the introduction of the new typhoid conjugate vaccine, Typbar-TCV, into the routine immunization schedules of eligible countries will help, but may take many years to be fully implemented and effective in endemic countries (*6*).

In addition to antimicrobial resistance, there are several issues in the management of enteric fever. The sensitivity of blood culture is low, only

approximately 40% of patients with enteric fever will have a positive blood culture (*5*, *7*). In low- and middle-income countries, blood culture facilities are often not available. There are no rapid tests with acceptable sensitivity and specificity (*3*, *5*). Treatment is usually empirical.

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**Summary of evidence** (from the application)

The application identified two Cochrane systematic reviews that evaluated antibiotic treatment of typhoid fever.

A 2011 Cochrane systematic review of 26 trials involving 3033 patients evaluated fluoroquinolones for treatment of typhoid and paratyphoid fever (*8*). The review did not include comparisons with antibiotics that are no longer recommended for use in enteric fever (e.g. norfloxacin due to its poor bioavailability).

Antibiotic resistance is an important consideration for efficacy; an earlier version of this SR combined different generations of fluoroquinolones in one sub-group, stratified according to the prevalence of MDR and nalidixic-resistant (NaR) strains (*9*). However, the updated version grouped studies by each fluoroquinolone individually. Results are presented as risk ratios (RR; 95%CI) for categorical data and mean difference (MD; 95%CI) for continuous data.

*Ciprofloxacin versus chloramphenicol*

Four trials (293 patients) compared ciprofloxacin to chloramphenicol, only one trial included children above 12 years of age, none of the trials reported the prevalence of MDR and NaR strains. For clinical failure, the results favoured ciprofloxacin (RR 0.24, 95%CI 0.07 to 0.82), although confidence intervals were wide, due to the small sample size (low quality evidence). Fever clearance time (FCT) (two trials; 147 patients) also favoured ciprofloxacin, the mean difference (MD) was −62.46 hours (95%CI −75.52 to −49.39) (moderate quality evidence). Small numbers of events occurred for microbiological failure (two trials, 142 patients; RR 0.05, 95%CI 0.00 to 0.81) (low quality evidence) and relapse (four trials, RR 0.15, 95%CI 0.02 to 1.15) (low quality evidence). The results for serious adverse events (two trials) were indeterminate (RR 0.99, 95%CI 0.18 to 5.52) (very low quality evidence) and for non-serious adverse events (four trials), the results were comparable (RR 1.00, 95%CI 0.61 to 1.64), but with wide confidence intervals (low quality evidence) (*8*).

*Ofloxacin versus chloramphenicol*

Four trials (247 patients) compared ofloxacin to chloramphenicol. The results for clinical failure were in favour of ofloxacin, but with wide confidence intervals (RR 0.15, 95%CI 0.03 to 0.64) (low quality evidence). Fever clearance time (two trials, 140 patients) followed the same trends as clinical failures, the MD was −75.85 hours (95%CI −88.52 to −63.17) (moderate quality evidence).

Due to the small numbers of events, the results for microbiological failure (three trials, RR 0.16, 95%CI 0.02 to 1.07) (low quality evidence) and relapse (RR 0.14, 95%CI 0.01 to 2.65) (low quality evidence) were indeterminate. For serious adverse events (one trial), the RR was not estimable due to zero events. For non-serious adverse event (four trials), the results were comparable, with a RR of 1.06 and wide confidence intervals (95%CI 0.60 to 1.87) (low quality).

The SR included one trial (252 patients) that compared gatifloxacin (which was not proposed in the application for EML listing), versus chloramphenicol (RR for clinical failure was 0.79, 95%CI 0.32 to 1.96) (*7*). Non-serious adverse events favoured gatifloxacin (RR 0.58, 95%CI 0.44 to 0.78).

#### *Ciprofloxacin/ofloxacin versus cotrimoxazole and ampicillin/amoxicillin*

The application reported comparisons of ciprofloxacin versus cotrimoxazole (two trials, 132 patients), ofloxacin versus cotrimoxazole (one trial, 99 patients), ofloxacin versus ampicillin (one trial, 40 patients), ofloxacin versus amoxicillin (one trial, 50 patients). However, due to the small sample sizes the results were indeterminate and the individual outcomes were assessed as low or very low quality. Therefore, cotrimoxazole and ampicillin/amoxicillin were not proposed in the application for EML listing.

#### *Ciprofloxacin/ofloxacin versus cefixime*

The comparisons of ciprofloxacin versus cefixime and ofloxacin versus cefixime were each based on one trial. Due to the weakness and low/very low quality of the evidence, cefixime was not proposed in the application for EML listing.

A randomized controlled trial that compared gatifloxacin versus cefixime (158 patients), was stopped early by the Independent Data Safety and Monitoring Board due to the high number of failures (19/70) in the cefixime arm (RR 0.04, 95%CI 0.01 to 0.31) ($p<0.001$) (*10*). This trial was included in the SR but was not part of the comparisons evaluated in the application for inclusion in the EML.

#### *Ciprofloxacin versus ceftriaxone*

For this comparison, only one trial (42 adult participants) was available. Due to the very small number of patients, the result was indeterminate. There is no estimate for FCT and adverse events were not reported. The overall quality of the evidence was accessed as very low. More than 50% of strains were MDR.

#### *Ofloxacin versus ceftriaxone*

For this comparison, only one trial (47 adult participants) was available. More than 50% of strains were MDR, no NaR was reported. For clinical failure, a non-significant result in favour of ofloxacin was reported, (RR 0.09, 95%CI 0.01 to 1.46), the MD in FCT was −115 hours (95%CI −150.67 to −79.33).

*Ciprofloxacin versus azithromycin*

For this comparison, only one trial (64 participants) was available. Due to the small sample size (0 events in both arms), clinical failure, microbiological failure and relapse were not estimable. The MD for FCT was −12 hours (95%CI −24.39 to 0.39). The quality of the evidence was low/very low.

*Ofloxacin versus azithromycin*

Two trials were available (213 patients) for this comparison. Clinical failure favoured azithromycin with a RR of 2.2 (95%CI 1.23 to 3.94) (high quality of evidence), the MD in FCT of 30.41 hours (95%CI −22.12 to 82.93) (moderate quality evidence) supported azithromycin. The higher failure rates in the ofloxacin arm in the more recent of the two trials, reflected the increasing prevalence of NaR *S. typhi* isolates in this region.

The systematic review included one azithromycin trial (287 patients), that compared gatifloxacin to azithromycin (*11*). Gatifloxacin and azithromycin had similar high efficacy (RR for clinical failure 0.98, 95%CI 0.32 to 2.96) in this setting with high proportions of NaR *S. typhi* strains.

A 2008 Cochrane systematic review of seven trials involving 773 patients evaluated azithromycin for treatment of uncomplicated typhoid and paratyphoid fever (*12*).

The comparison azithromycin versus chloramphenicol (one trial, 77 patients) showed a benefit for azithromycin, but due to the small sample size and wide confidence intervals no inferences can be made (odds ratio (OR) for clinical failure 0.16, 95%CI 0.01 to 3.4 (low quality evidence)). Four trials (564 patients) compared azithromycin to the fluoroquinolones (including gatifloxacin) and were discussed above.

Two trials (132 patients) compared azithromycin versus ceftriaxone. Clinical failure (OR 2.58, 95%CI 0.48 to 13.87) and FCT (MD 9.12 h. 95%CI −1.11 to 19.36) favoured ceftriaxone (moderate quality evidence). No data were available to assess adverse events.

The application described a systematic search for randomized controlled trials (RCTs) in enteric fever to supplement evidence obtained from the two SRs. The majority of identified RCTs had small sample sizes, few events and lacked sufficient power to detect significant differences. Four trials with sample sizes greater than 30 patients in each arm were reviewed. Two trials had zero events for clinical failure. A trial of gatifloxacin versus ofloxacin (218 culture-positive patients) showed similar numbers of treatment failures in both arms (hazard ratio, HR 0.81, 95%CI 0.25 to 2.65), however the FCT was significantly shorter in the gatifloxacin arm (HR 1.59, 95%CI 1.16 to 2.18) in this setting with high NaR (*13*). Similar proportions of patients experienced adverse events, most of which were mild (Grade 1 or Grade 2).

A trial of gatifloxacin versus ceftriaxone (116 culture-positive patients) showed similar number of failures in the intention-to-treat (ITT) patients, but in the culture-confirmed patients, the comparison favoured ceftriaxone (HR 0.24, 95%CI 0.08 to 0.73) (*14*). Treatment failure was associated with the emergence of high-level fluoroquinolone resistance in *S. typhi*, requiring the trial to be stopped. A similar number of non-serious adverse events occurred in each treatment group, and no serious events were reported.

**Guidelines** (from the application)

The 2003 WHO guidelines on the diagnosis, treatment and prevention of typhoid fever (*5*) make the following recommendations for treatment of uncomplicated typhoid fever, based on susceptibility of infection:

- Fully sensitive: a fluoroquinolone (ofloxacin or ciprofloxacin) as optimal therapy. Chloramphenicol, amoxicillin or sulfamethoxazole + trimethoprim are alternatives.
- Multidrug resistance: a fluoroquinolone or cefixime as optimal therapy. Azithromycin or cefixime are alternatives.
- Quinolone resistance: azithromycin or ceftriaxone as optimal therapy. Cefixime is an alternative.

The 2012 WHO pocket book recommendations for management of common childhood conditions (*15*) make the following recommendations for the treatment of typhoid fever in children:

- Children with typhoid fever should be treated with a fluoroquinolone (i.e. ciprofloxacin, gatifloxacin, ofloxacin and perfloxacin) as a first-line treatment for 7–10 days (strong recommendation, moderate quality evidence).
- If response to treatment is poor, consider drug-resistant typhoid and treat with a second-line antibiotic such as a third-generation cephalosporin or azithromycin for 5–7 days (strong recommendation, moderate quality evidence).
- Where drug resistance to antibiotics among salmonella isolates is known, follow national guidelines according to local susceptibility data (strong recommendations, moderate quality evidence).

**Rationale for antibiotic selection** (from the application)

Although recommended in the 2003 WHO guidelines, ampicillin/amoxicillin and trimethoprim-sulfamethoxazole were not proposed in the application for inclusion in the EML for typhoid fever due to the lack of data showing any benefit over comparators based on evidence from the SRs identified.

Chloramphenicol is recommended in the 2003 WHO guidelines but not in the 2012 WHO pocket book. There has been conflicting evidence from smaller trials, however, a large trial showed similar efficacy to gatifloxacin, a fourth-generation fluoroquinolone, but higher numbers of Grade 1 and 2 adverse events. Due to the need to monitor blood counts, the long treatment duration and the availability of alternative drugs, chloramphenicol was not proposed in the application for inclusion on the EML.

The application proposed the inclusion of ofloxacin and ciprofloxacin on the EML and EMLc, supported by evidence from the SRs and clinical practice guidelines (CPGs). More clinical trials evaluating ofloxacin have been performed, however, ofloxacin is not currently included on the EML. As ciprofloxacin is currently listed and has similar clinical performance, for parsimony, ciprofloxacin only could be considered.

Although included in the 2003 WHO guidelines, the evidence from the SRs did not support listing of cefixime. In comparisons with fluoroquinolones, cefixime, showed higher number of failures and longer FCTs, however, in comparisons with chloramphenicol, it compared favourably.

The application also proposed listing ceftriaxone and azithromycin on the EML and EMLc for typhoid fever, supported by evidence from SR and CPGs.

**Committee considerations** (additional evidence, dose/duration, costs, etc.)

The Expert Committee agreed that knowledge of the local resistance patterns for *S. typhi* and *S. paratyphi* strains was critical for making empiric treatment choices in the treatment of enteric fever, noting that there are reports of high rates of fluoroquinolone resistance in some settings. This is the first time the Expert Committee has considered resistance patterns in making specific recommendations for empiric treatment.

The Expert Committee considered the various antibiotics proposed in the application under the guiding principle of parsimony and selected first- and second-choice antibiotics for this indication for inclusion on the EML and EMLc.

**EML listings**

Antibiotics proposed for both EML and EMLc unless specified
***Endorsement*** indicates those antibiotics currently included on EML/EMLc

| | *First choice* | *Second choice* |
|---|---|---|
| ***Endorsement*** | Ciprofloxacin (except where high prevalence of fluoroquinolone resistance exists)<br>Azithromycin<br>Ceftriaxone | |

**Committee recommendations**

The Expert Committee endorsed listing of ciprofloxacin, ceftriaxone and azithromycin as first-choice treatments for typhoid and paratyphoid (enteric) fever on the core list of the EML and EMLc. Ciprofloxacin is recommended as first-choice in settings with low prevalence of fluoroquinolone resistance, while ceftriaxone and azithromycin are recommended first-choice treatments in settings where there is a high prevalence of fluoroquinolone resistance.

Ciprofloxacin, azithromycin and ceftriaxone are all classified as Watch group antibiotics (Section 6.2.2).

Following the principle of parsimony, the Expert Committee did not recommend the addition of ofloxacin for this indication, noting that ofloxacin and ciprofloxacin have demonstrated similar clinical performance for this indication in clinical trials.

## References


1. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1151–210.
2. Levine MM, Simon R. The Gathering Storm: Is Untreatable Typhoid Fever on the Way? mBio. 2018;9(2).
3. Parry CM, Hien TT, Dougan G, White NJ, Farrar JJ. Typhoid fever. N Engl J Med. 2002;347(22): 1770–82.
4. Klemm EJ, Shakoor S, Page AJ, Qamar FN, Judge K, Saeed DK, et al. Emergence of an Extensively Drug-Resistant Salmonella enterica Serovar Typhi Clone Harboring a Promiscuous Plasmid Encoding Resistance to Fluoroquinolones and Third-Generation Cephalosporins. mBio. 2018;9(1).
5. World Health Organization. Background document: The diagnosis, treatment and prevention of typhoid fever. Geneva: World Health Organization; 2003.
6. Gavi. New typhoid vaccine to receive Gavi support [website]. Geneva: Gavi; 2018. (https://www.gavi.org/library/news/statements/2018/new-typhoid-vaccine-to-receive-gavi-support/, accessed 7 March 2019).
7. Arjyal A, Basnyat B, Koirala S, Karkey A, Dongol S, Agrawaal KK, et al. Gatifloxacin versus chloramphenicol for uncomplicated enteric fever: an open-label, randomised, controlled trial. Lancet Infect Dis. 2011;11(6):445–54.
8. Effa EE, Lassi ZS, Critchley JA, Garner P, Sinclair D, Olliaro PL, et al. Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever). Cochrane Database Syst Rev. 2011(10):CD004530.
9. Thaver D, Zaidi AK, Critchley JA, Azmatullah A, Madni SA, Bhutta ZA. Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever). Cochrane Database Syst Rev. 2008(4):CD004530.
10. Pandit A, Arjyal A, Day JN, Paudyal B, Dangol S, Zimmerman MD, et al. An open randomized comparison of gatifloxacin versus cefixime for the treatment of uncomplicated enteric fever. PLoS One. 2007;2(6):e542.
11. Dolecek C, Tran TP, Nguyen NR, Le TP, Ha V, Phung QT, et al. A multi-center randomised controlled trial of gatifloxacin versus azithromycin for the treatment of uncomplicated typhoid fever in children and adults in Vietnam. PLoS One. 2008;3(5):e2188.

12. Effa EE, Bukirwa H. Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever). Cochrane Database Syst Rev. 2008(4):CD006083.

13. Koirala S, Basnyat B, Arjyal A, Shilpakar O, Shrestha K, Shrestha R, et al. Gatifloxacin versus ofloxacin for the treatment of uncomplicated enteric fever in Nepal: an open-label, randomized, controlled trial. PLoS Negl Trop Dis. 2013;7(10):e2523.

14. Arjyal A, Basnyat B, Nhan HT, Koirala S, Giri A, Joshi N, et al. Gatifloxacin versus ceftriaxone for uncomplicated enteric fever in Nepal: an open-label, two-centre, randomised controlled trial. Lancet Infect Dis. 2016;16(5):535–45.

15. WHO. Recommendations for management of common childhood conditions. Evidence for technical update of pocket book recommendations. Newborn conditions, dysentery, pneumonia, oxygen use and delivery, common causes of fever, severe acute malnutrition and supportive care. Geneva: World Health Organization; 2012. Available from http://www.who.int/maternal_child_adolescent/documents/management_childhood_conditions/en/, accessed 10 September 2019.

*Antibiotics for surgical prophylaxis*

## Surgical antibiotic prophylaxis

**Applicant(s)**

WHO Department of Service Delivery and Safety (SDS)

**Introduction**

Surgical site infections (SSIs) are the most frequent health care-associated infection (HAI) in low- and middle-income countries (LMICs) and the second most frequent HAI in Europe and the United States of America (*1–4*). In LMICs: 11% of patients who undergo surgery are infected in the process. In Africa, infection is the most frequent complication in surgery and up to 20% of women who have a caesarean section develop a postoperative wound infection, compromising both their health and the ability to care for their infants (WHO, unpublished data, 2017; (*5*)). SSIs are mainly caused by bacteria that enter through incisions made during surgery. Some involve only skin and subcutaneous tissue, but others are more serious and involve muscle, fascia, organ spaces or implanted material (*6*).

SSIs are associated with longer postoperative hospital stays and may require additional surgical procedures and even intensive care, thus resulting in a higher attributable morbidity and mortality (*7*). They also add a financial burden to the health care system and patient out- of-pocket costs. In the Unites States, they contribute to patients spending more than 400 000 extra days in hospital at a cost of an additional US$ 10 billion per year (*8*).

Surgical antibiotic prophylaxis (SAP) is one of the pillars of SSI prevention and is defined as the prevention of infectious complications by administering an effective antimicrobial agent prior to exposure to contamination during surgery (*9*). It has also been described as "the rational, safe and effective use of antimicrobial agents for the prevention of (initial) SSIs" (*10*) and as "the use of antibiotics to prevent postoperative infection" (*11*). WHO provides strong recommendations on the administration of SAP prior to surgical incision when indicated, depending on the type of operation, its timing and duration. However, SAP is often used inappropriately in many settings around the world and this misuse diminishes patient safety and increases acquisition and transmission of antimicrobial resistance (AMR) in surgical services. Inappropriate SAP mainly consists of incorrect antibiotic choice, dose, timing and/or means of administration, and/or duration.

Results of a WHO global survey conducted in 2014[20] showed that inappropriate SAP duration is a major problem worldwide, with prolongation of antibiotic use beyond international standards (that is, one preoperative dose and repetition during the intervention if necessary, according to specific criteria) in 43.5% of procedures on average. The frequency of prolongation was higher than 60% in African, Eastern Mediterranean and Western Pacific countries. Inappropriate SAP is particularly frequent in LMICs (*12*–*16*).

Based on these and other findings, and considering the central role of SAP in SSI prevention, there is need for standardized, evidence-based global guidance on appropriate SAP, which involves several key aspects based on high quality evidence: correct antibiotic choice, dose, timing, route of administration and duration.

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**Summary of evidence** (from the application)

The application presented the results of a rapid systematic literature review of SRs on SAP. Inclusion criteria were that the SR addressed the effect of intravenous SAP on SSIs and either: (1) recommended SAP; (2) recommended a specific agent; and/or (3) provided a head-to-head comparison of antibiotics used for SAP. In addition, SRs based on insufficient evidence (for example, one or two RCTs with small sample sizes) were excluded. (Refer to the application for full details of the search strategy and study selection).

Seventeen systematic reviews were included: 13 compared SAP regimens for specific procedure types including: neurosurgery (*17*, *18*); neck surgery (*19*, *20*); cardiac surgery (*21*, *22*); upper gastrointestinal surgery (*23*); colorectal surgery (*24*, *25*); caesarean section (*26*); gynaecological surgery (*27*); hernia surgery (*28*); and plastic surgery (29). Three compared specific SAP regimens for several procedure types combined (cardiac-, vascular-, orthopaedic- and neurosurgery; cardiac-, vascular- and orthopaedic surgery; and cardiac- and orthopaedic surgery) (*30*–*32*). One specifically addressed SAP for methicillin-resistant *Staphylococcus aureus* (MRSA) SSI prevention (*33*). The included SRs provided evidence that was generally in line with the recommendations for SAP from the evidence-based guideline issued jointly in 2013 by the American Society of Health System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Surgical Infection Society (SIS) and the Society for Healthcare Epidemiology of America (SHEA) (10) (see Guidelines section, below).

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**Guidelines** (from the application)

The application presented the results of systematic review and inventory of available relevant evidence-based SAP guidelines and protocols. Inclusion criteria

[20] https://www.who.int/gpsc/5may/global-surveys/en/

were that the guideline was: (1) issued by a country, region or organization/society (that is, not adopted locally or by a single centre); (2) issued within the past five years; and (3) based on a systematic, evidence-based approach. (Refer to the application for full details of the search strategy and guideline selection).

Thirty records were included: 19 records met all three inclusion criteria (*9–11*, *34–49*). Ten met the first two criteria, but did not rely on a systematic evidence-based approach (*50–59*) and one, which included recommendations on all relevant types of surgery, was systematically updated, but not issued in a national context or by a scientific society (*60*). The 11 records that did not meet all three inclusion criteria were deemed relevant as they were of high quality and/or addressed unique situations, such as LMICs or paediatric settings.

All identified guidelines covered at least one of the most common surgical procedures. The most frequently recommended first-line antibiotics (first-choice antibiotics and second-choice agents as alternatives to first-choice) for SAP across all procedures were cefazolin, by far, followed by cefuroxime, then metronidazole (in combination with another agent), gentamicin and ampicillin-sulbactam. The most frequently recommended second-line antibiotics to be used for SAP in cases of known immediate severe or delayed severe penicillin hypersensitivity were vancomycin, clindamycin, gentamicin and metronidazole across all procedures.

When considering wound classification (*61–63*), the most frequently recommended first-line antibiotics in clean surgical procedures with potential severe consequences of infection and/or procedures involving implantation of foreign material (for example, cardiac, breast or hernia surgery, central and peripheral vascular surgery, orthopaedic [excluding arthroscopy or neurosurgery] and non-cardiac thoracic surgery) were a first-generation cephalosporin (cefazolin), by far, followed by a second-generation cephalosporin (cefuroxime). The most frequently recommended second-line antibiotics to be used in cases of known immediate severe or delayed severe penicillin hypersensitivity were vancomycin and clindamycin, both as single agents. For some procedures, some guidelines also mentioned a combination of vancomycin and gentamicin (cardiac and central vascular surgery) or a combination of clindamycin and gentamicin (breast surgery, hernia repair) or gentamicin and metronidazole (hernia repair) as possible second-line alternatives.

In clean-contaminated surgical procedures (for example, head and neck, abdominal, gynaecological, obstetric, urologic and vascular surgery), the most frequently recommended first-line antibiotic was cefazolin (usually combined with metronidazole), by far, followed by metronidazole (in combination with another agent), then cefuroxime, cefoxitin, ampicillin-sulbactam and gentamicin. The most frequently recommended second-line antibiotic to be used in cases of known immediate severe or delayed severe penicillin hypersensitivity was

gentamicin, followed by clindamycin, then metronidazole and vancomycin. For most procedures, guidelines recommended a combination of gentamicin with either clindamycin or vancomycin or metronidazole as possible second-line alternatives.

Many guidelines recommended to consider the use of vancomycin across procedures in addition to the recommended agent(s) as a single pre-operative dose for patients known to be colonized with MRSA or at high risk for MRSA colonization (for example, recently hospitalized patients, nursing home residents, haemodialysis patients) or in the absence of screening data (*10*, *11*, *53*, *56*, *59*, *60*).

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**Rationale for antibiotic selection** (from the application)

The application proposed the antibiotics of choice for SAP for inclusion on the EML by type of surgical procedures and provided alternative options when the first-line choices are unavailable or contraindicated due to severe allergy. The proposed antibiotics were selected by consensus at a meeting of technical experts after consideration of the review findings.

Among first-line antibiotics, the first choice recommended for most procedures was cefazolin or its second-generation equivalent, cefuroxime. It was noted that ceftriaxone and other antibiotics are often inappropriately used as first-line SAP options in many LMICs.

Experts stressed the importance of ensuring that cefazolin and/or cefuroxime are broadly available worldwide at a reasonable price and as good quality products with good manufacturing practice labelling.

For patients with confirmed immediate severe or delayed severe penicillin hypersensitivity, a non–beta-lactam antibiotic must be used instead. It was emphasized that the second-line antibiotics listed are sub-optimal and should only be used in cases of known or highly suspected allergies. However, appropriate documentation of allergies prior to surgery is not common practice in all settings, particularly in LMICs.

It was agreed that there is no good reason to use ceftriaxone for SAP as it belongs to the EML Watch group (*64*). In addition, it is included in the WHO highest priority, critically important antimicrobials (CIA) list (*65*) as it is a third-generation cephalosporin, and thus has a high risk of selection of bacterial resistance (in particular, extended spectrum beta-lactamase [ESBL]-producing enterobacteriacae). Therefore, ceftriaxone should be reserved for the limited number of infectious conditions where it is indicated for therapeutic purposes. Conversely, it is widely overused, including for SAP for which ceftriaxone has no indication and does not add any value as it does not offer additional coverage for ESBL. It is also inferior to other antibiotics (for example, cefazolin) for methicillin-sensitive *S. aureus* and creates an unnecessary risk of collateral damage to the gut flora given its high biliary penetration.

Considering the high resistance rates to quinolones in LMICs and the fact that they feature in the EML Watch category (*64*) and are among the highest priority antimicrobials in the CIA list (*65*), participants agreed that the combination of an aminoglycoside (gentamicin or tobramycin) plus metronidazole is generally preferable as second-line antibiotics. However, for patients with renal insufficiency, quinolones may be more appropriate. Quinolones should be reserved for special circumstances where no other options are available. When they are used, ciprofloxacin should generally be favoured over levofloxacin.

It was noted that many hospitals in the United States have begun administering azithromycin in addition to cefazolin for pregnant women undergoing caesarean sections, based on the results of a RCT published in 2016 showing a 50% reduction in SSIs compared to a control group (*66*). Experts agreed that this study represents valuable evidence, but it would be premature to consider this option in the EML based on the results of a single study conducted in a high-income country (HIC). As additional evidence emerges, it might be appropriate to add adjunctive azithromycin as a first-line option for caesarean section in future editions of the EML.

**Antibiotics proposed in the application**

| PROCEDURE | FIRST-LINE | | ALTERNATIVES (when allergic to first-line choices) |
|---|---|---|---|
| | First choice | Second choice | |
| Neck surgery<br>– clean<br>– clean-contaminated | No SAP<br>Cefazolin (or cefuroxime) plus metronidazole | No SAP<br>Amoxicillin + clavulanic acid | No SAP<br>Clindamycin plus gentamicin |
| Cardiac surgery (in general) | Cefazolin (or cefuroxime) | N/A | Vancomycin |
| Thoracic surgery (non-cardiac) | Cefazolin (or cefuroxime) | N/A | Vancomycin |
| Breast surgery | Cefazolin (or cefuroxime) | N/A | Vancomycin |
| Upper gastrointestinal tract surgery | Cefazolin (or cefuroxime) | N/A | Clindamycin plus gentamicin |
| Hepato-pancreato-biliary surgery + Cholecystectomy[a] | Cefazolin (or cefuroxime) | Amoxicillin + clavulanic acid | Gentamicin plus metronidazole |
| Hernia surgery | Cefazolin (or cefuroxime) | N/A | Vancomycin |

Table *continued*

| PROCEDURE | FIRST-LINE | | ALTERNATIVES (when allergic to first-line choices) |
|---|---|---|---|
| | First choice | Second choice | |
| Appendectomy | Cefazolin (or cefuroxime) plus metronidazole | N/A | Gentamicin plus metronidazole |
| Colorectal surgery | Cefazolin (or cefuroxime) plus metronidazole | Amoxicillin + clavulanic acid | Gentamicin plus metronidazole |
| Hysterectomy | Cefazolin (or cefuroxime) | Amoxicillin + clavulanic acid | Clindamycin plus gentamicin |
| Caesarean section | Cefazolin (or cefuroxime) | Amoxicillin + clavulanic acid | Clindamycin plus gentamicin |
| Central vascular surgery | Cefazolin (or cefuroxime) | N/A | Vancomycin |
| Peripheral vascular surgery | Cefazolin (or cefuroxime) | N/A | Vancomycin |
| Orthopaedic surgery (excluding arthroscopy) | Cefazolin (or cefuroxime) | N/A | Vancomycin |
| Bone fracture surgery | Cefazolin (or cefuroxime) | N/A | Vancomycin |
| Urologic | | | |
| – prostate surgery | Cefazolin (or cefuroxime) | Gentamicin | Gentamicin |
| – laparoscopic nephrectomy | No SAP | No SAP | No SAP |
| – laparotomy nephrectomy and partial nephrectomy | Cefazolin (or cefuroxime) | N/A | Gentamicin |
| Neurosurgery – cranium/spine | Cefazolin (or cefuroxime) | N/A | Vancomycin |

[a] Biliary tract open surgery or endoscopic in high-risk patients: factors that indicate a high risk of infectious complications in laparoscopic cholecystectomy include emergency procedures; diabetes; long procedure duration; intraoperative gallbladder rupture; age >70 years; conversion from laparoscopic to open cholecystectomy; American Society of Anesthesiologists classification of three or greater; episode of colic within 30 days before the procedure; re-intervention of less than one month for a non-infectious complication; acute cholecystitis; bile spillage; jaundice; pregnancy; non-functioning gallbladder; immunosuppression; and insertion of a prosthetic device. As a number of these risk factors are not possible to determine before the surgical intervention, it may be reasonable to give a single dose of antimicrobial prophylaxis to all patients undergoing laparoscopic cholecystectomy (*10*).

**Committee considerations** (additional evidence, dose/duration, costs, etc.)

The Expert Committee agreed with the views of the technical expert group that key factors for appropriate SAP include selecting the right antibiotic, taking into account the surgical procedure (as well as probable causative microorganisms and their resistance patterns based on SSI surveillance), route of administration, dosing, patient allergies and cost/availability; administering the antibiotic at the right time; and avoiding prolongation of the antibiotic after completion of the operation. For SAP to be effective, the tissue concentration of the antibiotic must be above the minimal inhibitory concentration at the time of incision and throughout the procedure. This depends on the half-life of the antibiotic chosen and may require re-dosing accordingly during the procedure.

The Expert Committee agreed that administering SAP close to the time of incision is important for antibiotics with a short half-life and, in general, this could avoid the need for re-dosing during the procedure (depending again on the half-life of the particular antibiotic used). For example, administration closer to the incision time (<60 minutes) can be considered for antibiotics with a short half-life such as cefazolin.

The Expert Committee noted the key considerations for dosing and re-dosing identified by the technical expert group:

- Observational data suggest that higher serum and tissue levels throughout the surgical procedure reduce the risk of SSIs.
- Higher doses should be favoured, as long as there are no concerns about toxicity.
- Re-dosing should generally be provided after twice the half-life of the antibiotic has passed since the initial preoperative dose.
- There is little evidence to support weight-based dosing, but higher doses of cephalosporins may be advisable in morbidly obese patients.

**EML listings**

Antibiotics proposed for both EML and EMLc unless specified
***Endorsement*** indicates those antibiotics currently included on EML/EMLc

| | ***First choice*** | ***Second choice*** |
|---|---|---|
| ***Endorsement*** | Cefazolin<br>(alone or in combination with)<br>Metronidazole | Amoxicillin + clavulanic acid<br>Gentamicin |
| ***Addition*** | | Cefuroxime |

### Committee recommendations

The Expert Committee considered the various antibiotics proposed in the application under the guiding principle of parsimony and selected first- and second-choice antibiotics for this indication for inclusion. In line with previous decisions for infectious syndromes, alternatives for use in case of allergy were not recommended.

The Expert Committee endorsed listing of cefazolin, alone or in combination with metronidazole as first-choice options, and of amoxicillin + clavulanic acid and gentamicin as second-choice options for surgical prophylaxis on the core list of the EML and EMLc, as Access group antibiotics (Section 6.2.1).

The Committee also recommended the addition of cefuroxime to the core list of the EML and EMLc as a second-choice option for surgical prophylaxis, as a Watch group antibiotic (Section 6.2.2), as an alternative to cefazolin.

## References

1. Suetens C, Latour K, Karki T, Ricchizzi E, Kinross P, Moro ML, et al. Prevalence of healthcare-associated infections, estimated incidence and composite antimicrobial resistance index in acute care hospitals and long-term care facilities: results from two European point prevalence surveys, 2016 to 2017. Euro Surveill. 2018;23(46).
2. Allegranzi B, Bagheri Nejad S, Combescure C, Graafmans W, Attar H, Donaldson L, et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. Lancet. 2011;377(9761):228–41.
3. Report on the burden of endemic health care-associated infection worldwide. Geneva: World Health Organization; 2011.
4. Magill SS, O'Leary E, Janelle SJ, Thompson DL, Dumyati G, Nadle J, et al. Changes in Prevalence of Health Care-Associated Infections in U.S. Hospitals. N Engl J Med. 2018;379(18):1732–44.
5. Biccard BM, Madiba TE, Kluyts HL, Munlemvo DM, Madzimbamuto FD, Basenero A, et al. Perioperative patient outcomes in the African Surgical Outcomes Study: a 7-day prospective observational cohort study. Lancet. 2018;391(10130):1589–98.
6. Anderson DJ, Chen LF, Sexton DJ, Kaye KS. Complex surgical site infections and the devilish details of risk adjustment: important implications for public reporting. Infect Control Hosp Epidemiol. 2008;29(10):941–6.
7. Cassini A, Plachouras D, Eckmanns T, Abu Sin M, Blank HP, Ducomble T, et al. Burden of Six Healthcare-Associated Infections on European Population Health: Estimating Incidence-Based Disability-Adjusted Life Years through a Population Prevalence-Based Modelling Study. PLoS Med. 2016;13(10):e1002150.
8. de Lissovoy G, Fraeman K, Hutchins V, Murphy D, Song D, Vaughn BB. Surgical site infection: incidence and impact on hospital utilization and treatment costs. Am J Infect Control. 2009;37(5):387–97.
9. Global guidelines for the prevention of surgical site infection. Geneva: World Health Organization; 2016.
10. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm. 2013;70(3):195–283.

11. Surgical antibiotic prophylaxis, In: Therapeutic Guidelines: Antibiotic, version 16 (2019) [website]. Melbourne: Therapeutic Guidelines Ltd. 2019. (https://www.tg.org.au/, accessed 30 October 2019).
12. Allegranzi B, Aiken AM, Zeynep Kubilay N, Nthumba P, Barasa J, Okumu G, et al. A multimodal infection control and patient safety intervention to reduce surgical site infections in Africa: a multicentre, before–after, cohort study. Lancet Infect Dis. 2018;18(5):507–15.
13. Aiken AM, Wanyoro AK, Mwangi J, Juma F, Mugoya IK, Scott JA. Changing use of surgical antibiotic prophylaxis in Thika Hospital, Kenya: a quality improvement intervention with an interrupted time series design. PLoS One. 2013;8(11):e78942.
14. Talaam RC, Abungana MM, Ooko PB. An antibiotic audit of the surgical department at a rural hospital in Western Kenya. Pan Afr Med J. 2018;29:219.
15. Halawi E, Assefa T, Hussen S. Pattern of antibiotics use, incidence and predictors of surgical site infections in a Tertiary Care Teaching Hospital. BMC Res Notes. 2018;11(1):538.
16. Palacios-Saucedo GDC, de la Garza-Camargo M, Briones-Lara E, Carmona-Gonzalez S, Garcia-Cabello R, Islas-Esparza LA, et al. [Assessment of antibiotic use and impact of an intervention intended to modify the prescribing behavior in surgical prophylaxis in 6 hospitals in the metropolitan area of Monterrey, Mexico]. Cir Cir. 2017;85(6):459–70.
17. Liu W, Neidert MC, Groen RJ, Woernle CM, Grundmann H. Third-generation cephalosporins as antibiotic prophylaxis in neurosurgery: what's the evidence? Clin Neurol Neurosurg. 2014;116:13–9.
18. Abraham P, Lamba N, Acosta M, Gholmie J, Dawood HY, Vestal M, et al. Antibacterial prophylaxis for gram-positive and gram-negative infections in cranial surgery: A meta-analysis. J Clin Neurosci. 2017;45:24–32.
19. Garnier M, Blayau C, Fulgencio JP, Baujat B, Arlet G, Bonnet F, et al. Rational approach of antibioprophylaxis: Systematic review in ENT cancer surgery. [French]. Ann Fr Anesth Reanim. 2013;32(5):315–24.
20. Thorn C, Faber A, Schultz JD, Hormann K, Stuck BA. [Prophylactic antibiotic use in ENT surgery]. HNO. 2015;63(2):118–24.
21. Lador A, Nasir H, Mansur N, Sharoni E, Biderman P, Leibovici L, et al. Antibiotic prophylaxis in cardiac surgery: systematic review and meta-analysis. J Antimicrob Chemother. 2012;67(3):541–50.
22. Vos RJ, Van Putte BP, Kloppenburg GTL. Prevention of deep sternal wound infection in cardiac surgery: a literature review. J Hosp Infect. 2018; 100(4):411–420.
23. Fischer MI, Dias C, Stein A, Meinhardt NG, Heineck I. Antibiotic prophylaxis in obese patients submitted to bariatric surgery. A systematic review. Acta Cir Bras. 2014;29(3):209–17.
24. Nelson RL, Gladman E, Barbateskovic M. Antimicrobial prophylaxis for colorectal surgery. Cochrane Database Syst Rev. 2014;5:CD001181.
25. Rangel SJ, Islam S, St Peter SD, Goldin AB, Abdullah F, Downard CD, et al. Prevention of infectious complications after elective colorectal surgery in children: an American Pediatric Surgical Association Outcomes and Clinical Trials Committee comprehensive review. J Pediatr Surg. 2015;50(1):192–200.
26. Dahlke JD, Mendez-Figueroa H, Rouse DJ, Berghella V, Baxter JK, Chauhan SP. Evidence-based surgery for cesarean delivery: an updated systematic review. Am J Obstet Gynecol. 2013;209(4):294–306.

27. Morrill MY, Schimpf MO, Abed H, Carberry C, Margulies RU, White AB, et al. Antibiotic prophylaxis for selected gynecologic surgeries. Int J Gynaecol Obstet. 2013;120(1):10–15.
28. Boonchan T, Wilasrusmee C, McEvoy M, Attia J, Thakkinstian A. Network meta-analysis of antibiotic prophylaxis for prevention of surgical-site infection after groin hernia surgery. Br J Surg. 2017;104(2):e106-e17.
29. Dauwe PB, Pulikkottil BJ, Scheuer JF, Stuzin JM, Rohrich RJ. Infection in face-lift surgery: an evidence-based approach to infection prevention. Plast Reconstr Surg. 2015;135(1):58e–66e.
30. Saleh A, Khanna A, Chagin KM, Klika AK, Johnston D, Barsoum WK. Glycopeptides versus beta-lactams for the prevention of surgical site infections in cardiovascular and orthopedic surgery: a meta-analysis. Ann Surg. 2015;261(1):72–80.
31. Chambers D, Worthy G, Myers L, Weatherly H, Elliott R, Hawkins N, et al. Glycopeptide vs. non-glycopeptide antibiotics for prophylaxis of surgical site infections: a systematic review. Surg Infect (Larchmt). 2010;11(5):455–62.
32. Luo S, Lai Y, Liu C, Chen Y, Qiao X. Prophylactic use of gentamicin/flucloxacillin versus cefuroxime in surgery: a meta analysis of clinical studies. Int J Clin Exp Med. 2015;8(10):17856–67.
33. Gurusamy KS, Koti R, Wilson P, Davidson BR. Antibiotic prophylaxis for the prevention of methicillin-resistant Staphylococcus aureus (MRSA) related complications in surgical patients. Cochrane Database Syst Rev.. 2013;8:CD010268.
34. Surgical site infections: prevention and treatment. Clinical guideline [CG74]; London: National Institute for Health and Care Excellence; 2008. Available from https://www.nice.org.uk/guidance/cg74, accessed 30 October 2019.
35. van Schalkwyk J, Van Eyk N. Antibiotic prophylaxis in obstetric procedures. J Obstet Gynaecol Can. 2010;32(9):878–84.
36. Grabe M, Bjerklund-Johansen TE, Botto H, et al. Guidelines on urological infections. Arnhem: European Association of Urology; 2011. (https://uroweb.org/wp-content/uploads/17_Urological-infections_LR-II.pdf, accessed 30 October 2019).
37. Systematic review and evidence-based guidance on perioperative antibiotic prophylaxis. Stockholm: European Centre for Disease Prevention and Control; 2013.
38. Caesarean section. Clinical guideline [CG132]: London: National Institute for Health and Care Excellence; 2011. Available from https://www.nice.org.uk/guidance/cg132, accessed 30 October 2019.
39. Shaffer WO, Baisden JL, Fernand R, Matz PG. An evidence-based clinical guideline for antibiotic prophylaxis in spine surgery. Spine J. 2013;13(10):1387–92.
40. Safer Healthcare Now. Prevent Surgical Site Infections Getting Started Kit. Edmonton: Canadian Patient Safety Institute; 2014.
41. Targeted literature review: What are the key infection prevention and control recommendations to inform a surgical site infection (SSI) prevention quality improvement tool? Glasgow: Health Protection Scotland; 2015.
42. Ariyan S, Martin J, Lal A, Cheng D, Borah GL, Chung KC, et al. Antibiotic prophylaxis for preventing surgical-site infection in plastic surgery: an evidence-based consensus conference statement from the American Association of Plastic Surgeons. Plast Reconstr Surg. 2015;135(6):1723–39.
43. Khashab MA, Chithadi KV, Acosta RD, Bruining DH, Chandrasekhara V, Eloubeidi MA, et al. Antibiotic prophylaxis for GI endoscopy. Gastrointest Endosc. 2015;81(1):81–9.
44. Mrkobrada M, Ying I, Mokrycke S, Dresser G, Elsayed S, Bathini V, et al. CUA Guidelines on antibiotic prophylaxis for urologic procedures. Can Urol Assoc J. 2015;9(1-2):13–22.

45. Ban KA, Minei JP, Laronga C, Harbrecht BG, Jensen EH, Fry DE, et al. American College of Surgeons and Surgical Infection Society: Surgical Site Infection Guidelines, 2016 Update. J Am Coll Surg. 2017;224(1):59–74.
46. Berrios-Torres SI, Umscheid CA, Bratzler DW, Leas B, Stone EC, Kelz RR, et al. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. JAMA Surg. 2017;152(8):784–91.
47. Antibioprophylaxie en chirurgie et médecine interventionnelle (patients adultes). Paris: Société Française d'Anesthésie et de Réanimation; 2018.
48. Hézode C, Alric L, Brown A, Hassanein T, Rizzetto M, Buti M, et al. Daclatasvir in Combination with Peginterferon Alfa-2a and Ribavirin for Treatment-Naive Patients with HCV Genotype 4 Infection: Phase 3 COMMAND-4 Results. Open Forum Infect Dis. 2014;1(suppl 1):S233.
49. Broaddus E, Topham A, Singh AD. Incidence of retinoblastoma in the USA: 1975-2004. Br J Ophthalmol. 2009;93(1):21–3.
50. Vitale MG, Riedel MD, Glotzbecker MP, Matsumoto H, Roye DP, Akbarnia BA, et al. Building consensus: development of a Best Practice Guideline (BPG) for surgical site infection (SSI) prevention in high-risk pediatric spine surgery. J Pediatr Orthop. 2013;33(5):471–8.
51. Anderson DJ, Podgorny K, Berríos-Torres SI, Bratzler DW, Dellinger EP, Greene L, et al. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol. 2014;35(6):605–27.
52. National Treatment Guidelines for Infectious Diseases. New Delhi: Indian National Centre for Disease Control; 2016.
53. National Antibiotic Guidelines 2016. Colombo: Sri Lanka College of Microbiologists; 2016.
54. Yamamoto S, Shigemura K, Kiyota H, Wada K, Hayami H, Yasuda M, et al. Essential Japanese guidelines for the prevention of perioperative infections in the urological field: 2015 edition. Int J Urol. 2016;23(10):814–24.
55. Children's Health Queensland: Paediatric surgical antibiotic prophylaxis 2017. Brisbane: Government of Queensland; 2017.
56. Clinical Guideline: Surgical Antimicrobial Prophylaxis. Adelaide: Government of South Australia; 2017.
57. Haas H, Launay E, Minodier P, Cohen R, Gras-Le Guen C. Surgical and medical antibiotic prophylaxis. Arch Pediatr. 2017;24(12, Supplement):S46–S51.
58. Treament Guidelines for Antimicrobial Prophylaxis 2017. New Delhi: Indian Council of Medical Research; 2017.
59. ACOG Practice Bulletin No. 199: Use of Prophylactic Antibiotics in Labor and Delivery. Obstet Gynecol. 2018;132(3):e103–e19.
60. Anderson DJ, Sexton DJ. Antimicrobial prophylaxis for prevention of surgical site infection in adults [Internet]. Available from https://www.uptodate.com/contents/antimicrobial-prophylaxis-for-prevention-of-surgical-site-infection-in-adults, accessed 10 September 2019.
61. Garner JS. CDC guideline for prevention of surgical wound infections, 1985. Supersedes guideline for prevention of surgical wound infections published in 1982. (Originally published in November 1985). Revised. Infect Control. 1986;7(3):193–200.
62. Simmons BP. Guideline for prevention of surgical wound infections. Infect Control. 1982;3:185–96.
63. Marr KA, Crippa F, Leisenring W, Hoyle M, Boeckh M, Balajee SA, et al. Itraconazole versus fluconazole for prevention of fungal infections in patients receiving allogeneic stem cell transplants. Blood. 2004;103(4):1527–33.

64. WHO Model list of essential medicines, 20th list (March 2017, amended August 2017). Geneva: World Health Organization; 2017. Available from https://apps.who.int/iris/handle/10665/273826, accessed 30 October 2019.

65. Critically important antimicrobials for human medicine, 4th rev. Geneva: World Health Organization; 2016.

66. Tita AT, Szychowski JM, Boggess K, Saade G, Longo S, Clark E, et al. Adjunctive Azithromycin Prophylaxis for Cesarean Delivery. N Engl J Med. 2016;375(13):1231–41.

*Antibiotics for oral and dental infections*

## Antibiotics for oral/dental infections

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**Introduction**

Antibiotics are the most widely prescribed category of medicines used by general dental practitioners, a group that was shown to be responsible for 7–11% of all antimicrobials prescribed, and for 45% of all prescriptions of metronidazole (*1*, *2*). Studies have also shown a wide variation in the prescribing habits suggesting inappropriate use of antibiotics in this setting (*3*–*8*).

Dentoalveolar infections are polymicrobial in nature, mostly strictly anaerobic Gram-positive cocci and Gram-negative rods mixed with facultative anaerobic flora (*9*–*12*). The types of infections where antibiotics may be used include periodontitis, pulpitis, pericoronitis, acute necrotizing ulcerative gingivitis, and periodontal abscesses. The choice of antibiotics is typically empirical in the treatment of these infections. Drainage and removal of the cause of the infection is key in infections such as abscesses, with antibiotics to be considered in certain patients such as those with systemic illness or immunocompromised individuals.

**Summary of evidence** (from the application)

The application presented the results of a search undertaken for systematic reviews and meta-analyses of systemic antibiotic therapy for dental infections. A total of 20 systematic reviews were included covering chronic periodontitis, apical periodontitis and acute apical abscess, and irreversible pulpitis.

*Chronic periodontitis*

Although patient important outcomes such as pain or quality of life would have been optimal, the outcomes reported in the literature for periodontitis were surrogate markers of activity such as reduction in probing depth, improvement in clinical attachment level, and bleeding on probing. Microbiological outcomes were disregarded as they were not considered to be of high patient importance. The scope of the identified systematic reviews ranged from assessment of the overall effect of antibiotics, to assessment of specific antibiotics or specific sub-populations such as diabetics or smokers.

*SRs of any antibiotics for any patients*

A systematic review and network meta-analysis of 14 RCTs of systemic antibiotics for patients with periodontitis reported that using metronidazole or

a combination of amoxicillin and metronidazole as an adjuvant to scaling and root planing (SRP) improved clinical attachment gain and reduction in probing depth compared to no antibiotics (*13*). A greater gain in clinical attachment level (MD 1.08 mm) and reduction in probing depth (1.05 mm) was noted with metronidazole, and clinical attachment level (0.45 mm) and probing depth (0.53 mm) with amoxicillin/metronidazole. These antibiotics showed a better effect than doxycycline.

A systematic review of 14 RCTs compared systemic antibiotics in combination with scaling and root planing compared to SRP alone (*14*). They found that systemic antibiotics significantly improved pocket depth reduction and clinical attachment gain. Results suggested that metronidazole with amoxicillin was the most potent combination.

A systematic review of systemic antibiotics for non-surgical periodontal therapy identified a single eligible RCT in which benefit was noted in probing depth reduction (0.9 mm) and clinical attachment gain (0.7 mm). However, the authors concluded that findings were insufficient at this time and larger RCT with longer follow up was needed (*15*).

*SRs of amoxicillin with metronidazole*

A systematic review of 20 RCTs comparing efficacy of amoxicillin and metronidazole adjunctive to SRP compared to SRP alone found a beneficial effect of adjunctive antibiotic therapy for probing depth reduction (0.86 mm, (95%CI 0.65 to 1.07 mm) and clinical attachment level gain 0.75 mm (95%CI 0.40 to 1.09) (*16*).

Another systematic review of six RCTs evaluated the effectiveness of amoxicillin and metronidazole as an adjunct to full-mouth SRP compared to full-mouth SRP alone. Adjunctive antibiotic treatment was associated with significant clinical attachment gain (0.42 mm, 95%CI 0.23 to 0.61) and probing depth reduction (0.58 mm, 95%CI 0.39 to 0.77) (*17*).

A systematic review of six RCTs that assessed the effect of adjunctive antibiotics for refractory periodontitis found greater reduction in probing depth and in loss of clinical attachment level with antibiotics compared to debridement alone across all studies, however a meta-analysis was not conducted. The authors concluded that no firm conclusions could be drawn due to the low quality of the evidence (*18*).

A systematic review of 18 RCTs found no clinically important difference between amoxicillin plus metronidazole compared to no antibiotics as an adjunct to non-surgical treatment of periodontitis (*19*).

*SRs of metronidazole alone*

A systematic review of three RCTs that assessed metronidazole as an adjuvant to SRP found benefit of the antibiotic with respect to probing depth reduction

(0.18 mm, 95%CI 0.09 to 0.28) and clinical attachment (0.10 mm, 95%CI 0.08 to 0.12) (*20*). Another, older systematic review of eight RCTs also found that metronidazole may offer a benefit for periodontitis in pockets of 4 mm and greater, but only for short-term outcomes (*21*).

*SRs of azithromycin*

Two systematic reviews (6 and 14 RCTs) comparing azithromycin as an adjuvant therapy for SRP to SRP alone both reported significant beneficial effects of azithromycin for outcomes of probing depth, clinical attachment level and bleeding on probing (*22*, *23*).

*SRs of doxycycline*

A systematic review of three RCTs assessed the long-term efficacy of systemic use of low-dose (sub-antimicrobial dose) doxycycline (SSD, 20 mg twice daily) as an adjunctive treatment to SRP compared to SRP alone (*24*). Significant reductions in probing depth reduction (0.9 mm, 95%CI 0.43 to 1.37), clinical attachment gain (0.88 mm, 95%CI 0.08 to 1.67), changes in plaque index, gingival index and gingival crevicular fluid at the nine-months stage were observed with adjunctive doxycycline. The authors concluded that the evidence supported a 3-month course of low-dose doxycycline. However, two of the studies were conducted by the same author, and all three studies were conducted in Turkey, potentially limiting the generalizability of the finding. The two studies driving the effect were both evaluated as being at high risk of bias.

*SRs in smokers*

Three systematic reviews of trials of antibiotic therapy in smokers with chronic periodontitis yielded variable findings of no benefit (*25*), inconsistent findings (*26*) and statistically significant benefit of questionable clinical relevance (*27*) associated with adjunctive antibiotic therapy.

*SRs in diabetics*

Two systematic reviews of trials of antibiotic therapy in diabetic patients both reported benefits associated with antibiotic therapy for the outcome of probing depth reduction, but not for other outcomes (*28*, *29*).

#### *Apical periodontitis and acute apical abscess*

A Cochrane systematic review and meta-analysis of two RCTs (62 participants) comparing penicillin to placebo (with surgical intervention and analgesics) found no significant differences for pain or swelling between groups. The authors concluded that there were insufficient data to determine the effects of systemic antibiotics (*30*). Another systematic review of eight RCTs comparing antibiotics to placebo or no pharmacotherapy for acute apical abscesses found no benefit of

antibiotics as an adjuvant to surgical intervention. However, a single identified study showed a benefit of azithromycin over amoxicillin+clavulanic acid in terms of reduction of pain, with no benefit for the co-primary outcome "absence of infection" (*31*).

### *Irreversible pulpitis*

A Cochrane systematic review of systemic antibiotics for pulpitis was based only on one small trial which included the use of penicillin for which there was a lack of significant differences in outcomes between groups (*32*).

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**Guidelines** (from the application)

The application presented the results of a search undertaken of clinical practice guidelines for recommendations on the use of antibiotics for dental infections.

### *Chronic periodontitis*

A 2015 clinical practice guideline developed by an expert panel convened by the American Dental Association on the prevention and treatment of periodontal diseases in primary care recommended use of systemic sub-antimicrobial dose doxycycline (20 mg twice daily for three to nine months) as an adjunct to SRP. The recommendation was made based on moderate evidence of a small net benefit in clinical attachment level from 11 RCTs (813 participants). There was also a weak recommendation for other systemic antimicrobials as adjunct therapy to SRP which showed a similar effect size as sub-antimicrobial dose doxycycline but more significant risk for harm based on 24 RCTs (*33*).

2014 guidelines published by the Scottish Dental Clinical Effectiveness Programme recommended against the use of antimicrobials for chronic periodontitis or peri-implantitis due to a lack of convincing evidence (*34*).

### *Apical periodontitis and acute apical abscess*

The European Society of Endodontology position statement recommended against the use of antibiotics in patients with acute apical periodontitis and acute apical abscess and emphasized the importance of surgical drainage. However, a recommendation for adjunctive antibiotics was made for the following patient groups: medically compromised patients (not defined in detail) and patients with systemic involvement (fluctuant swelling, temperature >38 degrees C, malaise, lymphadenopathy, trismus), and patients with progressive infections where referral to oral surgeons may be necessary (rapid <24 h severe infection, cellulitis, spreading infections, osteomyelitis). They also recommended against antibiotic treatment in patients with chronic apical periodontitis with a sinus tract. In the sub-group of patients with an indication for antibiotics treatment, penicillin VK (phenoxymethylpenicillin) was the first choice, while amoxicillin, amoxicillin + clavulanic acid, and metronidazole were recommended after 48–72 hours

if penicillin VK fails. Further listings include clindamycin, clarithromycin, azithromycin for penicillin allergic patients. Duration should be re-assessed after 2–3 days, with a statement that 3–7 days is often sufficient (*35*).

The Canadian Collaboration on Clinical Practice Guidelines in Dentistry (CCCD) also recommend against the use of antibiotics for acute apical periodontitis and acute apical abscess as no benefit had been shown over drainage alone. They suggest that antibiotics may be helpful in the setting of systemic complications (fever, lymphadenopathy, cellulitis), diffuse swelling or in patients with medical indications. There is a statement that no antibiotic can be recommended over another, and that antibiotics may be used if drainage is not possible (*36*).

#### *Irreversible pulpitis*

The European Society of Endodontology position statement recommends against the use of antibiotics for the treatment of irreversible pulpitis (*35*).

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**Rationale for antibiotic selection** (from the application)

#### *Periodontitis*

The application stated that the overall evidence on antibiotics as an adjunct to SRP for periodontitis was limited, conflicting, and in general at high risk of bias. Where benefits had been shown, the summary estimates tended to be small to modest and as such of questionable clinical benefit. Also, recommendations in the two clinical practice guidelines identified were conflicting. It seems reasonable to conclude that the majority of patients likely do not benefit significantly from adjunctive systemic antibiotics, and as such the potential negative effects are outweighing the potential benefits. There might be a sub-group of patients who may clinically benefit from adjunctive antibiotics, but the current evidence does not allow drawing firm conclusions what these sub-groups might be. It does not seem that large treatment effects can be seen in smokers or diabetics, and as such these groups should not be treated any differently from others.

If, in a specific patient there is a perceived potential benefit with antibiotic treatment, low-dose long-term doxycycline that may have the least ecologic impact, or short-term courses with amoxicillin/metronidazole, seem to be the most promising regimens.

#### *Apical periodontitis and acute apical abscess*

The systematic reviews identified in the application provided no evidence supporting the routine use of antibiotics for apical periodontitis and acute apical abscess. The identified guidelines also recommend against the use of antibiotics for the majority of patients, emphasizing the importance of source control and drainage. However, the guidelines recommend antibiotic use for sub-groups of patients at risk for complicated/severe infections that may not be

controlled with drainage alone. In the absence of convincing evidence preferring one antibiotic regimen over the other, we agree with the European guideline listing phenoxymethylpenicillin or amoxicillin, with the potential of adding metronidazole if first-line treatment fails. For penicillin-allergic patients, the use of clindamycin seems to be the best option given the microbiology of periodontal infections.

*Irreversible pulpitis*

There is insufficient evidence to support the use of antibiotics for irreversible pulpitis. Guidelines do not support antibiotics for this indication.

**Committee considerations** (additional evidence, dose/duration, costs, etc.)

The Expert Committee noted that the evidence supporting antibiotic use in the treatment of oral and dental infections is limited and did not recommend EML listing of antibiotics for most dental conditions, including acute or chronic periodontitis or irreversible pulpitis.

**EML listings**

Antibiotics proposed for both EML and EMLc unless specified
***Endorsement*** indicates those antibiotics currently included on EML/EMLc

| | *First choice* | *Second choice* |
|---|---|---|
| ***Endorsement*** | Amoxicillin<br>Phenoxymethylpenicillin | |

**Committee recommendations**

The Expert Committee endorsed listing of amoxicillin and phenoxymethylpenicillin on the core list of the EML and EMLc as first-choice treatment for progressive (systemically complicated) apical dental abscess. These antibiotics are also recommended as first-choice treatment of apical dental abscess in medically compromised patients.

Amoxicillin and phenoxymethylpenicillin are classified as Access group antibiotics (Section 6.2.1).

## References

1. Dar-Odeh NS, Abu-Hammad OA, Al-Omiri MK, Khraisat AS, Shehabi AA. Antibiotic prescribing practices by dentists: a review. Ther Clin Risk Manag. 2010;6:301–6.
2. Poveda Roda R, Bagan JV, Sanchis Bielsa JM, Carbonell Pastor E. Antibiotic use in dental practice. A review. Med Oral Patol Oral Cir Bucal. 2007;12(3):E186–92.
3. Dailey YM, Martin MV. Are antibiotics being used appropriately for emergency dental treatment? Br Dent J. 2001;191(7):391–3.

4. Palmer N, Martin M. An investigation of antibiotic prescribing by general dental practitioners: a pilot study. Prim Dent Care. 1998;5(1):11–4.
5. Palmer NA, Pealing R, Ireland RS, Martin MV. A study of therapeutic antibiotic prescribing in National Health Service general dental practice in England. Br Dent J. 2000;188(10):554–8.
6. Palmer NO, Martin MV, Pealing R, Ireland RS. An analysis of antibiotic prescriptions from general dental practitioners in England. J Antimicrob Chemother. 2000;46(6):1033–5.
7. Palmer NO, Martin MV, Pealing R, Ireland RS, Roy K, Smith A, et al. Antibiotic prescribing knowledge of National Health Service general dental practitioners in England and Scotland. J Antimicrob Chemother. 2001;47(2):233–7.
8. Thomas DW, Satterthwaite J, Absi EG, Lewis MA, Shepherd JP. Antibiotic prescription for acute dental conditions in the primary care setting. Br Dent J. 1996;181(11-12):401–4.
9. Dirks SJ, Terezhalmy GT. The patient with an odontogenic infection. Quintessence Int. 2004;35(6):482–502.
10. Stefanopoulos PK, Kolokotronis AE. The clinical significance of anaerobic bacteria in acute orofacial odontogenic infections. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004;98(4):398–408.
11. Sandor GK, Low DE, Judd PL, Davidson RJ. Antimicrobial treatment options in the management of odontogenic infections. J Can Dent Assoc. 1998;64(7):508–14.
12. Marsh P, Martin M. Oral microbiology. 4th ed. Oxford: Wright; 1999.
13. Rabelo CC, Feres M, Goncalves C, Figueiredo LC, Faveri M, Tu YK, et al. Systemic antibiotics in the treatment of aggressive periodontitis. A systematic review and a Bayesian Network meta-analysis. J Clin Periodontol. 2015;42(7):647–57.
14. Keestra JA, Grosjean I, Coucke W, Quirynen M, Teughels W. Non-surgical periodontal therapy with systemic antibiotics in patients with untreated aggressive periodontitis: a systematic review and meta-analysis. J Periodontal Res. 2015;50(6):689–706.
15. Fritoli A, Goncalves C, Faveri M, Figueiredo LC, Perez-Chaparro PJ, Fermiano D, et al. The effect of systemic antibiotics administered during the active phase of non-surgical periodontal therapy or after the healing phase: a systematic review. J Appl Oral Sci. 2015;23(3):249–54.
16. Zandbergen D, Slot DE, Niederman R, Van der Weijden FA. The concomitant administration of systemic amoxicillin and metronidazole compared to scaling and root planing alone in treating periodontitis: a systematic review. BMC Oral Health. 2016;16:27.
17. Sgolastra F, Petrucci A, Gatto R, Monaco A. Effectiveness of systemic amoxicillin/metronidazole as an adjunctive therapy to full-mouth scaling and root planing in the treatment of aggressive periodontitis: a systematic review and meta-analysis. J Periodontol. 2012;83(6):731–43.
18. Santos RS, Macedo RF, Souza EA, Soares RS, Feitosa DS, Sarmento CF. The use of systemic antibiotics in the treatment of refractory periodontitis: A systematic review. J Am Dent Assoc. 2016;147(7):577–85.
19. McGowan K, McGowan T, Ivanovski S. Optimal dose and duration of amoxicillin-plus-metronidazole as an adjunct to non-surgical periodontal therapy: A systematic review and meta-analysis of randomized, placebo-controlled trials. J Clin Periodontol. 2018;45(1):56–67.
20. Sgolastra F, Severino M, Petrucci A, Gatto R, Monaco A. Effectiveness of metronidazole as an adjunct to scaling and root planing in the treatment of chronic periodontitis: a systematic review and meta-analysis. J Periodontal Res. 2014;49(1):10–9.
21. Elter JR, Lawrence HP, Offenbacher S, Beck JD. Meta-analysis of the effect of systemic metronidazole as an adjunct to scaling and root planing for adult periodontitis. J Periodontal Res. 1997;32(6):487–96.

22. Renatus A, Herrmann J, Schonfelder A, Schwarzenberger F, Jentsch H. Clinical Efficacy of Azithromycin as an Adjunctive Therapy to Non-Surgical Periodontal Treatment of Periodontitis: A Systematic Review and Meta-Analysis. J Clin Diagn Res. 2016;10(7):Ze01–7.
23. Zhang Z, Zheng Y, Bian X. Clinical effect of azithromycin as an adjunct to non-surgical treatment of chronic periodontitis: a meta-analysis of randomized controlled clinical trials. J Periodontal Res. 2016;51(3):275–83.
24. Sgolastra F, Petrucci A, Gatto R, Giannoni M, Monaco A. Long-term efficacy of subantimicrobial-dose doxycycline as an adjunctive treatment to scaling and root planing: a systematic review and meta-analysis. J Periodontol. 2011;82(11):1570–81.
25. Chambrone L, Vargas M, Arboleda S, Serna M, Guerrero M, de Sousa J, et al. Efficacy of Local and Systemic Antimicrobials in the Non-Surgical Treatment of Smokers With Chronic Periodontitis: A Systematic Review. J Periodontol. 2016;87(11):1320–32.
26. Angaji M, Gelskey S, Nogueira-Filho G, Brothwell D. A systematic review of clinical efficacy of adjunctive antibiotics in the treatment of smokers with periodontitis. J Periodontol. 2010;81(11):1518–28.
27. Assem NZ, Alves MLF, Lopes AB, Gualberto ECJ, Garcia VG, Theodoro LH. Antibiotic therapy as an adjunct to scaling and root planing in smokers: a systematic review and meta-analysis. Braz Oral Res. 2017;31:e67.
28. Grellmann AP, Sfreddo CS, Maier J, Lenzi TL, Zanatta FB. Systemic antimicrobials adjuvant to periodontal therapy in diabetic subjects: a meta-analysis. J Clin Periodontol. 2016;43(3):250–60.
29. Rovai ES, Souto ML, Ganhito JA, Holzhausen M, Chambrone L, Pannuti CM. Efficacy of Local Antimicrobials in the Non-Surgical Treatment of Patients With Periodontitis and Diabetes: A Systematic Review. J Periodontol. 2016;87(12):1406–17.
30. Cope AL, Francis N, Wood F, Chestnutt IG. Systemic antibiotics for symptomatic apical periodontitis and acute apical abscess in adults. Cochrane Database Syst Rev. 2018;9:CD010136.
31. Matthews DC, Sutherland S, Basrani B. Emergency management of acute apical abscesses in the permanent dentition: a systematic review of the literature. J Can Dent Assoc. 2003;69(10):660.
32. Agnihotry A, Fedorowicz Z, van Zuuren EJ, Farman AG, Al-Langawi JH. Antibiotic use for irreversible pulpitis. Cochrane Database Syst Rev. 2016;2:CD004969.
33. Smiley CJ, Tracy SL, Abt E, Michalowicz BS, John MT, Gunsolley J, et al. Evidence-based clinical practice guideline on the nonsurgical treatment of chronic periodontitis by means of scaling and root planing with or without adjuncts. J Am Dent Assoc. 2015;146(7):525–35.
34. Matthews DC. Prevention and treatment of periodontal diseases in primary care. Evid Based Dent. 2014;15(3):68–9.
35. Segura-Egea JJ, Gould K, Sen BH, Jonasson P, Cotti E, Mazzoni A, et al. European Society of Endodontology position statement: the use of antibiotics in endodontics. Int Endod J. 2018;51(1):20–5.
36. Canadian Collaboration on Clinical Practice Guidelines in D. Clinical practice guideline on treatment of acute apical abscess (AAA) in adults. Evid Based Dent. 2004;5(1):8.

*Ceftazidime + avibactam – addition - EML*

**Ceftazidime + avibactam** **ATC Code: J01DD52**

**Proposal**

The application requested the inclusion on the EML of ceftazidime + avibactam as a last-resort treatment option for infections due to multidrug-resistant organisms (MDROs).

**Applicant**

EML Secretariat on behalf of the EML Antibiotics Working Group

**WHO Technical Department**

Essential Medicines and Health Products

**EML/EMLc**

EML and EMLc

**Section**

6.2.3 Reserve group antibiotics

**Dose form(s) & strengths(s)**

Powder for injection: 2 g + 0.5 g in vial

**Core/Complementary**

Complementary

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

This combination antibiotic had not previously been considered for inclusion on the EML. Ceftazidime is third-generation cephalosporin listed on the EML complementary list and classified within the Watch group. Avibactam is a non-beta-lactam beta-lactamase inhibitor active against certain types of carbapenemases (e.g. KPC and OXA-48 but not active against metallo-beta-lactamases).

**Public health relevance** (burden of disease)

Antibiotic-resistant bacteria are a significant threat to public health, both in HICs as well as LMICs (*1–3*). A recent study estimated that infections with antibiotic-

resistant bacteria were responsible for approximately 33 000 attributable deaths in Europe in 2015 (*1*). Fewer data are available for LMICs, but a retrospective study in ten hospitals in India found that resistant pathogens were associated with two to three times higher mortality than infections with susceptible strains after adjusting for several confounders (*2*).

Over the past decade there has been increasing spread of multidrug-resistant Gram-negative pathogens such as carbapenemase-producing *Enterobacteriaceae* (*4*). The Global Antimicrobial Resistance Surveillance System (GLASS) report published in 2018 found high levels of carbapenem resistance in *Enterobacteriaceae* and non-fermenters in many of the LMICs providing data for the report (*2*). The 2015 WHO *Global action plan on antimicrobial resistance* calls for the development of new antimicrobial medicines (*3*). To provide a framework for this endeavour, in 2017 WHO published a priority list of antibiotic-resistant bacteria (*5*). The "Priority 1: critical" category includes four types of pathogens, all of which are Gram-negative: carbapenem-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacteriaceae*; and third-generation cephalosporin-resistant *Enterobacteriaceae* (*6*).

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**Summary of evidence: benefits** (from the application)

Several RCTs have been conducted comparing ceftazidime + avibactam to carbapenems or best available therapy for complicated intra-abdominal Infections (cIAIs) and complicated urinary tract infection (cUTIs) (*7–10*). Of note, all but one of the RCTs (*7*) included patients based on clinical syndromes and not based on the presence of infections confirmed to be caused by MDROs. In that 'descriptive' trial of patients with cUTI (plus some patients with cIAI) caused by ceftazidime-resistant Gram-negatives, ceftazidime + avibactam treatment resulted in similar clinical response compared to best available therapy.

So far, few data on the real-life clinical use of ceftazidime + avibactam have been published. A retrospective single centre study at the University of Pittsburgh Medical Centre in the United States examined outcomes of 109 patients with bacteraemia caused by carbapenem-resistant *Klebsiella pneumoniae* (97% of which were Klebsiella pneumoniae carbapenemase (KPC) producers) over the time period from 2009 to 2017. The 30-day survival rate was 92% (12/13) in patients treated with ceftazidime + avibactam versus 69% (66/96) for patients treated with other regimens, but this obviously has to be interpreted with caution given the many potential confounding factors (*11*).

Published data about use of ceftazidime + avibactam in children is very scarce and limited to a Phase I study and case reports (*12–14*). However, two Phase II RCTs have been conducted in children with cUTIs and cIAI and are awaiting publication (ClinicalTrials.gov Identifier: NCT02475733 and NCT02497781). Of note, ceftazidime + avibactam may have a role in combination with aztreonam to

treat infections caused by *Enterobacteriaceae* producing metallo-beta-lactamases at least until the combination of aztreonam with avibactam becomes available (*15*, *16*).

**Summary of evidence: harms** (from the application)

In the RCTs the incidence of adverse events in the groups treated with ceftazidime + avibactam was similar to the control groups (*7–10*). However, in a meta-analysis of eight RCTs including 4093 patients, serious adverse events (SAEs) were more common with ceftazidime + avibactam (RR 1.24, 95%CI 1.00 to 1.54, $I^2=0\%$) but detailed data regarding the nature of these SAE were not available (*17*).

**Additional evidence** (not in the application)

N/A

**WHO Guidelines**

There are no available WHO guidelines for the treatment of infections due to MDROs.

**Costs/cost-effectiveness**

United Kingdom: Basic National Health Service (NHS) price: 10 vial pack £ 857.00 = £ 257.1 (about US$ 340) per day (standard dosing).

Few data are available regarding the cost-effectiveness of ceftazidime + avibactam. A decision analytic model presented at the IDWeek conference in October 2018 aimed to estimate the cost-effectiveness of treatment with ceftazidime + avibactam compared with colistin for a hypothetical cohort of patients with pneumonia and bacteraemia caused by carbapenemase-resistant *Enterobacteriaceae* over a 12-month period. The researchers assumed a 41% mortality with colistin treatment, a 23% (and hence very large) absolute reduction in mortality with ceftazidime + avibactam, daily costs of ceftazidime + avibactam of US$ 1080, a 42% incidence of nephrotoxicity with colistin treatment, a 56% probability of transfer to long-term care and a 1.8 fold improved odds of discharge home with ceftazidime + avibactam treatment (*18*). The authors estimated an incremental cost-effectiveness ratio for ceftazidime + avibactam compared with colistin of US$ 110 300 per quality-adjusted life-year (QALY).

**Availability**

Ceftazidime + avibactam has US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval for cUTI and cIAI (for cIAI in combination with metronidazole) (*11*). EMA lists "HAP and other infections due to Gram-negative bacteria with limited treatment options" as a further indication.

### Other considerations

The Committee noted that there was very limited clinical trial evidence of the efficacy of recently approved antibiotics for infections caused by carbapenem-resistant bacteria, with activity against this type of infection based on studies with small sample sizes, methodological limitations and including heterogenous populations. The Committee was concerned that the current regulatory approval process for novel agents effective against "critical priority" pathogens (according to the WHO priority pathogens list (*5*)) does not adequately inform the urgent public health need for clear evidence-based guidance on the optimal management of these infections, which are associated with important morbidity and mortality.

### Committee recommendations

The Expert Committee recommended the inclusion of ceftazidime + avibactam on the complementary list of the EML and EMLc for the treatment of infections caused by carbapenem-resistant organisms, which are pathogens classified as "critical priority" in the WHO Priority Pathogen List.

The Committee agreed with the EML Antibiotic Working Group's recommendation that this antibiotic should be classified in the AWaRe Reserve group.

The Committee recommended further collaboration between relevant stakeholders to design and implement strategic public health orientated studies that will help to inform the choice of optimal single or combination treatment of both novel and older antibiotics for adults and children in different settings, with the goal of improving clinical outcomes, minimizing toxicity and reducing selection of resistance.

## References

1. Cassini A, Hogberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis. 2019:19(1):56–66.
2. Gandra S, Tseng KK, Arora A, Bhowmik B, Robinson ML, Panigrahi B, et al. The mortality burden of multidrug-resistant pathogens in India: a retrospective observational study. Clin Infect Dis. 2019;69(4): 563–570.
3. Global action plan on antimicrobial resistance. Geneva: World Health Organization; 2015.
4. van Duin D, Doi Y. The global epidemiology of carbapenemase-producing Enterobacteriaceae. Virulence. 2017;8(4):460–9.
5. Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. Geneva: World Health Organization; 2017. Available from: https://apps.who.int/iris/handle/10665/311820, accessed 30 October 2019.

6. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2018;18(3):318–27.
7. Carmeli Y, Armstrong J, Laud PJ, Newell P, Stone G, Wardman A, et al. Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and Pseudomonas aeruginosa complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study. Lancet Infect Dis. 2016;16(6):661–73.
8. Mazuski JE, Gasink LB, Armstrong J, Broadhurst H, Stone GG, Rank D, et al. Efficacy and Safety of Ceftazidime-Avibactam Plus Metronidazole Versus Meropenem in the Treatment of Complicated Intra-abdominal Infection: Results From a Randomized, Controlled, Double-Blind, Phase 3 Program. Clin Infect Dis. 2016;62(11):1380–9.
9. Qin X, Tran BG, Kim MJ, Wang L, Nguyen DA, Chen Q, et al. A randomised, double-blind, phase 3 study comparing the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem for complicated intra-abdominal infections in hospitalised adults in Asia. Int J Antimicrob Agents. 2017;49(5):579–88.
10. Wagenlehner FM, Sobel JD, Newell P, Armstrong J, Huang X, Stone GG, et al. Ceftazidime-avibactam Versus Doripenem for the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis: RECAPTURE, a Phase 3 Randomized Trial Program. Clin Infect Dis. 2016;63(6):754–62.
11. Pogue JM, Bonomo RA, Kaye KS. Ceftazidime/avibactam, Meropenem/vaborbactam or both? Clinical and formulary considerations. Clin Infect Dis. 2019; 68(3):519–524.
12. Bradley JS, Armstrong J, Arrieta A, Bishai R, Das S, Delair S, et al. Phase I Study Assessing the Pharmacokinetic Profile, Safety, and Tolerability of a Single Dose of Ceftazidime-Avibactam in Hospitalized Pediatric Patients. Antimicrob Agents Chemother. 2016;60(10):6252–9.
13. Rodriguez BA, Girotto JE, Nicolau DP. Ceftazidime/Avibactam and Ceftolozane/Tazobactam: Novel Therapy for Multidrug Resistant Gram Negative Infections in Children. Curr Pediatr Rev. 2018;14(2):97–109.
14. Tamma PD, Fan Y, Bergman Y, Sick-Samuels AC, Hsu AJ, Timp W, et al. Successful Treatment of Persistent Burkholderia cepacia Complex Bacteremia with Ceftazidime-Avibactam. Antimicrob Agents Chemother. 2018;62(4). pii: e02213–17.
15. Hobson CA, Bonacorsi S, Fahd M, Baruchel A, Cointe A, Poey N, et al. Successful treatment of a bacteremia due to NDM-1-producing Morganella morganii with Aztreonam and Ceftazidime-avibactam combination in a pediatric patient with hematologic malignancy. Antimicrob Agents Chemother. 2018; 63(2). pii: e02463–18.
16. Barlow G, Morice A. Successful treatment of resistant Burkholderia multivorans infection in a patient with cystic fibrosis using ceftazidime/avibactam plus aztreonam. J Antimicrob Chemother. 2018;73(8):2270–1.
17. Sternbach N, Leibovici Weissman Y, Avni T, Yahav D. Efficacy and safety of ceftazidime/avibactam: a systematic review and meta-analysis. J Antimicrob Chemother. 2018;73(8):2021–9.
18. Sfeir M, Satlin M, Calfee DP, Simon MS. Cost-Effectiveness of Ceftazidime–Avibactam Compared With Colistin for Treatment of Carbapenem-Resistant Enterobacteriaceae Bacteremia and Pneumonia. Open Forum Infect Dis. 2018;5: S539–S40.

*Ceftolozane + tazobactam – addition – EML*

**Ceftolozane + tazobactam** **ATC Code: J01DI54**

**Proposal**

The application requested the inclusion on the EML of ceftolozane + tazobactam as a last-resort treatment option for infections due to multi-drug resistant organisms (MDROs).

**Applicant**

EML Secretariat on behalf of the EML Antibiotics Working Group

**WHO Technical Department**

Essential Medicines and Health Products

**EML/EMLc**

EML

**Section**

6.2.3 Reserve group antibiotics

**Dose form(s) & strengths(s)**

Powder for injection: 1 g + 0.5 g in vial

**Core/Complementary**

Complementary

**Individual/Square box listing**

Individual listing

**Background** (if relevant, eg. resubmission, previous EC consideration)

Ceftolozane + tazobactam is the combination of a new cephalosporin with a structure similar to ceftazidime with a beta-lactam inhibitor that has been in clinical use for decades (tazobactam). Ceftolozane + tazobactam retains *in vitro* activity against some strains of multidrug-resistant *P. aeruginosa* and against *Enterobacteriaceae* producing ESBL. It only has limited activity against Gram-positive pathogens and anaerobes (*1*).

**Public health relevance** (burden of disease)

Antibiotic-resistant bacteria are a significant threat to public health, both in HICs as well as LMICs (*2–4*). A recent study estimated that infections with antibiotic-

resistant bacteria were responsible for approximately 33 000 attributable deaths in Europe in 2015 (*2*). Fewer data are available for LMICs, but a retrospective study in ten hospitals in India found that resistant pathogens were associated with two to three times higher mortality than infections with susceptible strains after adjusting for several confounders (*3*).

Over the past decade there has been increasing spread of multidrug-resistant Gram-negative pathogens such as carbapenemase producing *Enterobacteriaceae* (*5*). The Global Antimicrobial Resistance Surveillance System (GLASS) report published in 2018 found high levels of carbapenem resistance in *Enterobacteriaceae* and non-fermenters in many of the LMICs providing data for the report (*3*). The 2015 WHO Global action plan on antimicrobial resistance calls for the development of new antimicrobial medicines (*4*). To provide a framework for this endeavour, in 2017 WHO published a priority list of antibiotic-resistant bacteria (*6*). The "Priority 1: critical" category includes four types of pathogens, all of which are Gram-negative: carbapenem resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacteriaceae*; and third-generation cephalosporin-resistant *Enterobacteriaceae* (*7*).

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**Summary of evidence: benefits** (from the application)

Ceftolozane + tazobactam has been assessed in two non-inferiority RCTs, one for cUTI and one for cIAI (*8*, *9*). Of note, in the cUTI trial levofloxacin was used as comparator agent, a highly debatable choice given that resistance to levofloxacin in Gram-negatives isolated in urine cultures at baseline was nearly 10 times more prevalent at baseline (2.7% for C+T vs 26.7% for levofloxacin) (9). An RCT in ventilator-associated pneumonia is currently being conducted (ClinicalTrials.gov Identifier: NCT01853982).

A retrospective cohort study in of 101 patients treated with ceftolozane + tazobactam in 22 Italian centres for a variety of infections causes by *P. aeruginosa*, including 51% of extensively drug-resistant (XDR) strains, showed overall clinical success of 83.2% and a good safety profile (*10*). A secondary analysis of the 150 of 1346 (11.1%) patients with ESBL-producing organisms in the original two RCTs reported high clinical cure rates with ceftolozane + tazobactam (overall 97.4%), better than the comparators (82.6% for levofloxacin (cUTI only) and 88.5% for meropenem (cIAI only)) (*11*). The major methodological limitations of these studies mean, however, that the data have to be interpreted with caution.

Data for children are scarce and no specific recommendations regarding use in the paediatric population can be made (*12*, *13*).

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**Summary of evidence: harms** (from the application)

In the two non-inferiority Phase III RCTs published so far adverse events (AE) occurred with similar frequency in the ceftolozane + tazobactam and comparator

groups with headache and gastrointestinal symptoms being the most frequent AE (*8*, *9*).

**Additional evidence** (not in the application)

N/A

**WHO Guidelines**

There are no available WHO guidelines for the treatment of infections due to MDROs.

**Costs/cost-effectiveness**

United States: About US$ 1140 for 10 vials (1/0.5g) => about US$ 340 per day

A decision-analytic Monte Carlo simulation model aimed to assess the costs of empiric treatment with ceftolozane + tazobactam versus or piperacillin/tazobactam in hospitalized adults with cUTI due to Gram-negative pathogens in the United States setting. The study co-authored by multiple employees of the producer of ceftolozane + tazobactam estimated an incremental cost-effectiveness ratio of US$ 6128 per QALY (*14*). A similar study in the United Kingdom, for patients with cIAI estimated an incremental cost-effectiveness ratio of £ 4350 per QALY in favour of ceftolozane + tazobactam (with metronidazole) compared to piperacillin/tazobactam (*15*).

**Availability**

Ceftolozane + tazobactam has been approved for the treatment of cIAI and cUTI, including acute pyelonephritis in the United States and European Union.

**Other considerations**

N/A

**Committee recommendations**

The Expert Committee did not recommend the addition of ceftolozane + tazobactam to the EML. The Committee noted that although ceftolozane + tazobactam is active against some strains of carbapenem-resistant *P. aeruginosa*, it lacks activity against carbapenemase-producing *Enterobacteriaceae*, which is more prevalent in the community and represents a greater public health threat. Alternative antibiotics are included on the list that are effective against carbapenem-resistant *P. aeruginosa*.

The Committee agreed with the EML Antibiotic Working Group's recommendation that this antibiotic should be classified in the AWaRe Reserve group.

## References


1. Giacobbe DR, Bassetti M, De Rosa FG, Del Bono V, Grossi PA, Menichetti F, et al. Ceftolozane/tazobactam: place in therapy. Expert Rev Anti Infect Ther. 2018;16(4):307–20.
2. Cassini A, Hogberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis. 2019; 19(1):56–66.
3. Gandra S, Tseng KK, Arora A, Bhowmik B, Robinson ML, Panigrahi B, et al. The mortality burden of multidrug-resistant pathogens in India: a retrospective observational study. Clin Infect Dis. 2019;69(4):563–570.
4. Global action plan on antimicrobial resistance. Geneva: World Health Organization; 2015. Available from https://www.who.int/antimicrobial-resistance/global-action-plan/en/, accessed 30 October 2019.
5. van Duin D, Doi Y. The global epidemiology of carbapenemase-producing Enterobacteriaceae. Virulence. 2017;8(4):460–9.
6. Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. Geneva: World Health Organization; 2017. Available from: https://apps.who.int/iris/handle/10665/311820, accessed 30 October 2019.
7. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2018;18(3):318–27.
8. Solomkin J, Hershberger E, Miller B, Popejoy M, Friedland I, Steenbergen J, et al. Ceftolozane/Tazobactam Plus Metronidazole for Complicated Intra-abdominal Infections in an Era of Multidrug Resistance: Results From a Randomized, Double-Blind, Phase 3 Trial (ASPECT-cIAI). Clin Infect Dis. 2015;60(10):1462–71.
9. Wagenlehner FM, Umeh O, Steenbergen J, Yuan G, Darouiche RO. Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI). Lancet. 2015;385(9981):1949–56.
10. Bassetti M, Castaldo N, Cattelan A, Mussini C, Righi E, Tascini C, et al. Ceftolozane/tazobactam for the treatment of serious P. aeruginosa infections: a multicenter nationwide clinical experience. Int J Antimicrob Agents. 2018.
11. Popejoy MW, Paterson DL, Cloutier D, Huntington JA, Miller B, Bliss CA, et al. Efficacy of ceftolozane/tazobactam against urinary tract and intra-abdominal infections caused by ESBL-producing Escherichia coli and Klebsiella pneumoniae: a pooled analysis of Phase 3 clinical trials. J Antimicrob Chemother. 2017;72(1):268–72.
12. Bradley JS, Ang JY, Arrieta AC, Larson KB, Rizk ML, Caro L, et al. Pharmacokinetics and Safety of Single Intravenous Doses of Ceftolozane/Tazobactam in Children With Proven or Suspected Gram-Negative Infection. Pediatr Infect Dis J. 2018;37(11):1130–6.
13. Tamma SM, Hsu AJ, Tamma PD. Prescribing Ceftolozane/Tazobactam for Pediatric Patients: Current Status and Future Implications. Paediatr Drugs. 2016;18(1):1–11.
14. Kauf TL, Prabhu VS, Medic G, Borse RH, Miller B, Gaultney J, et al. Cost-effectiveness of ceftolozane/tazobactam compared with piperacillin/tazobactam as empiric therapy based on the in-vitro surveillance of bacterial isolates in the United States for the treatment of complicated urinary tract infections. BMC Infect Dis. 2017;17(1):314.

15. Prabhu V, Foo J, Ahir H, Sarpong E, Merchant S. Cost-effectiveness of ceftolozane/tazobactam plus metronidazole compared with piperacillin/tazobactam as empiric therapy for the treatment of complicated intra-abdominal infections based on the in-vitro surveillance of bacterial isolates in the UK. J Med Econ. 2017;20(8):840–9.

*Delafloxacin – addition – EML*

## Delafloxacin — ATC Code: J01MA23

**Proposal**

The application requested the inclusion of delafloxacin on the complementary list of the EML as a last-resort treatment option for infections due to multidrug-resistant organisms (MRDOs).

**Applicant**

EML Secretariat on behalf of the EML Antibiotics Working Group

**WHO Technical Department**

Essential Medicines and Health Products

**EML/EMLc**

EML

**Section**

6.2.2 Watch group antibiotics

**Dose form(s) & strengths(s)**

Tablet: 450 mg
Lyophilized powder for injection: 300 mg

**Core/Complementary**

Complementary

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Delafloxacin had not previously been considered for inclusion on the EML. It is a new fluoroquinolone which, compared to the older molecules of this class, has activity against methicillin-resistant *S. aureus* (MRSA) (*1*, *2*). It has been approved for treatment of skin and soft tissue infections based on two Phase III multicentre, double-blind non-inferiority trials (*3*, *4*).

**Public health relevance** (burden of disease)

Antibiotic-resistant bacteria are a significant threat to public health, both in HICs as well as LMICs (*5*–*7*). A recent study estimated that infections with antibiotic-

resistant bacteria were responsible for approximately 33 000 attributable deaths in Europe in 2015 (*5*). Fewer data are available for LMICs, but a retrospective study in ten hospitals in India found that resistant pathogens were associated with two to three times higher mortality than infections with susceptible strains after adjusting for several confounders (*6*).

Over the past decade there has been increasing spread of multidrug-resistant Gram-negative pathogens such as carbapenemase producing *Enterobacteriaceae* (*8*). The Global Antimicrobial Resistance Surveillance System (GLASS) report published in 2018 found high levels of carbapenem resistance in *Enterobacteriaceae* and non-fermenters in many of the LMICs providing data for the report (*6*). The 2015 WHO *Global action plan on antimicrobial resistance* calls for the development of new antimicrobial medicines (*7*). To provide a framework for this endeavour, in 2017 WHO published a priority list of antibiotic-resistant bacteria (9). "Priority 1: critical" category includes four types of pathogens, all of which are Gram-negative: carbapenem resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacteriaceae*; and third-generation cephalosporin-resistant *Enterobacteriaceae* (*10*).

**Summary of evidence: benefits** (from the application)

In the two Phase III trials in adult patients with acute bacterial skin and skin structure infections, delafloxacin fulfilled criteria for non-inferiority compared to linezolid and vancomycin/aztreonam respectively (*3*, *4*). In respective trials, one third and one fourth of patients had infections due to MRSA.

A trial comparing delafloxacin to moxifloxacin (or linezolid in the case of confirmed MRSA) in patients with community-acquired pneumonia (NCT02679573) has been completed in 2018 but results have not yet been published.

**Summary of evidence: harms** (from the application)

A review of the safety data of the two Phase III non-inferiority RCTs and additional Phase I and II trials showed few discontinuations (<1%) due to treatment-related adverse events (*3*, *4*, *11*). The proportion of patients with AEs was similar to the proportion observed in the comparator arms. No fluoroquinolone-specific AE such as tendinitis or neuropathy were observed in the delafloxacin arm. Gastrointestinal events (notably diarrhoea), headache and infusion site pain were the most frequently reported AEs. Adverse events associated with fluoroquinolones (tendinitis, myopathy, dysglycaemia, neuropathy, neurotoxicity) were not more frequent when compared with vancomycin/aztreonam with the caveat that the combined Phase III trials only included 1492 patients and rare, potentially severe events were unlikely to be detected.

There are no data for use of delafloxacin in children, and similar to other fluoroquinolones it is not recommended for use in patients younger than 18 years.

**Additional evidence** (not in the application)

Delafloxacin has been suggested as a treatment option for gonorrhoea with good *in vitro* activity even against strains with reduced susceptibility to ciprofloxacin (*12*). The results of an open-label, multicentre study with 460 participants with uncomplicated gonorrhoea was recently published (*13*). Patients were randomized (2:1) to either a single oral dose of 900 mg of delafloxacin or 250 mg of intramuscular ceftriaxone. Delafloxacin did not fulfil the predefined criteria for non-inferiority for the primary outcome urogenital cure (85.1% (194/228) vs 91.0% (91/100); 95%CI −13.18% to 1.36%; the lower bound of the CI thus exceeding the pre-specified −10% non-inferiority margin).

**WHO Guidelines**

There are no available WHO guidelines for the treatment of infections due to MDROs. Delafloxacin is not mentioned in the 2016 WHO *Guidelines for the treatment of Neisseria gonorrhoeae* (issued before the availability of delafloxacin) (*14*).

**Costs/cost-effectiveness**

Approximately US$ 260 per day

**Availability**

Delafloxacin is approved in the United States and Europe for the treatment of acute bacterial skin and skin structure infections.

**Other considerations**

N/A

**Committee recommendations**

The Expert Committee did not recommend the addition of delafloxacin to the EML. The Committee noted that although delafloxacin has demonstrated activity against some MRSA strains ranked as "high priority" on the WHO priority pathogens list, effective alternatives are currently available on the EML. In addition, delafloxacin was not associated with greater activity against "critical priority" pathogens compared to other, older fluoroquinolones currently available on the Model List.

The Expert Committee agreed with the EML Antibiotic Working Group's recommendation that this antibiotic should be classified in the AWaRe Watch group.

## References


1. Jorgensen SCJ, Mercuro NJ, Davis SL, Rybak MJ. Delafloxacin: Place in Therapy and Review of Microbiologic, Clinical and Pharmacologic Properties. Infect Dis Ther. 2018;7(2):197–217.
2. Saravolatz LD, Stein GE. Delafloxacin: A New Anti-methicillin-resistant *Staphylococcus aureus* Fluoroquinolone. Clin Infect Dis. 2019;68(6):1058-62. Clin Infect Dis. 2019;68(6):1058-62.
3. Pullman J, Gardovskis J, Farley B, Sun E, Quintas M, Lawrence L, et al. Efficacy and safety of delafloxacin compared with vancomycin plus aztreonam for acute bacterial skin and skin structure infections: a Phase 3, double-blind, randomized study. J Antimicrob Chemother. 2017;72(12):3471–80.
4. O'Riordan W, McManus A, Teras J, Poromanski I, Cruz-Saldariagga M, Quintas M, et al. A Comparison of the Efficacy and Safety of Intravenous Followed by Oral Delafloxacin With Vancomycin Plus Aztreonam for the Treatment of Acute Bacterial Skin and Skin Structure Infections: A Phase 3, Multinational, Double-Blind, Randomized Study. Clin Infect Dis. 2018;67(5):657–66.
5. Cassini A, Hogberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis. 2019; 19(1):56–66.
6. Gandra S, Tseng KK, Arora A, Bhowmik B, Robinson ML, Panigrahi B, et al. The mortality burden of multidrug-resistant pathogens in India: a retrospective observational study. Clin Infect Dis. 2019; 69(4): 563–570.
7. Global action plan on antimicrobial resistance. Geneva: World Health Organization; 2015. Available from: https://apps.who.int/iris/handle/10665/311820, accessed 30 October 2019.
8. van Duin D, Doi Y. The global epidemiology of carbapenemase-producing Enterobacteriaceae. Virulence. 2017;8(4):460–9.
9. Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. Geneva: World Health Organization; 2017. Available from: https://apps.who.int/iris/handle/10665/311820, accessed 30 October 2019.
10. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2018;18(3):318–27.
11. Lodise T, Corey R, Hooper D, Cammarata S. Safety of Delafloxacin: Focus on Adverse Events of Special Interest. Open Forum Infect Dis. 2018;5(10):ofy220.
12. Soge OO, Salipante SJ, No D, Duffy E, Roberts MC. In Vitro Activity of Delafloxacin against Clinical Neisseria gonorrhoeae Isolates and Selection of Gonococcal Delafloxacin Resistance. Antimicrob Agents Chemother. 2016;60(5):3106–11.
13. Hook EW, 3rd, Golden MR, Taylor SN, Henry E, Tseng C, Swerdlow J, et al. Efficacy and safety of single dose oral delafloxacin compared with intramuscular ceftriaxone for uncomplicated gonorrhea treatment: an open-label, non-inferiority, Phase 3, multicenter, randomized study. Sex Transm Dis. 2019 (epub ahead of print).
14. Guidelines for the treatment of Neisseria gonorrhoeae. Geneva: World Health Organization; 2016.

*Eravacycline – addition – EML*

## Eravacycline — ATC Code: J01AA13

**Proposal**

The application requested the inclusion of eravacycline on the complementary list of the EML as a last-resort treatment option for infections due to multidrug-resistant organisms (MRDOs).

**Applicant**

EML Secretariat on behalf of the EML Antibiotics Working Group

**WHO Technical Department**

Essential Medicines and Health Products

**EML/EMLc**

EML

**Section**

6.2.3 Reserve group antibiotics

**Dose form(s) & strengths(s)**

Lyophilized powder for injection: 50 mg

**Core/Complementary**

Complementary

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Eravacycline had not previously been considered for inclusion on the EML. Eravacycline is a fully synthetic tetracycline antibiotic that has a spectrum of activity similar to tigecycline and maintains its activity in the presence of two common resistance mechanisms: ribosomal protection and active drug efflux. It retains activity against most ESBL producing *Enterobacteriaceae* and some strains of carbapenem-resistant *Enterobacteriaceae* and *Acinetobacter baumannii* but has limited activity against *Pseudomonas aeruginosa* (*1–4*).

**Public health relevance (burden of disease)**

Antibiotic-resistant bacteria are a significant threat to public health, both in HICs as well as LMICs (*5*–*7*). A recent study estimated that infections with antibiotic-resistant bacteria were responsible for approximately 33 000 attributable deaths in Europe in 2015 (*5*). Fewer data are available for LMICs, but a retrospective study in ten hospitals in India found that resistant pathogens were associated with two to three times higher mortality than infections with susceptible strains after adjusting for several confounders (*6*).

Over the past decade there has been increasing spread of multidrug-resistant Gram-negative pathogens such as carbapenemase producing *Enterobacteriaceae* (*8*). The Global Antimicrobial Resistance Surveillance System (GLASS) report published in 2018 found high levels of carbapenem resistance in *Enterobacteriaceae* and non-fermenters in many of the LMICs providing data for the report (*6*). The 2015 WHO *Global action plan on antimicrobial resistance* calls for the development of new antimicrobial medicines (*7*). To provide a framework for this endeavour, in 2017 WHO published a priority list of antibiotic-resistant bacteria (*9*). "Priority 1: critical" category includes four types of pathogens, all of which are Gram-negative: carbapenem resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacteriaceae*; and third-generation cephalosporin-resistant Enterobacteriaceae (*10*).

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**Summary of evidence: benefits** (from the application)

Eravacycline achieved the predefined criteria for non-inferiority compared with ertapenem in one trial and meropenem in another trial in the treatment of cIAI in hospitalized adults (*11*, *12*). A further trial has been conducted in adult patients with cUTI using levofloxacin as comparator, but the results have so far only been published on cinicaltrials.gov (NCT01978938) and eravacycline "did not achieve its primary endpoint of statistical non-inferiority compared to levofloxacin" (*13*).

Like for other tetracyclines, eravacycline use is not recommended in children younger than 8 years and pregnant or breastfeeding women due to the risk of tooth discoloration and enamel hypoplasia. A Phase I multicentre study to assess the pharmacokinetics and safety of intravenous (IV) eravacycline in children aged 8 to 18 years is currently recruiting patients (ClinicalTrials.gov Identifier: NCT03696550).

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**Summary of evidence: harms** (from the application)

In the trials comparing eravacycline to a carbapenem (ertapenem and meropenem respectively) more treatment-emergent AEs were observed in the eravacycline treatment groups (*11*, *12*). The difference was mostly attributable to nausea and phlebitis.

**Additional evidence (not in the application)**

N/A.

**WHO Guidelines**

There are no available WHO guidelines for the treatment of infections due to MDROs.

**Costs/cost-effectiveness**

United States: wholesale acquisition cost of US$ 175 per day of treatment (*14*).

No cost-effectiveness data are available.

**Availability**

Eravacycline has been approved in the United States and the European Union for the treatment of cIAI in adults.

**Other considerations**

Safety concerns exist for tigecycline, a pharmacologically similar agent with a similar spectrum of activity to eravacycline, with an increased risk of mortality compared with other antimicrobials being reported (*15–17*). The FDA issued a boxed warning about this risk in 2013 (18). In a separate recommendation made during the meeting, the Expert Committee recommended the removal of tigecycline from the EML and EMLc.

**Committee recommendations**

The Expert Committee did not recommend the addition of eravacycline to the EML. The Committee considered that although eravacycline demonstrates activity against some strains of carbapenemase-producing *Enterobacteriaceae*, there are some concerns with regard to efficacy, as eravacycline failed to demonstrate non-inferiority compared to levofloxacin in one RCT for cUTI. In addition, the Committee considered that there could be safety concerns, with no long-term safety data currently available. The Committee noted pharmacological similarities between eravacycline and tigecycline, and the reported increased mortality associated with tigecycline in some meta-analyses.

The Expert Committee agreed with the EML Antibiotic Working Group's recommendation that eravacycline be classified in the AWaRe Reserve group.

## References


1. Livermore DM, Mushtaq S, Warner M, Woodford N. In Vitro Activity of Eravacycline against Carbapenem-Resistant Enterobacteriaceae and Acinetobacter baumannii. Antimicrob Agents Chemother. 2016;60(6):3840–4.
2. Seifert H, Stefanik D, Sutcliffe JA, Higgins PG. In-vitro activity of the novel fluorocycline eravacycline against carbapenem non-susceptible Acinetobacter baumannii. Int J Antimicrob Agents. 2018;51(1):62–4.
3. Zhanel GG, Baxter MR, Adam HJ, Sutcliffe J, Karlowsky JA. In vitro activity of eravacycline against 2213 Gram-negative and 2424 Gram-positive bacterial pathogens isolated in Canadian hospital laboratories: CANWARD surveillance study 2014-2015. Diagn Microbiol Infect Dis. 2018;91(1):55–62.
4. Zhanel GG, Cheung D, Adam H, Zelenitsky S, Golden A, Schweizer F, et al. Review of Eravacycline, a Novel Fluorocycline Antibacterial Agent. Drugs. 2016;76(5):567–88.
5. Cassini A, Hogberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis. 2019; 19(1):56–66.
6. Gandra S, Tseng KK, Arora A, Bhowmik B, Robinson ML, Panigrahi B, et al. The mortality burden of multidrug-resistant pathogens in India: a retrospective observational study. Clin Infect Dis. 2019; 69(4): 563–570.
7. Global action plan on antimicrobial resistance. Geneva: World Health Organization; 2015. Available from: https://apps.who.int/iris/handle/10665/311820, accessed 30 October 2019.
8. van Duin D, Doi Y. The global epidemiology of carbapenemase-producing Enterobacteriaceae. Virulence. 2017;8(4):460–9.
9. Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. Geneva: World Health Organization; 2017. Available from: https://apps.who.int/iris/handle/10665/311820, accessed 30 October 2019.
10. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2018;18(3):318–27.
11. Solomkin J, Evans D, Slepavicius A, Lee P, Marsh A, Tsai L, et al. Assessing the Efficacy and Safety of Eravacycline vs Ertapenem in Complicated Intra-abdominal Infections in the Investigating Gram-Negative Infections Treated With Eravacycline (IGNITE 1) Trial: A Randomized Clinical Trial. JAMA Surg. 2017;152(3):224–32.
12. Solomkin JS, Gardovskis J, Lawrence K, Montravers P, Sway A, Evans D, et al. IGNITE4: Results of a Phase 3, Randomized, Multicenter, Prospective Trial of Eravacycline vs. Meropenem in the Treatment of Complicated Intra-Abdominal Infections. Clin Infect Dis. 2019;69(6):921–929.
13. Tetraphase Pharmaceuticals Inc. (2015). Tetraphase announces top-line results from IGNITE2 phase 3 clinical trial of eravacycline in cUTI [website]. (https://ir.tphase.com/news-releases/news-release-details/tetraphase-announces-top-line-results-ignite2-phase-3-clinical, accessed 20 March 2019).
14. Tetraphase Pharmaceuticals Inc. (2018). Tetraphase Pharmaceuticals announces commercial launch of Xerava in the United States [website]. (https://ir.tphase.com/news-releases/news-release-details/tetraphase-pharmaceuticals-announces-commercial-launch-xeravatm, accessed 20 March 2019).

15. McGovern PC, Wible M, El-Tahtawy A, Biswas P, Meyer RD. All-cause mortality imbalance in the tigecycline phase 3 and 4 clinical trials. Int J Antimicrob Agents. 2013;41(5):463–7.

16. Shen F, Han Q, Xie D, Fang M, Zeng H, Deng Y. Efficacy and safety of tigecycline for the treatment of severe infectious diseases: an updated meta-analysis of RCTs. Int J Infect Dis. 2015;39:25–33.

17. Prasad P, Sun J, Danner RL, Natanson C. Excess deaths associated with tigecycline after approval based on noninferiority trials. Clin Infect Dis. 2012;54(12):1699–709.

18. US Food and Drug Administration (2013). FDA Drug Safety Communication: FDA warns of increased risk of death with IV antibacterial Tygacil (tigecyclne) and approves new Boxed Warning [website]. (https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-increased-risk-death-iv-antibacterial-tygacil-tigecycline, accessed 20 March 2019).

*Meropenem + vaborbactam – addition – EML*

**Meropenem + vaborbactam** **ATC Code: J01DH52**

**Proposal**

The application requested the inclusion on the EML of meropenem + vaborbactam as a last-resort treatment option for infections due to multidrug-resistant organisms (MDROs).

**Applicant**

EML Secretariat on behalf of the EML Antibiotics Working Group

**WHO Technical Department**

Essential Medicines and Health Products

**EML/EMLc**

EML

**Section**

6.2.3 Reserve group antibiotics

**Dose form(s) & strengths(s)**

Powder for injection: 1 g + 1 g

**Core/Complementary**

Complementary

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Meropenem + vaborbactam is a combination of the carbapenem meropenem with the non-suicidal cyclic boronic acid–based beta-lactamase inhibitor vaborbactam (*1*, *2*). Vaborbactam inhibits Ambler class A and C beta-lactamases, of which KPC-carbapnemases and some extended spectrum beta-lactamases are currently the clinically most relevant examples. Metallo-beta-lactamases (e.g. NDM, VIM) and class D beta-lactamases are not inhibited by vaborbactam.

**Public health relevance (burden of disease)**

Antibiotic-resistant bacteria are a significant threat to public health, both in HICs as well as LMICs (*3*–*5*). A recent study estimated that infections with antibiotic-

resistant bacteria were responsible for approximately 33 000 attributable deaths in Europe in 2015 (*3*). Fewer data are available for LMICs, but a retrospective study in ten hospitals in India found that resistant pathogens were associated with two to three times higher mortality than infections with susceptible strains after adjusting for several confounders (*4*).

Over the past decade there has been increasing spread of multidrug-resistant Gram-negative pathogens such as carbapenemase producing *Enterobacteriaceae* (*6*). The Global Antimicrobial Resistance Surveillance System (GLASS) report published in 2018 found high levels of carbapenem resistance in *Enterobacteriaceae* and non-fermenters in many of the LMICs providing data for the report (*4*). The 2015 WHO *Global action plan on antimicrobial resistance* calls for the development of new antimicrobial medicines (5). To provide a framework for this endeavour, in 2017 WHO published a priority list of antibiotic-resistant bacteria (*7*). The "Priority 1: critical" category includes four types of pathogens, all of which are Gram-negative: carbapenem-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacteriaceae*; and third-generation cephalosporin-resistant *Enterobacteriaceae* (*8*).

**Summary of evidence: benefits** (from the application)

As of December 2018, meropenem + vaborbactam was assessed in two Phase III RCTs (*9*, *10*). The TANGO I trial showed non-inferiority of meropenem + vaborbactam versus piperacillin + tazobactam for the treatment of cUTI (infection with a pathogen resistant to standard antibiotics was not an inclusion criterion) (*9*). The TANGO II trial, a Phase III, multicentre, multinational, open-label randomized clinical trial, compared meropenem + vaborbactam to the best available therapy (BAT; often a combination of antibiotics) in patients with a variety of infections caused by carbapenem-resistant *Enterobacteriaceae* and showed decreased 28-day all-cause mortality (15.6% (5/32) vs BAT 33.3% (5/15)) with meropenem + vaborbactam compared to BAT, with a wide confidence interval given the small sample size (95%CI of difference, −44.7% to 9.3%) (*10*).

**Summary of evidence: harms** (from the application)

In the TANGO I and TANGO II trials adverse events were similar in the meropenem + vaborbactam group and in the comparator group.

**Additional evidence (not in the application)**

N/A

**WHO Guidelines**

There are no available WHO guidelines for the treatment of infections due to MDROs.

**Costs/cost-effectiveness**

United States: about US$ 200 for 1 g + 1 g, equivalent to US$ 1200 for an average daily dose of 2 g + 2 g every 8 hours.

No data about cost-effectiveness are available.

**Availability**

Meropenem + vaborbactam is approved by the FDA for patients 18 years of age and older with cUTI, including pyelonephritis.

EMA approved its use in the European Union for:

- cUTI, including pyelonephritis, a sudden and severe infection causing the kidneys to swell and which may permanently damage them;
- cIAI;
- hospital-acquired pneumonia, including ventilator associated pneumonia;
- bacteria in the blood associated with any of the infections listed above;
- infections due to aerobic Gram-negative organisms in adults with limited treatment options.

**Other considerations**

The Committee noted that there was very limited clinical trial evidence of the efficacy of recently approved antibiotics against carbapenem-resistant infections, with activity based on small sample size studies including heterogenous populations. The Committee was concerned that the current regulatory approval process for novel agents effective against the WHO priority pathogen list "critical priority" pathogens does not adequately inform the urgent public health need for clear evidence-based guidance on the optimal management of these infections, which are associated with high mortality.

**Committee recommendations**

The Expert Committee recommended the inclusion of meropenem + vaborbactam on the complementary list of the EML of meropenem + vaborbactam for the treatment of infections caused by carbapenem-resistant organisms which are pathogens classified as "critical priority" in the WHO priority pathogen list.

The Committee agreed with the EML Antibiotic Working Group's recommendation that this antibiotic should be classified in the AWaRe Reserve group.

The Committee recommended further collaboration between relevant stakeholders to design and implement strategic public health-orientated studies

that will help to inform the choice of optimal single or combinations of both novel and older antibiotics for adults and children in different settings, with the goal of improving clinical outcomes, minimizing toxicity and reducing selection of resistance.

## References


1. Cho JC, Zmarlicka MT, Shaeer KM, Pardo J. Meropenem/Vaborbactam, the First Carbapenem/beta-Lactamase Inhibitor Combination. Ann Pharmacother. 2018;52(8):769–79.
2. Lee YR, Baker NT. Meropenem-vaborbactam: a carbapenem and beta-lactamase inhibitor with activity against carbapenem-resistant Enterobacteriaceae. Eur J Clin Microbiol Infect Dis. 2018;37(8):1411–9.
3. Cassini A, Hogberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis. 2019; 19(1):56–66.
4. Gandra S, Tseng KK, Arora A, Bhowmik B, Robinson ML, Panigrahi B, et al. The mortality burden of multidrug-resistant pathogens in India: a retrospective observational study. Clin Infect Dis. 2019; 69(4):563–570.
5. Global action plan on antimicrobial resistance. Geneva: World Health Organization; 2015. Available from: https://apps.who.int/iris/handle/10665/311820, accessed 30 October 2019.
6. van Duin D, Doi Y. The global epidemiology of carbapenemase-producing Enterobacteriaceae. Virulence. 2017;8(4):460–9.
7. Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. Geneva: World Health Organization; 2017.
8. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2018;18(3):318–27.
9. Kaye KS, Bhowmick T, Metallidis S, Bleasdale SC, Sagan OS, Stus V, et al. Effect of Meropenem-Vaborbactam vs Piperacillin-Tazobactam on Clinical Cure or Improvement and Microbial Eradication in Complicated Urinary Tract Infection: The TANGO I Randomized Clinical Trial. JAMA. 2018;319(8):788–99.
10. Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, Mathers AJ, Bassetti M, Vazquez J, et al. Effect and Safety of Meropenem-Vaborbactam versus Best-Available Therapy in Patients with Carbapenem-Resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial. Infect Dis Ther. 2018;7(4):439–55.

*Omadacycline – addition – EML*

| **Omadacycline** | **ATC Code: to be assigned** |
|---|---|

**Proposal**

The application requested the inclusion of omadacycline on the complementary list of the EML as a last-resort treatment option for infections due to multidrug-resistant organisms (MDROs).

**Applicant**

EML Secretariat on behalf of the EML Antibiotics Working Group

**WHO Technical Department**

Essential Medicines and Health Products

**EML/EMLc**

EML

**Section**

6.2.3 Reserve group antibiotic

**Dose form(s) & strengths(s)**

Lyophilized powder for injection: 100 mg
Tablet: 300 mg

**Core/Complementary**

Complementary

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Omadacycline had not previously been considered for inclusion on the EML. Omadacycline, a recently approved tetracycline antibiotic, has a broad spectrum of activity against many Gram-positive and Gram-negative pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) (*1*). MRSA is ranked as a "high priority" pathogen on the WHO priority pathogens list (*2*).

**Public health relevance (burden of disease)**

Antibiotic-resistant bacteria are a significant threat to public health, both in HICs as well as LMICs (*3–5*). A recent study estimated that infections with antibiotic-

resistant bacteria were responsible for approximately 33 000 attributable deaths in Europe in 2015 (*3*). Fewer data are available for LMICs, but a retrospective study in ten hospitals in India found that resistant pathogens were associated with two to three times higher mortality than infections with susceptible strains after adjusting for several confounders (*4*).

Over the past decade there has been increasing spread of multidrug-resistant Gram-negative pathogens such as carbapenemase producing *Enterobacteriaceae* (*6*). The Global Antimicrobial Resistance Surveillance System (GLASS) report published in 2018 found high levels of carbapenem resistance in *Enterobacteriaceae* and non-fermenters in many of the LMICs providing data for the report (*4*). The 2015 WHO *Global action plan on antimicrobial resistance* calls for the development of new antimicrobial medicines (*5*). To provide a framework for this endeavour, in 2017 WHO published a priority list of antibiotic-resistant bacteria (*2*). "Priority 1: critical" category includes four types of pathogens, all of which are Gram-negative: carbapenem resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacteriaceae*; and third-generation cephalosporin-resistant *Enterobacteriaceae* (*7*).

**Summary of evidence: benefits** (from the application)

Several RCTs of omadacycline had been conducted or were currently ongoing, but at the time of writing the application the results had not yet been published in the peer-reviewed literature.

- Omadacycline versus moxifloxacin for the treatment of community-acquired bacterial pneumonia (CABP) (NCT02531438), Phase III, double-blind, multicentre non-inferiority RCT (2015–2017) in 774 adult patients with CABP. Primary outcome: Number of participants with early clinical response 81.1% vs 82.7% (difference −1.6 percentage points, 95%CI −7.1 to 3.8).
- Omadacycline versus linezolid for the treatment of acute bacterial skin and skin structure infections (ABSSSI) (NCT02378480), Phase III, double-blind, multicentre non-inferiority RCT (2015-2016): results not yet available.
- Oral omadacycline versus oral linezolid for the treatment of ABSSSI (NCT02877927), Phase III, double-blind, multicentre non-inferiority RCT (2016–2017) in 735 adult patients with ABSSSI, Primary outcome: Early clinical response 87.5% vs 82.5% (difference +5.0 percentage points, 95%CI −0.2 to 10.3).
- Oral omadacycline versus oral nitrofurantoin for the treatment of cystitis (NCT03425396): trial still recruiting.

The results of NCT02531438 and NCT02378480 have since been published (see additional evidence).

**Summary of evidence: harms** (from the application)

See additional evidence.

**Additional evidence** (not in the application)

Two noninferiority RCTs of omadacycline in adults with CABP and ABSSSI were published in February 2019.

A double-blind, noninferiority (10 percentage point margin) RCT allocated adults with CABP to either omadacycline or moxifloxacin with possible transition to the oral equivalent after three days for a total treatment duration of between 7 and 14 days. The primary outcome was early clinical response (according to predefined criteria) at 72 to 120 hours. Omadacycline fulfilled criteria for noninferiority for early clinical response (81.1% vs 82.7%, difference, −1.6 percentage points; 95%CI −7.1 to 3.8) (*8*). The frequency of adverse events (AE) was similar in both groups, with gastrointestinal side effects being the most commonly observed AE (10.2% vs 18.0%). There was a slight imbalance in mortality with eight deaths occurring in the omadacycline group versus four in the moxifloxacin group, disproportionately affecting patients with more severe pneumonia.

A second double-blind, noninferiority (10 percentage point margin) trial, randomly assigned adults with ABSSSI to treatment with omadacycline or linezolid with possible transition to the oral equivalent after three days for a total treatment duration between 7 and 14 days. The primary outcome was early clinical response (48–72 hours), defined as survival, absence of rescue antibiotic therapy and ≥ 20% reduction in lesion size. Omadacycline fulfilled criteria for non-inferiority for early clinical response (84.8% vs 85.5%, difference −0.7 percentage points, 95%CI −6.3 to 4.9) (*9*). The frequency of adverse events was similar in both groups, with gastrointestinal side effects being the most commonly observed AE (18.0% vs 15.8%).

**WHO Guidelines**

There are no available WHO guidelines for the treatment of infections due to multidrug-resistant organisms.

**Costs/cost-effectiveness**

No information regarding costs available.

Few data are available regarding the cost-effectiveness of omadacycline. A modelling study estimated potential cost savings with omadacycline treatment compared with inpatient IV vancomycin treatment in patients with acute

bacterial skin and skin-structure infections by shifting care to the outpatient setting due to the availability of an oral formulation of omadacycline (*10*). The study assumed that a large proportion (50%) of patients would continue with IV vancomycin (rather than a switch to an oral agent), limiting applicability to 'real-world' scenarios. It was noted that the first author of this study was an employee of the pharmaceutical company producing omadacycline.

**Availability**

The drug has been approved for the treatment of community acquired bacterial pneumonia and acute bacterial skin and skin structure infections in the United States (*11*).

**Other considerations**

N/A

**Committee recommendations**

The Expert Committee did not recommend the addition of omadacycline to the EML. The Committee considered that although omadacycline demonstrates activity against both Gram-positive and Gram-negative pathogens, including MRSA, available data for its effectiveness and safety are currently limited. The Committee noted the finding of potentially increased mortality associated with omadacycline in one RCT of patients with community-acquired pneumonia.

The Expert Committee agreed with the EML Antibiotic Working Group's recommendation that omadacycline be classified in the AWaRe Reserve group.

## References

1. Montravers P, Tran-Dinh A, Tanaka S. The role of omadacycline in skin and soft tissue infections. Curr Opin Infect Dis. 2018;31(2):148–54.
2. Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. Geneva: World Health Organization; 2017. Available from: https://apps.who.int/iris/handle/10665/311820, accessed 30 October 2019.
3. Cassini A, Hogberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis. 2019; 19(1):56–66.
4. Gandra S, Tseng KK, Arora A, Bhowmik B, Robinson ML, Panigrahi B, et al. The mortality burden of multidrug-resistant pathogens in India: a retrospective observational study. Clin Infect Dis. 2019; 69(4): 563–570.
5. Global action plan on antimicrobial resistance. Geneva: World Health Organization; 2015. Available from: https://apps.who.int/iris/handle/10665/311820, accessed 30 October 2019.
6. van Duin D, Doi Y. The global epidemiology of carbapenemase-producing Enterobacteriaceae. Virulence. 2017;8(4):460–9.

7. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2018;18(3):318–27.
8. Stets R, Popescu M, Gonong JR, Mitha I, Nseir W, Madej A, et al. Omadacycline for Community-Acquired Bacterial Pneumonia. N Engl J Med. 2019;380(6):517–27.
9. O'Riordan W, Green S, Overcash JS, Puljiz I, Metallidis S, Gardovskis J, et al. Omadacycline for Acute Bacterial Skin and Skin-Structure Infections. N Engl J Med. 2019;380(6):528–38.
10. LaPensee K, Lodise T. Potential Cost-Savings with Once-Daily Aminomethylcycline Antibiotic versus Vancomycin in Hospitalized Patients with Acute Bacterial Skin and Skin Structure Infections. Am Health Drug Benefits. 2018;11(9):449–59.
11. Markham A, Keam SJ. Omadacycline: First Global Approval. Drugs. 2018;78(18):1931–7.

*Plazomicin– addition – EML*

| Plazomicin | ATC Code: to be assigned |
|---|---|

**Proposal**

The application requested the inclusion of plazomicin on the complementary list of the EML as a last-resort treatment option for infections due to multidrug-resistant organisms (MDROs).

**Applicant**

EML Secretariat on behalf of the EML Antibiotics Working Group

**WHO Technical Department**

Essential Medicines and Health Products

**EML/EMLc**

EML

**Section**

6.2.3 Reserve group antibiotics

**Dose form(s) & strengths(s)**

Injection: 50 mg/mL in 10 mL vial (500 mg/10 mL concentrate for solution for infusion)

**Core/Complementary**

Complementary

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Plazomicin had not previously been considered for inclusion on the EML. Plazomicin is a next-generation aminoglycoside that is not affected by many aminoglycoside-modifying enzymes of *Enterobacteriaceae* that inactivate other types of aminoglycosides (*1*, *2*). This makes it a potentially useful drug for the treatment of carbapenemase-producing *Enterobacteriaceae* since aminoglycosides are not affected by carbapenemase production (metallo-beta-lactamases may be an exception since they often are associated with genes for methylases affecting and inactivating all types of aminoglycosides, including plazomicin).

**Public health relevance** (burden of disease)

Antibiotic-resistant bacteria are a significant threat to public health, both in HICs as well as LMICs (*3*–*5*). A recent study estimated that infections with antibiotic-resistant bacteria were responsible for approximately 33 000 attributable deaths in Europe in 2015 (*3*). Fewer data are available for LMICs, but a retrospective study in ten hospitals in India found that resistant pathogens were associated with two to three times higher mortality than infections with susceptible strains after adjusting for several confounders (*4*).

Over the past decade there has been increasing spread of multidrug-resistant Gram-negative pathogens such as carbapenemase producing *Enterobacteriaceae* (*6*). The Global Antimicrobial Resistance Surveillance System (GLASS) report published in 2018 found high levels of carbapenem resistance in *Enterobacteriaceae* and non-fermenters in many of the LMICs providing data for the report (*4*). The 2015 WHO *Global action plan on antimicrobial resistance* calls for the development of new antimicrobial medicines (5). To provide a framework for this endeavour, in 2017 WHO published a priority list of antibiotic-resistant bacteria (7). The "Priority 1: critical" category includes four types of pathogens, all of which are Gram-negative: carbapenem resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacteriaceae*; and third-generation cephalosporin-resistant *Enterobacteriaceae* (*8*).

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**Summary of evidence: benefits** (from the application)

See additional evidence.

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**Summary of evidence: harms** (from the application)

Like all aminoglycosides plazomicin is potentially nephrotoxic. Increases in serum creatinine levels of 0.5 mg or more per decilitre (≥40 μmol per litre) above baseline occurred in 7.0% of patients in the plazomicin group and in 4.0% in the meropenem group in the non-inferiority trial comparing plazomicin to meropenem for patients with cUTIs (see additional evidence) (*9*).

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**Additional evidence** (not in the application)

Results of a non-inferiority trial comparing plazomicin to meropenem for patients with cUTIs were published in January 2019 (*9*). 609 patients with a diagnosis of cUTI were randomly allocated 1:1 to IV plazomicin or meropenem with the option for oral step-down treatment after at least 4 days of IV treatment with a total treatment duration of 7 to 10 days of therapy. The primary outcome was "composite cure" (clinical cure and microbiologic eradication) at day 5, and 15 to 19 days after treatment start in the microbiologic modified ITT population. Plazomicin fulfilled the non-inferiority criteria for both endpoints (with a prespecified non-inferiority margin of 15 percentage points): 88.0% (168/191) vs

91.4% (180/197) (difference, −3.4 percentage points; 95%CI −10.0 to 3.1) and 81.7% (156/191) vs 70.1% (138/197) (difference, 11.6 percentage points; 95%CI 2.7 to 20.3) respectively.

**WHO Guidelines**

There are no available WHO guidelines for the treatment of infections due to MDROs.

**Costs/cost-effectiveness**

United States: Dosing is weight-based but a dose of 1000 mg for a 70 kg person with good renal function is reported to be approximately US$ 750.

No data regarding the cost-effectiveness of plazomicin compared to other treatment options are available.

**Availability**

Plazomicin is approved by the FDA for patients 18 years of age or older for the treatment of cUTI, including pyelonephritis caused by the following susceptible microorganism(s): *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Enterobacter cloacae*. An application has been filed in Europe by the producing company but is currently pending.

**Other considerations**

The Committee noted that there was very limited clinical trial evidence of the efficacy of recently approved antibiotics against carbapenem-resistant infections, with activity based on small sample size studies including heterogenous populations. The Committee was concerned that the current regulatory approval process for novel agents effective against the WHO priority pathogen list "critical priority" pathogens does not adequately inform the urgent public health need for clear evidence-based guidance on the optimal management of these infections, which are associated with high mortality.

**Committee recommendations**

The Expert Committee recommended the inclusion of plazomicin on the complementary list of the EML for the treatment of infections caused by carbapenem-resistant organisms that are classified as "critical priority" in the WHO priority pathogen list.

The Committee agreed with the EML Antibiotic Working Group's recommendation that this antibiotic should be classified in the AWaRe Reserve group (Section 6.2.3).

The Committee recommended further collaboration between relevant stakeholders to design and implement strategic public health-orientated studies

that will help to inform the choice of optimal single or combinations of both novel and older antibiotics for adults and children in different settings, with the goal of improving clinical outcomes, minimizing toxicity and reducing selection of resistance.

## References

1. Shaeer KM, Zmarlicka MT, Chahine EB, Piccicacco N, Cho JC. Plazomicin: A Next-Generation Aminoglycoside. Pharmacotherapy. 2019;39(1):77–93.
2. Theuretzbacher U, Paul M. Developing a new antibiotic for extensively drug-resistant pathogens: the case of plazomicin. Clin Microbiol Infect. 2018;24(12):1231–3.
3. Cassini A, Hogberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis. 2019; 19(1):56–66.
4. Gandra S, Tseng KK, Arora A, Bhowmik B, Robinson ML, Panigrahi B, et al. The mortality burden of multidrug-resistant pathogens in India: a retrospective observational study. Clin Infect Dis. 2019; 69(4): 563–570.
5. Global action plan on antimicrobial resistance. Geneva: World Health Organization; 2015. Available from: https://apps.who.int/iris/handle/10665/311820, accessed 30 October 2019.
6. van Duin D, Doi Y. The global epidemiology of carbapenemase-producing Enterobacteriaceae. Virulence. 2017;8(4):460–9.
7. Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. Geneva: World Health Organization; 2017.
8. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2018;18(3):318–27.
9. Wagenlehner FME, Cloutier DJ, Komirenko AS, Cebrik DS, Krause KM, Keepers TR, et al. Once-Daily Plazomicin for Complicated Urinary Tract Infections. N Engl J Med. 2019;380(8):729–40.

### 6.2.5 Antituberculosis medicines

*Antituberculosis medicines – new formulations for addition – EML and EMLc*

| | |
|---|---|
| **Cycloserine** | **ATC Code: J04AB01** |
| **Ethambutol** | **ATC Code: J04AK02** |
| **Ethionamide** | **ATC Code: J04AD03** |
| **Isoniazid** | **ATC Code: J04AC01** |
| **Levofloxacin** | **ATC Code: J01MA12** |
| **Linezolid** | **ATC Code: J01XX08** |
| **Moxifloxacin** | **ATC Code: J01MA14** |
| **Clofazimine** | **ATC Code: J04BA01** |
| **Rifabutin** | **ATC Code: J04AB04** |

**Proposal**

The application requested:

- the addition of various new formulations of currently listed medicines for tuberculosis (TB) for use in children;
- amendments to the dosage form terminology used to describe clofazimine and rifabutin.

**Applicant**

Stop TB Partnership/Global Drug Facility

**WHO Technical Department**

Comments on the application were received from the WHO Global TB Programme. The technical unit advised that it supported the application, which was developed in consultation with the Global TB Programme, and was fully in line with the latest WHO recommendations on the management of multidrug-resistant TB (MDR-TB), rifampicin-resistant TB (RR-TB) and isoniazid-resistant TB. The technical unit stated that the addition of child-friendly formulations of second-line antituberculosis medicines will greatly benefit children with drug-resistant tuberculosis.

**EML/EMLc**

EML and EMLc

**Section**

6.2.5 Antituberculosis medicines

**Dose form(s) & strengths(s)**

Cycloserine: solid oral dose form 125 mg (add)
Ethambutol: dispersible tablet 100 mg (add)
Ethionamide: dispersible tablet 125 mg (add)
Isoniazid: dispersible tablet 100 mg (add)
Levofloxacin: dispersible tablet 100 mg (add)
Linezolid: dispersible tablet 150 mg (add)
Moxifloxacin: dispersible tablet 100 mg (add)

Clofazimine: capsule to solid oral dosage form 50 mg, 100 mg (amend)
Rifabutin: capsule to solid oral dosage form 150 mg (amend)

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**Core/Complementary**

Core: ethambutol, isoniazid, rifabutin
Complementary: clofazimine, cycloserine, ethionamide, levofloxacin, linezolid, moxifloxacin

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**Individual/Square box listing**

Individual

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**Background** (if relevant, eg. resubmission, previous EC consideration)

All of the medicines for which additional formulations are requested for listing are currently included on the Model Lists in various formulations and strengths.

In 2007, the World Health Assembly called for WHO to promote the development of child-friendly medicines with a particular focus on treatment for HIV, tuberculosis, malaria and chronic disease (*1*).

In 2017, the Expert Committee recommended the addition to the EMLc of two fixed-dose combination, child-friendly dispersible tablet formulations of isoniazid + rifampicin +/– pyrazinamide for use in children with drug-sensitive tuberculosis infection. The Committee considered that the availability of these age-appropriate formulations would offer benefits including appropriate dosing, ease of administration and reduced pill burden (*2*).

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**Public health relevance** (burden of disease)

It is estimated that of the 10 million people who developed TB in 2017, 1 million of them were children. Children aged <15 years accounted for 7.1% of the 6.4 million new or relapsed cases of TB notified to national TB programmes and reported to WHO. Children aged <15 years accounted for 15% and 10% of total TB deaths among HIV-negative and HIV-positive people, respectively – higher than their share of estimated cases, suggesting poorer access to diagnosis and treatment (*3*).

**Summary of evidence: benefits** (from the application)

Evidence for the clinical effectiveness of the medicines was evaluated at the time of their individual listings.

*Paediatric-friendly formulations*

The proposed new formulations are mostly dispersible formulations, meaning they can be mixed in liquid, making it easier to get the correct doses and for children to swallow. They are flavoured to overcome the bitterness associated with breaking, crushing and otherwise manipulating adult formulations.

The proposed formulations are at lower strengths, aligned with the dosing needs of children according to the 2019 update of the WHO *consolidated guidelines on drug-resistant tuberculosis treatment* (*4*). With the exception of linezolid 150 mg dispersible tablet (which is still in development), the proposed formulations are all quality-assured, either through the WHO Prequalification for Medicines Programme, or by the Global Fund Expert Review Panel.

*Amended dosage form terminology*

Until recently there has been a single supplier of clofazimine in a capsule formulation. This creates a risk to the global supply security of this key medicine, especially as it is increasing in importance and will likely have greater use in national programmes. Many organizations have worked to improve the supply security and have new suppliers developing clofazimine; in 2018 a new tablet formulation of clofazimine was quality-assured and is now eligible for procurement by programmes. The current listing on the Model List refers only to clofazimine capsules. The specificity of having the dosage form limited to only capsules could create a barrier to accessing the new tablet formulations. This situation also applies to other products, such as rifabutin capsules, where it is possible that different manufacturing approaches could mean that products may be produced in tablet and/or capsule formulations. Having robust quality assurance approaches, such as the WHO Prequalification for Medicines Programme, ensures that the efficacy of the medicines remains regardless of the formulation.

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**Summary of evidence: harms** (from the application)

Evidence for the safety of the medicines was evaluated at the time of their individual listings.

---

**Additional evidence** (not in the application)

N/A

### WHO Guidelines

These medicines are all recommended the most recent WHO guidelines for treatment of drug-sensitive tuberculosis (2017) (*5*), treatment of latent TB infection (2018) (*6*), treatment of isoniazid mono-resistant TB (2018) (*7*) and treatment of drug-resistant TB (2019) (*4*).

### Costs/cost-effectiveness

No information was provided in the application.

### Availability

The proposed new formulations are in the Stop TB Partnership's Global Drug Facility product catalogue and are reportedly being procured by programmes.

### Other considerations

N/A

### Committee recommendations

The Expert Committee recommended the addition of the proposed dispersible tablet formulations of ethambutol and isoniazid to the core list of the EMLc, and of cycloserine, ethionamide, levofloxacin, linezolid and moxifloxacin to the complementary list of the EMLc for the treatment of children with drug-sensitive and drug-resistant TB.

The Committee considered that the availability of quality-assured, age-appropriate formulations will help improve access to effective treatment for children with TB.

The Committee also recommended the requested amendments to the dosage form terminology for clofazimine and rifabutin.

## References

1. Resolution WHA60.20. Better medicines for children. In: Sixtieth World Health Assembly, Geneva, 14–23 May 2007. Resolutions and decisions. Geneva: World Health Organization; 2007. Available from: http://apps.who.int/gb/ebwha/pdf_files/WHASSA_WHA60-Rec1/E/reso-60-en.pdf, accessed 30 October 2019.
2. The selection and use of essential medicines. Report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children) (WHO Technical Report Series, No. 1006). Geneva: World Health Organization; 2017. Available from https://apps.who.int/iris/bitstream/handle/10665/259481/9789241210157-eng.pdf, accessed 30 October 2019.
3. Global tuberculosis report 2018. Geneva: World Health Organization; 2018. Available from https://apps.who.int/iris/bitstream/handle/10665/274453/9789241565646-eng.pdf, accessed 30 October 2019.

4. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019. Available from: https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf, accessed 30 October 2019.
5. Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update. Geneva: World Health Organization; 2017. Available from: https://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf, accessed 30 October 2019).
6. Latent tuberculosis infection: Updated and consolidated guidelines for programmatic management. Geneva: World Health Organization; 2018. Available from https://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/, accessed 30 October 2019.
7. WHO treatment guidelines for isoniazid-resistant tuberculosis: Supplement to the WHO treatment guidelines for drug-resistant tuberculosis. Geneva: World Health Organization; 2018. Available from: https://apps.who.int/iris/bitstream/handle/10665/260494/9789241550079-eng.pdf, accessed 30 October 2019.

*Antituberculosis medicines – formulations for deletion – EML*

| | |
|---|---|
| **Ethambutol + isoniazid** | **ATC Code: J04AM03** |
| **Isoniazid + pyrazinamide + rifampicin** | **ATC Code: J04AM05** |
| **Isoniazid + rifampicin** | **ATC Code: J04AM02** |

**Proposal**

The application requested the removal from the EML of specific fixed-dose combination formulations/strengths of ethambutol + isoniazid, isoniazid + pyrazinamide + rifampicin, and isoniazid + rifampicin based on updated recommendations in WHO guidelines.

**Applicant**

WHO Global TB Programme

**WHO Technical Department**

Global TB Programme

**EML/EMLc**

EML

**Section**

6.2.5 Antituberculosis medicines

**Dose form(s) & strengths(s)**

Ethambutol + isoniazid: Tablet 400 mg + 150 mg
Isoniazid + pyrazinamide + rifampicin: Tablet: 150 mg + 500 mg + 150 mg (For intermittent use three times weekly)
Isoniazid + rifampicin: Tablet 60 mg + 60 mg and 150 mg + 150 mg (For intermittent use three times weekly)

**Core/Complementary**

Core

**Individual/Square box listing**

Individual

**Background**

Abbreviations used for tuberculosis (TB) medicines:
H = isoniazid, R = rifampicin, Z = pyrazinamide, E = ethambutol

**Public health relevance** (burden of disease)

N/A

**Summary of evidence: benefits** (from the application)

N/A

**Summary of evidence: harms** (from the application)

N/A

**Additional evidence** (not in the application)

N/A

**WHO Guidelines**

The proposed deletions are in alignment with recommendations made in current WHO guidelines for treatment of tuberculosis.

*Ethambutol + isoniazid (= HE)*

The 2010 WHO *Treatment of tuberculosis guidelines* (*1*) recommended that the two-month rifampicin regimen, 2HRZE/6HE, should be phased out, based on evidence that showed it to be associated with more relapses and deaths than the six-month rifampicin regimen, 2HRZE/4HR.

*Isoniazid + pyrazinamide + rifampicin/isoniazid + rifampicin*

The 2017 *WHO guidelines for treatment of drug-susceptible tuberculosis and patient care* (*2*) reviewed the effectiveness of intermittent (three times weekly) dosing schedules of TB medicines in both the intensive and continuation phases of treatment. Evidence showed that patients who received three times weekly dosing had a higher risk of treatment failure, disease relapse and acquired drug resistance than patients who received daily dosing.

**Costs/cost-effectiveness**

N/A

**Availability**

N/A

**Other considerations**

Alternative strength fixed-dose formulations of isoniazid + pyrazinamide + rifampicin and isoniazid + rifampicin remain available on the EML for use in daily dosing regimens.

### Committee recommendations

The Expert Committee recommended the deletion of the proposed formulations from the core list of the EML, noting the advice of the WHO Global TB Programme that their use is no longer recommended in current WHO guidelines based on evidence that treatment regimens involving these formulations have been associated with greater rates of treatment failure, relapse, mortality and acquired drug resistance.

## References

1. Treatment of tuberculosis guidelines, 4th edition. Geneva: World Health Organization; 2010. Available from https://apps.who.int/iris/bitstream/handle/10665/44165/9789241547833_eng.pdf, accessed 30 October 2019.
2. Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update. Geneva: World Health Organization; 2017. Available from https://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf, accessed 30 October 2019.

*Antituberculosis medicines – intravenous formulations for addition – EML and EMLc*

| | |
|---|---|
| **Ethambutol** | **ATC Code: J04AK02** |
| **Isoniazid** | **ATC Code: J04AC01** |
| **p-aminosalicylic acid** | **ATC Code: J04AA01** |
| **Rifampicin** | **ATC Code: J04AB02** |

**Proposal**

Four separate applications requested addition of injectable formulations of ethambutol, isoniazid, p-aminosalicylic acid (PAS) and rifampicin to the EML and EMLc for treatment of drug-susceptible tuberculosis in combination with other first-line medicines.

**Applicant**

INCURE CU

**WHO Technical Department**

Comments on the applications were received from the WHO Global TB Programme. The technical unit advised that it did not support inclusion of the proposed IV formulations of tuberculosis (TB) medicines emphasizing the following:

- WHO recommends oral treatment regimens, ideally administered in fixed-dose combinations (where such formulations exist) for the treatment of drug-sensitive TB.
- WHO has recently updated treatment guidelines for MDR-TB and RR-TB, recommending that injectable agents are no longer among the priority medicines when designing longer MDR-TB regimens.
- In view of these WHO policy recommendations, in the large majority of TB patients, IV administration for first- or second-line medicines is not indicated.
- For the majority of indications listed in the applications for IV formulations, patients can be treated with oral formulations, if necessary, using alternative forms of oral administration.
- For adult patients with drug-sensitive TB, a four-drug regimen is recommended; therefore, with only three of the four medicines available as intravenous formulations, patients would still be required to take pyrazinamide orally.

**EML/EMLc**

EML and EMLc

**Section**

6.2.5 Antituberculosis medicines

**Dose form(s) & strengths(s)**

Ethambutol: injection 1000 mg and 2000 mg
Isoniazid: injection 300 mg, 500 mg and 900 mg
p-aminosalicylic acid: injection 3 g, 9 g and 12 g
Rifampicin: injection 450 mg and 600 mg

**Core/Complementary**

Core

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Ethambutol, isoniazid, PAS and rifampicin are all currently included on the EML and EMLc in oral dose forms.

**Public health relevance** (burden of disease)

Worldwide, tuberculosis is one of the top 10 causes of death, and the leading cause from a single infectious agent. In 2017, TB caused an estimated 1.3 million deaths among HIV-negative people, and there were an additional 300 000 deaths from the disease among HIV-positive people. There were an estimated 10.0 million new cases of TB, equivalent to 133 cases per 100 000 population (*1*).

The IV formulations are proposed in the applications for use in cases of severe forms of disease, such as central nervous system (CNS) TB or TB sepsis, patients with gastrointestinal diseases and reduced oral absorption rates, and other patient groups unwilling or unable to take oral dose forms.

There is evidence that there is a decrease in the functional absorptive area of the intestine in TB patients, resulting in reduced serum concentrations of orally administered antituberculosis drugs. Patients with malabsorption syndromes can require higher doses to achieve minimum therapeutic levels (*2*, *3*). Malabsorption of anti-mycobacterial drugs has been reported HIV-coinfected patients (*4*, *5*).

A retrospective cohort study in Brazil found that among TB patients admitted to intensive care units (ICU), over 90% have acute respiratory failure

(ARF) and require mechanical ventilation. The in-hospital mortality rate for ICU-admitted patients was around 65% (*6*).

CNS TB has been reported to account for 5–10% of extrapulmonary TB cases and approximately 1% of all TB cases (*7*). It is associated with high morbidity and mortality (*8*).

No information was provided in the applications regarding the proportion of total TB cases that would require IV treatment.

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**Summary of evidence: benefits** (from the application)

The clinical benefits and place in therapy of these medicines (per se) are well established and have been evaluated previously by the Expert Committee.

Limited pharmacokinetic data were presented in the applications indicating higher achievable concentrations with IV versus oral formulations, which is to be expected from IV administration where 100% bioavailability is achieved.

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**Summary of evidence: harms** (from the application)

The adverse events (AE) associated with the medicines, rather than of the proposed IV formulations, were described in the applications. The safety profiles of these medicines are well established and have been evaluated previously by the Expert Committee. It is reasonable to assume that the known safety profiles would be applicable to the IV formulations.

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**Additional evidence** (not in the application)

An RCT investigating the efficacy and safety of IV chemotherapy during the intensive treatment phase in patients newly diagnosed with pulmonary TB was identified during the review process (*9*). 92 patients were randomized to receive oral treatment with isoniazid, rifampicin, pyrazinamide and ethambutol or IV isoniazid, IV rifampicin, IV ethambutol and oral pyrazinamide. Alleviation of chest symptoms (cough, dyspnoea, chest pain) and intoxication symptoms (weakness, loss of appetite, fatigue, night sweats, increased body temperature) was more rapid in the IV therapy group. No serious adverse events associated with IV therapy were observed.

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**WHO Guidelines**

WHO guidelines recommend ethambutol, isoniazid, rifampicin and PAS in treatment regimens for drug-susceptible TB and MDR-TB/RR-TB (*10*, *11*).

The guidelines recommend the use of oral, preferably fixed-dose combination therapy for TB treatment.

In the WHO *Target regimen profiles for TB treatment*, it is recommended that IV formulations be reserved for cases of severe forms of disease such as CNS TB or TB sepsis (*12*).

**Costs/cost-effectiveness**

Due to the limited availability of the proposed IV formulations on world markets, no information on the comparative cost and cost-effectiveness of these products are available. The applications suggest that the IV formulations will be more expensive than the currently available oral formulations.

**Availability**

The proposed formulations have limited market approval and global availability:

IV ethambutol: Germany, Kazakhstan, Switzerland, Tajikistan, Ukraine and Uzbekistan.

IV isoniazid: Italy, Kazakhstan, Ukraine, United Kingdom, United States and Uzbekistan.

IV PAS: Belarus, Germany and Ukraine.

IV rifampicin: United States.

**Other considerations**

N/A

**Committee recommendations**

The Expert Committee did not recommend the addition of injectable formulations of ethambutol, isoniazid, PAS and rifampicin to the EML and EMLc for treatment of drug-susceptible TB in combination with other first-line medicines.

The Committee noted that WHO guidelines recommend use of oral, preferably fixed-dose combination therapy for TB, but acknowledged that parenteral administration of TB medicines may be useful in a small number of critically unwell patients unable to tolerate oral therapy or patients with TB meningitis. The Committee considered that the inclusion of these parenteral TB formulations on the EML could result in inappropriate use of parenteral therapy in patients otherwise able to take oral therapy.

The Committee also noted that the global market availability of these products was limited, and the comparative cost unknown.

## References

1. Global tuberculosis report 2018. Geneva: World Health Organization; 2018. Available from https://apps.who.int/iris/bitstream/handle/10665/274453/9789241565646-eng.pdf, accessed 30 October 2019.
2. Kuzhko MM, Butov DO, Hulchuk NM, Avramchuk OV, Protsyk LM, Kuzhko ZF. Clinical case of using intravenous forms of anti-tuberculosis drugs to improve the treatment efficiency of tuberculosis in patients with malabsorption syndrome. J Pulm Respir Med. 2015;5(269).

3. Frame RN, Johnson MC, Eichenhorn MS, Bower GC, Popovich J, Jr. Active tuberculosis in the medical intensive care unit: a 15-year retrospective analysis. Crit Care Med. 1987;15(11):1012–4.
4. Peloquin CA, Nitta AT, Burman WJ, Brudney KF, Miranda-Massari JR, McGuinness ME, et al. Low antituberculosis drug concentrations in patients with AIDS. Ann Pharmacother. 1996;30(9): 919–25.
5. Gordon SM, Horsburgh CR, Jr., Peloquin CA, Havlik JA, Jr., Metchock B, Heifets L, et al. Low serum levels of oral antimycobacterial agents in patients with disseminated Mycobacterium avium complex disease. J Infect Dis. 1993;168(6):1559–62.
6. Silva DR, Menegotto DM, Schulz LF, Gazzana MB, Dalcin PT. Mortality among patients with tuberculosis requiring intensive care: a retrospective cohort study. BMC Infect Dis. 2010;10:54.
7. Cherian A, Thomas SV. Central nervous system tuberculosis. Afr Health Sci. 2011;11(1):116–27.
8. Efsen AM, Panteleev AM, Grint D, Podlekareva DN, Vassilenko A, Rakhmanova A, et al. TB meningitis in HIV-positive patients in Europe and Argentina: clinical outcome and factors associated with mortality. 2013;2013:373601.
9. Butov D, Feshchenko Y, Kuzhko M, Gumeniuk M, Butova T. Efficacy and safety of intravenous chemotherapy during intensive treatment phase in patients with newly diagnosed pulmonary tuberculosis. Adv Respir Med. 2018; 86(4):159-167.
10. Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update. Geneva: World Health Organization; 2017. Available from https://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf, accessed 30 October 2019.
11. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019. Available from https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf, accessed 30 October 2019.
12. World Health Organization. Target regimen profiles for TB treatment: candidates: rifampicin-susceptible, rifampici-resistant and pan-TB treatment regimens. 2016. Geneva, World Health Organization. Available from https://apps.who.int/iris/bitstream/handle/10665/250044/9789241511339-eng.pdf, accessed 30 October 2019.

*Bedaquiline – addition – EMLc*

| **Bedaquiline** | **ATC Code: J04AK05** |
|---|---|

**Proposal**

The application requested the addition of bedaquiline to the complementary list of the EMLc as a reserve second-line medicine for the treatment of multidrug-resistant tuberculosis (MDR-TB) in children aged 6 years and older.

**Applicant**

WHO Global TB Programme

**WHO Technical Department**

Global TB Programme

**EML/EMLc**

EMLc

**Section**

6.2.5 Antituberculosis medicines

**Dose form(s) & strengths(s)**

Tablet 100 mg

**Core/Complementary**

Complementary

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

In 2015, bedaquiline was included on the complementary list of the EML as a reserve second-line medicine for treatment of MDR-TB in adults (*1*).

**Public health relevance** (burden of disease)

It is estimated that of the 10 million people who developed TB in 2017, 1 million of them were children. Children aged <15 years accounted for 7.1% of the 6.4 million new or relapsed cases of TB notified to national TB programmes and reported to WHO. Children aged <15 years accounted for 15% and 10% of total TB deaths among HIV-negative and HIV-positive people, respectively –

higher than their share of estimated cases, suggesting poorer access to diagnosis and treatment. In 2017, it was estimated that about 558,000 new MDR-TB/RR-TB cases emerged and about 230,000 MDR-TB/RR-TB patients died (2).

The contribution of bedaquiline to MDR-TB regimens is crucial to compose regimens, particularly in frequent situations in which other effective and safe medicines are not available. In a substantial proportion of MDR-TB/RR-TB patients the susceptibility to fluoroquinolones is lost and other TB medicines cannot be given because of safety concerns. Reports of sporadic cases and outbreaks of MDR-TB and XDR-TB among patients not previously treated for TB attests to the transmissibility of such strains, an additional public health concern, making the provision of effective treatment for all M/XDR-TB patients very important. The likelihood of treatment success in MDR-TB patients diminishes with the acquisition of additional drug resistance. Bedaquiline can increase the prospects of lasting cure in these patients.

The WHO Global TB Programme considers that bedaquiline should also be viewed as an essential medicine in children aged 6 years and older following the update by WHO of its treatment recommendations for adults and children with MDR-TB/RR-TB in December 2018 (*3*).

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**Summary of evidence: benefits** (from the application)

As part of the WHO guideline development process, a meta-analysis of individual patient data with 13 104 records from 53 studies in 40 countries was used to evaluate treatment success of bedaquiline. This dataset was largely composed of adult patients, with only 181 of the 13 104 (1.4%) cases being under 15 years of age.

Paediatric data for bedaquiline were reviewed to explore the extent to which adult data could be extrapolated to children. The focus of this review was on safety and pharmacologic exposure data available from two ongoing paediatric studies of bedaquiline: TMC207-C211 and IMPAACT P1108 (*4*). Assuming that bedaquiline exposure-response (efficacy) profiles could be extrapolated from adults to children, the WHO Guideline Development Group concluded that the bedaquiline doses evaluated in the trials did not appear to produce bedaquiline exposures that would put children aged 6 to 17 years at greater risk of therapeutic failure.

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**Summary of evidence: harms** (from the application)

With regard to harms, the Guideline Development Group concluded that the safety risk of bedaquiline in children aged 6 years and older did not appear to exceed that observed in adults. However, it was noted that children included in the trials were all HIV negative and had limited exposure to other QT-interval prolonging medicines (*4*).

**Additional evidence (not in the application)**

N/A

**WHO Guidelines**

The 2019 *WHO consolidated guidelines on drug-resistant tuberculosis treatment* (*3*) make the following recommendation with regard to bedaquiline:

"Bedaquiline should be included in longer MDR-TB regimens for patients aged 18 years or more (strong recommendation, moderate certainty in the estimates of effect). Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years (conditional recommendation, very low certainty in the estimates of effect)."

The updated guidelines include a weight-based dosage regimen for children 6–17 years:

15–29 kg: 2 x 100 mg tablets once daily for two weeks, then 1 x 100 mg tablet once daily on Monday, Wednesday and Friday for 22 weeks;

>29 kg: 4 x 100 mg tablets once daily for 2 weeks then 1 x 100 mg tablets once daily on Monday, Wednesday and Friday for 22 weeks (equivalent to the adult dose).

**Costs/cost-effectiveness**

Bedaquiline is available via the Global Drug Facility (GDF), at a price of US$ 400 for a 6-month course of adult treatment (*5*). There is a marked differential in the price of bedaquiline between HICs and countries eligible for concessional pricing through the GDF. Prices for a 6-month course of adult treatment have been reported as EUR 26 481 in Italy (*6*), £ 18 880 in the United Kingdom (*7*) and US$ 26 500 in the Republic of Korea (*8*).

**Availability**

Bedaquiline is manufactured by Janssen Pharmaceuticals. It is available to eligible countries through the GDF.

**Other considerations**

The Committee recalled that bedaquiline is associated with an increased risk of QT interval prolongation, which may be further increased when bedaquiline is administered with other medicines that prolong the QT interval. The Committee also noted the potential for drug–drug interactions between bedaquiline and other commonly co-prescribed medicines. These factors should be taken into consideration when bedaquiline is prescribed.

**Committee recommendations**

The Expert Committee recommended the addition of bedaquiline to the complementary list of the EMLc for the treatment of MDR-TB in children aged 6 years and older, in line with updated WHO treatment guidelines. The Committee noted that the extrapolation of evidence from adult data to children suggested therapeutic bedaquiline exposure in children and no increased safety risk.

## References


1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of Essential Medicines and the 5rd WHO Model List of Essential Medicines for Children) (WHO Technical Report Series, No. 994). Geneva: World Health Organization; 2015. Available from https://apps.who.int/iris/bitstream/handle/10665/189763/9789241209946_eng.pdf, accessed 30 October 2019.
2. Global tuberculosis report 2018. Geneva: World Health Organization; 2018. Available from https://apps.who.int/iris/bitstream/handle/10665/274453/9789241565646-eng.pdf, accessed 30 October 2019.
3. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019. Available from https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf, accessed 30 October 2019.
4. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Annexes 3–9. Geneva: World Health Organization; 2019. Available from https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf, accessed 30 October 2019.
5. Stop TB Partnership - Global Drug Facility (GDF) - GDF Products List [website]. (http://www.stoptb.org/gdf/drugsupply/bedaquiline.asp, accessed 22 February 2019).
6. Codecasa LR, Toumi M, D'Ausilio A, Aiello A, Damele F, Termini R, et al. Cost-effectiveness of bedaquiline in MDR and XDR tuberculosis in Italy. J Mark Access Health Policy. 2017;5(1):1283105.
7. Wolfson LJ, Walker A, Hettle R, Lu X, Kambili C, Murungi A, et al. Cost-effectiveness of adding bedaquiline to drug regimens for the treatment of multidrug-resistant tuberculosis in the UK. PLoS One. 2015;10(3):e0120763.
8. Park HY, Ku HM, Sohn HS, Seo HS, Yung Lee H, Hwa Lim K, et al. Cost-effectiveness of Bedaquiline for the Treatment of Multidrug-resistant Tuberculosis in the Republic of Korea. Clin Ther. 2016;38(3):655-67.e1–2.

*Capreomycin and kanamycin – deletion – EML and EMLc*

| | |
|---|---|
| **Capreomycin** | **ATC Code: J04AB30** |
| **Kanamycin** | **ATC Code: J01GB04** |

**Proposal**

The application requested the removal from the EML and EMLc of capreomycin and kanamycin for use in treatment regimens for multidrug-resistant tuberculosis (MDR-TB).

**Applicant**

WHO Global TB Programme

**WHO Technical Department**

Global TB Programme

**EML/EMLc**

EML and EMLc

**Section**

6.2.5 Antituberculosis medicines

**Dose form(s) & strengths(s)**

Capreomycin: Powder for injection 1 g (as sulfate) in vial
Kanamycin: Powder for injection 1 g (as sulfate) in vial

**Core/Complementary**

Complementary

**Individual/Square box listing**

Individual

**Background**

N/A

**Public health relevance** (burden of disease)

N/A

**Summary of evidence: benefits** (from the application)

N/A

**Summary of evidence: harms** (from the application)

N/A

**Additional evidence (not in the application)**

N/A

**WHO Guidelines**

The proposed deletions are in alignment with recommendations in the 2019 update of the *WHO consolidated guidelines on drug-resistant tuberculosis treatment* (*1*). One of the key outcomes of the updated guidelines was a re-classification of medicines recommended for inclusion in regimens for MDR-TB/RR-TB.

Capreomycin and kanamycin had previously been recommended as Group B, second-line injectable agents along with amikacin and streptomycin (*2*). The 2019 guidelines no longer recommend the use of capreomycin and kanamycin as treatment options. Use of capreomycin and kanamycin was associated with poorer outcomes when compared with regimens not containing these medicines in the latest data analysis.

**Costs/cost-effectiveness**

N/A

**Availability**

N/A

**Other considerations**

Amikacin and streptomycin remain available on the Model List for use in treatment regimens for drug-resistant TB.

**Committee recommendations**

The Expert Committee recommended the deletion of capreomycin and kanamycin from the complementary list of the EML and EMLc, noting the advice of the WHO Global TB Programme that their use is no longer recommended in WHO guidelines due to evidence that regimens involving these agents were associated with worse outcomes compared with regimens that did not include them, and that fully oral regimens should be preferred for most patients.

## References

1. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019. Available from https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf, accessed 30 October 2019.

2. WHO treatment guidelines for drug-resistant tuberculosis, 2016 update (WHO/HTM/TB/2016.4). Geneva,World Health Organization. 2016. Available from https://apps.who.int/iris/bitstream/handle/10665/250125/9789241549639-eng.pdf, accessed 30 October 2019.

*Delamanid – change age restriction – EMLc*

| Delamanid | ATC Code: J04AK06 |
|---|---|

**Proposal**

The application requested a change to the age restriction that applies to the listing of delamanid on the Model Lists.

**Applicant**

WHO Global TB Programme

**WHO Technical Department**

Global TB Programme

**EML/EMLc**

EML and EMLc

**Section**

6.2.5 Antituberculosis medicines

**Dose form(s) & strengths(s)**

Tablet 50 mg

**Core/Complementary**

Complementary

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

In 2017, delamanid was added to the EMLc as a reserve second-line drug for multidrug-resistant tuberculosis (MDR-TB) in children aged 6–17 years. The current Model Lists include an age limit for delamanid of >6 years.

**Public health relevance** (burden of disease)

N/A

**Summary of evidence: benefits** (from the application)

As part of the MDR-TB guideline development process, paediatric data for delamanid were reviewed to examine whether the recommendations for delamanid use in children could be lowered to children under 6 years of age.

Safety and pharmacologic exposure data were available from ongoing paediatric studies (*1*). The WHO Guideline Development Group (GDG) concluded that based on the pharmacokinetic data, exposure profiles in children aged 3 to 5 years were comparable to adults and no higher than in children aged 6 and older. From the available data, there were no safety signals distinct from those reported in adults observed in children aged three to five years. The GDG concluded that extrapolations of efficacy and safety should be restricted to children 3 years of age and older.

**Summary of evidence: harms** (from the application)

N/A

**Additional evidence** (not in the application)

Children aged 3 to 5 years in the trials were administered delamanid at a dose of 25 mg twice daily, using a scored, dispersible paediatric formulation that is not currently available.

The only source of delamanid is the 50 mg adult formulation which poses potential problems when considered for children under 6 years of age.

The adult and paediatric formulations of delamanid are not bioequivalent or interchangeable. Equal doses of each formulation achieve different concentrations in the body. Substituting the adult formulation for the paediatric formulation will result in higher delamanid exposures than would be expected from the paediatric formulation.

In addition, splitting or crushing of the adult tablet for administration to children will affect the stability of the medicine and result in pill fragments that are exceedingly bitter.

**WHO Guidelines**

The 2019 *WHO consolidated guidelines on drug-resistant tuberculosis treatment* (*2*) make the following recommendation with regard to delamanid: "Delamanid may be included in the treatment of MDR-TB/RR-TB patients aged 3 years or more on longer regimens (conditional recommendation, moderate certainty in the estimates of effect."

**Costs/cost-effectiveness**

No information provided.

**Availability**

Delamanid 50 mg tablets are manufactured by Otsuka Pharmaceutical, Japan. They are available to eligible countries through the Global Drug Facility. The 25 mg paediatric dispersible tablet formulation is not currently commercially available.

**Other considerations**

N/A

**Committee recommendations**

The Expert Committee did not recommend the requested change to the age restriction that applies to the listing of delamanid on the Model Lists. The Committee noted that pharmacokinetic data used to inform the guideline development process used a different formulation of delamanid to that currently included on the Model Lists, which is not commercially available at this time, nor has it been demonstrated to be bioequivalent to the available, listed formulation.

## References

1. WHO consolidated guidelines on drug-resistant tuberculosis treatment (Annexes 3–9). Geneva: World Health Organization; 2019. Available from https://apps.who.int/iris/bitstream/handle/10665/311390/WHO-CDS-TB-2019.3-eng.pdf, accessed 30 October 2019.
2. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019. Available from https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf, accessed 30 October 2019.

*Group C antibiotics for MDR-TB – new indication – EML and EMLc*

| **Group C antibiotics for MDR-TB** | |
|---|---|
| **Amoxicillin + clavulanic acid** | **ATC Code: J01CR02** |
| **Imipenem + cilastatin** | **ATC Code: J01DH51** |
| **Meropenem** | **ATC Code: J01CR02** |

**Proposal**

The application requested listing on the complementary list for the new indication of treatment of multidrug-resistant tuberculosis (MDR-TB) of:

- amoxicillin + clavulanic acid (EML and EMLc)
- imipenem + cilastatin; (EML only) and
- meropenem (EML and EMLc)

**Applicant**

WHO Global TB Programme

**WHO Technical Department**

Global TB Programme

**EML/EMLc**

EML and EMLc
(EML only for imipenem + cilastatin)

**Section**

6.2.5 Antituberculosis medicines

**Dose form(s) & strengths(s)**

Amoxicillin + clavulanic acid:

- tablet: 500 mg (as trihydrate) + 125 mg (as potassium salt);
- powder for oral liquid: 125 mg + 31.25 mg per 5 mL; 250 mg + 62.5 mg per 5 mL

Imipenem + cilastatin:

- powder for injection: 250 mg (as monohydrate) + 250 mg (as sodium salt); 500 mg (as monohydrate) + 500 mg (as sodium salt) in vial

Meropenem:

- powder for injection 500 mg; 1 g (anhydrous) in vial

**Core/Complementary**

Complementary

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

These medicines have not been previously considered for use in MDR-TB. Amoxicillin + clavulanic acid and meropenem are currently included in the EML and EMLc for use as first- and second-choice treatment of specified infectious syndromes. Imipenem + cilastatin is noted as an acceptable alternative to meropenem for most clinical situations. Amoxicillin + clavulanic acid is classified as an AWaRe Access group antibiotic, while meropenem (and other carbapenems) are categorized as AWaRe Watch group antibiotics.

**Public health relevance** (burden of disease)

It is estimated that 558 000 new MDR-/RR-TB cases emerged in the world in 2017 and 230 000 patients died of this form of tuberculosis (*1*). Between 25 000 and 32 000 children are estimated to develop MDR-TB each year (*2*). Many of these cases go undetected and are not placed on appropriate treatment, increasing the risk of transmission of drug-resistant strains and death. In 2017, countries reported that about 139 000 people started MDR-TB treatment worldwide. The effectiveness of these efforts varies considerably, and data reported for treatment outcomes in recent years show that only about half the MDR-/RR-TB patients complete their treatment successfully. Among patients with XDR-TB the likelihood of successful outcomes is even lower. Patients who are not cured – often because their treatment fails or is interrupted – risk persistent disease or death. Given these low levels of treatment success, all efforts must be made to ensure that effective medications to treat drug-resistant TB become more widely available to the patients who need them, particularly in low-resource settings that carry the largest burden of MDR-/RR-TB (*1*).

The most recent data analysis conducted for the 2018 WHO MDR-TB treatment guidelines revision attests to the effectiveness of the carbapenems – imipenem + cilastatin and meropenem – in patients for whom other agents cannot be used to compose an adequate regimen, such as those with strains resistant to fluoroquinolones or who develop drug intolerance (*3*).

**Summary of evidence: benefits** (from the application)

A typical longer MDR-TB regimen starts with a combination of at least four TB medicines considered to be effective, primarily from Groups A and B (Table 1). The three proposed medications have a particular role in the composition of

longer treatment regimens for patients with MDR-/RR-TB, particularly those who have additional resistance or intolerance to one or more of the agents in Groups A and B. In such cases, the regimen is strengthened by Group C agents. Both carbapenems in this application belong to Group C and must be administered with clavulanic acid, which is only available in formulations combined with amoxicillin. Amoxicillin + clavulanic acid is not considered an additional effective TB agent, and should not be used without imipenem + cilastatin or meropenem.

Table 1
**Grouping of medicines recommended for use in longer MDR-TB regimens (3)**

| Groups | Medicine |
|---|---|
| Group A | Levofloxacin or moxifloxacin |
| | Bedaquiline |
| | Linezolid |
| Group B | Clofazimine |
| | Cycloserine or terizidone |
| Group C | Ethambutol |
| | Delamanid |
| | Pyrazinamide |
| | Imipenem + cilastatin or meropenem |
| | Amikacin (or streptomycin) |
| | Ethionamide or prothionamide |
| | p-aminosalicylic acid |

*Mycobacterium tuberculosis* (MTB) is resistant to most beta-lactam antibiotics because it contains the gene blaC, which encodes an extended spectrum beta-lactamase (*4*). BlaC beta-lactamase is only transiently inhibited by most beta-lactamase inhibitors (i.e. sulbactam and tazobactam) except for clavulanic acid, which irreversibly inhibits it (*4*, *5*). The use of amoxicillin + clavulanic acid against MTB has had mixed results. Of note, clavulanic acid is not available commercially without amoxicillin. An early bactericidal activity (EBA) study from South Africa showed no benefit of amoxicillin + clavulanic acid over the control (*6*). A study from Pakistan examining the minimum inhibitory concentration (MIC) of drug-resistant clinical isolates of MTB found that 98% of the isolates were resistant to amoxicillin + clavulanic acid (*7*). Another EBA study showed that over 7 days,

amoxicillin + clavulanic acid reduced the sputum colony-forming units (CFU) by an average of 0.1 log10 cfu/mL per day (in comparison, isoniazid reduced CFU by 0.27 log10 cfu/mL per day) (*8*). However, the mild efficacy of amoxicillin + clavulanic acid may not be shared by all the beta-lactam antibiotics. Meropenem is hydrolyzed five times slower than amoxicillin + clavulanic acid by blaC (*4*, *5*) and there have been several studies evaluating its activity (combined with clavulanic acid) against MTB (*9*). *In vitro* studies have shown that the combination of clavulanic acid improves the MIC of meropenem from 8 to 1 µg/mL (*10*), that this combination sterilizes aerobic and anaerobic MTB cultures and was active against drug susceptible and XDR-TB strains (*5*). Results have been mixed with respect to the effect of meropenem + clavulanic acid on mouse mortality and on MTB CFUs in the lung and spleen (*10–13*). The combination of imipenem + cilastatin with clavulanic acid also has activity against MTB, although in some studies meropenem + clavulanic acid seems to be superior (*5*).

Human data are sparse (case-control studies, case reports) (*11*, *14*), but meropenem with clavulanic acid as part of regimens (usually also containing linezolid) for patients with MDR-TB and XDR-TB has shown improved culture conversion and survival (*15–17*).

The updated WHO guidelines reported the relative and absolute effects for treatment failure or relapse and death (versus treatment success) for medicines used in longer regimens from the main IPD-MA dataset of 13 104 records from 53 studies in 40 countries (*3*, *18*).

For imipenem + cilastatin or meropenem, the adjusted odds ratio for treatment failure/relapse versus treatment success was 0.4 (95%CI 0.2 to 0.7) (n=206). In absolute terms, 11 fewer (95%CI 19 to 3 fewer) treatment failures/relapses per 100 patients treated (very low certainty evidence). For death versus treatment success the adjusted OR was 0.2 (95%CI 0.1 to 0.5) (n=204). In absolute terms, 18 fewer (95%CI 27 to 8 fewer) deaths per 100 patients treated (very low certainty evidence).

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**Summary of evidence: harms** (from the application)

Evidence for the safety of these medicines has been considered previously. The common and uncommon adverse effects associated with these medicines are well known.

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**Additional evidence** (not in the application)

N/A

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**WHO Guidelines**

The 2019 *WHO consolidated guidelines on drug-resistant tuberculosis treatment* (*3*) include the following recommendations regarding longer treatment regimens for MDR-/RR-TB:

- In MDR-/RR-TB patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of treatment after bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it (conditional recommendation, very low certainty in the estimates of effect).
- Imipenem + cilastatin or meropenem may be included in the treatment of MDR-/RR-TB patients on longer regimens (conditional recommendation, very low certainty in the estimates of effect).

**Costs/cost-effectiveness**

Reported costs from the Global Drug Facility product catalogue (*19*) are:

Imipenem + cilastatin 500 mg + 500 mg powder for injection: US$ 31–36/10 vials

Meropenem 1 g powder for injection: US$ 3.70/vial

Amoxicillin + clavulanic acid 500 mg + 125 mg tablets: US$ 10.21–13.28/ 100 tablets

Amoxicillin + clavulanic acid 125 mg/31.25 mg oral suspension: US$ 1.21/bottle

**Availability**

The proposed medicines are widely available globally and already included for other indication on the EML and EMLc.

**Other considerations**

N/A

**Committee recommendations**

The Expert Committee recommended the inclusion of meropenem and of amoxicillin + clavulanic acid on the complementary list of the EML and EMLc for the new indication of use in the treatment of MDR-TB. The Committee recommended that imipenem could be considered as an alternative to meropenem for use in adults, and that the EML should note this accordingly.

The Committee noted the limited clinical evidence base, and the very low certainty in the estimates of effect associated with the carbapenems in MDR-TB treatment regimens. However, the Committee accepted the public health need for effective treatments for MDR-TB and considered that the updated WHO guideline recommendations would be supported by the inclusion of these medicines on the EML.

The Committee expressed some concern in relation to increased use of carbapenem antibiotics in the empiric treatment of MDR-TB and the development of carbapenem resistance, and recommended that ongoing monitoring for the development of resistance be undertaken.

## References


1. Global tuberculosis report 2018. Geneva: World Health Organization; 2018. Available from https://apps.who.int/iris/bitstream/handle/10665/274453/9789241565646-eng.pdf, accessed 30 October 2019.
2. Jenkins HE, Yuen CM. The burden of multidrug-resistant tuberculosis in children. Int J Tuberc Lung Dis. 2018;22(5):3–6.
3. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019. Available from https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf, accessed 26 September 2019.
4. Hugonnet JE, Blanchard JS. Irreversible inhibition of the Mycobacterium tuberculosis beta-lactamase by clavulanate. Biochemistry. 2007;46(43):11998–2004.
5. Hugonnet JE, Tremblay LW, Boshoff HI, Barry CE, 3rd, Blanchard JS. Meropenem-clavulanate is effective against extensively drug-resistant Mycobacterium tuberculosis. Science. 2009; 323(5918):1215–8.
6. Donald PR, Sirgel FA, Venter A, Parkin DP, Van de Wal BW, Barendse A et al. Early bactericidal activity of amoxicillin in combination with clavulanic acid in patients with sputum smear-positive pulmonary tuberculosis. Scand J Infect Dis. 2001;33(6):466–9.
7. Ahmed I, Jabeen K, Inayat R, Hasan R. Susceptibility testing of extensively drug-resistant and pre-extensively drug-resistant Mycobacterium tuberculosis against levofloxacin, linezolid, and amoxicillin-clavulanate. Antimicrob Agents Chemother. 2013;57(6):2522–5.
8. Chambers HF, Kocagoz T, Sipit T, Turner J, Hopewell PC. Activity of amoxicillin/clavulanate in patients with tuberculosis. Clin Infect Dis. 1998;26(4):874–7.
9. Gonzalo X, Drobniewski F. Is there a place for beta-lactams in the treatment of multidrug-resistant/extensively drug-resistant tuberculosis? Synergy between meropenem and amoxicillin/clavulanate. J Antimicrob Chemother. 2013;68(2):366–9.
10. Solapure S, Dinesh N, Shandil R, Ramachandran V, Sharma S, Bhattacharjee D et al. In vitro and in vivo efficacy of beta-lactams against replicating and slowly growing/nonreplicating Mycobacterium tuberculosis. Antimicrob Agents Chemother. 2013;57(6):2506–10.
11. Chambers HF, Turner J, Schecter GF, Kawamura M, Hopewell PC. Imipenem for treatment of tuberculosis in mice and humans. Antimicrob Agents Chemother. 2005;49(7):2816–21.
12. Veziris N, Truffot C, Mainardi JL, Jarlier V. Activity of carbapenems combined with clavulanate against murine tuberculosis. Antimicrob Agents Chemother. 2011;55(6):2597–600.
13. England K, Boshoff HI, Arora K, Weiner D, Dayao E, Schimel D, et al. Meropenem-clavulanic acid shows activity against Mycobacterium tuberculosis in vivo. Antimicrob Agents Chemother. 2012;56(6):3384–7.
14. Dooley KE, Obuku EA, Durakovic N, Belitsky V, Mitnick C, Nuermberger EL. World Health Organization group 5 drugs for the treatment of drug-resistant tuberculosis: unclear efficacy or untapped potential? J Infect Dis. 2013;207(9):1352–8.

15. De Lorenzo S, Alffenaar JW, Sotgiu G, Centis R, D'Ambrosio L, Tiberi S et al. Efficacy and safety of meropenem-clavulanate added to linezolid-containing regimens in the treatment of MDR-/XDR-TB. Eur Respir J. 2013;41(6):1386–92.

16. Payen MC, De Wit S, Martin C, Sergysels R, Muylle I, Van Laethem Y et al. Clinical use of the meropenem-clavulanate combination for extensively drug-resistant tuberculosis. Int J Tuberc Lung Dis. 2012;16(4):558–60.

17. Dauby N, Muylle I, Mouchet F, Sergysels R, Payen MC. Meropenem/clavulanate and linezolid treatment for extensively drug-resistant tuberculosis. Pediatr Infect Dis J. 2011;30(9):812–3.

18. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Annexes 3–9. Geneva: World Health Organization; 2019. Available from https://apps.who.int/iris/bitstream/handle/10665/311390/WHO-CDS-TB-2019.3-eng.pdf, accessed 30 October 2019.

18. Stop TB Partnership | Global Drug Facility (GDF) – GDF Product Catalogue [website]. [cited 2017 Jul 7]. (http://www.stoptb.org/gdf/drugsupply/pc2.asp?CLevel=2&CParent=4, accessed 26 September 2019).

*Isoniazid – new formulation (oral liquid) – EMLc*

**Isoniazid** **ATC Code: J04AC01**

**Proposal**

The application requested addition of a new strength formulation of isoniazid oral liquid to the core list of the EMLc for treatment and preventive therapy of tuberculosis (TB) in infants and children.

**Applicant**

INCURE CU

**WHO Technical Department**

Comments on the application were received from the WHO Global TB Programme. The technical unit highlighted the current WHO recommendations and available alternative treatment options for latent tuberculosis infection (LTBI) and advised that the addition to the EMLc of the proposed new strength oral liquid formulation of isoniazid may not add value.

**EML/EMLc**

EMLc

**Section**

6.2.4 Antituberculosis medicines

**Dose form(s) & strengths(s)**

Oral liquid 100 mg/5 mL

**Core/Complementary**

Core

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Isoniazid oral liquid 50 mg/5 mL has been included on the EMLc since 2007. Solid oral dose forms of isoniazid have been included on the EML since 1977.

The recommended dose for isoniazid in children for treatment of TB or isoniazid preventive treatment (IPT) is 10 mg/kg per day (range 7–15 mg/kg); maximum dose 300 mg/day (*1*).

**Public health relevance** (burden of disease)

About 1.7 billion people globally are estimated to have a latent TB infection, and are thus at risk of developing active TB disease during their lifetime (*2*).

IPT for LTBI is indicated for an asymptomatic contact or a contact in whom TB disease has been excluded if the contact is less than 5 years of age or who is living with HIV (regardless of age). Preventive therapy for young children with LTBI who have not yet developed TB disease will greatly reduce the likelihood of TB disease developing during childhood *(*3).

Six months' daily monotherapy with isoniazid is the standard treatment for both adults and children living in countries with either high or low TB incidence (*4*).

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**Summary of evidence: benefits** (from the application)

Several systematic reviews have demonstrated the preventive efficacy of isoniazid monotherapy. A systematic review of RCTs involving people living with HIV showed that isoniazid monotherapy reduces the overall risk for TB by 33% (RR 0.67; 95%CI 0.51 to 0.87), and the preventive efficacy reached 64% for people with a positive TST (RR 0.36; 95%CI 0.22 to 0.61). Furthermore, the efficacy of the 6-month regimen was not significantly different from that of 12 months' daily isoniazid monotherapy (RR 0.58; 95%CI 0.3 to 1.12) (*5*).

A recent systematic review of RCTs also showed a significantly greater reduction in TB incidence among participants given the 6-month regimen than in those given a placebo (odds ratio (OR), 0.65; 95%CI 0.50 to 0.83) (*6*).

This application requested only the addition of a new strength formulation of isoniazid oral liquid.

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**Summary of evidence: harms** (from the application)

The safety profile of isoniazid is well known. Evidence for the safety of isoniazid was evaluated at the time of original listing.

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**Additional evidence** (not in the application)

N/A

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**WHO Guidelines**

The 2018 WHO guidelines for programmatic management of latent tuberculosis (*4*) make the following recommendations regarding TB preventive therapy in children:

- Infants aged <12 months living with HIV who are in contact with a case of TB and are investigated for TB should receive six months of isoniazid preventive treatment (IPT) if the investigation shows

no TB disease (*Strong recommendation*, *moderate quality evidence*. *Updated recommendation*).

- Children aged >12 months living with HIV who are considered unlikely to have TB disease on the basis of screening for symptoms and who have no contact with a case of TB should be offered six months of IPT as part of a comprehensive package of HIV prevention and care if they live in a setting with a high prevalence of TB (*Strong recommendation*, *low quality evidence*. *Existing recommendation*).
- All children living with HIV who have successfully completed treatment for TB disease may receive isoniazid for an additional six months (*Conditional recommendation*, *low quality evidence*. *Existing recommendation*).
- HIV-negative children aged under 5 years who are household contacts of people with bacteriologically confirmed pulmonary TB and who are found not to have active TB on an appropriate clinical evaluation or according to national guidelines should be given TB preventive treatment (*Strong recommendation*, *high quality evidence*. *Updated recommendation*).
- In countries with a low TB incidence, adults, adolescents and children who are household contacts of people with bacteriologically confirmed pulmonary TB should be systematically tested and treated for LTBI (*Strong recommendation*, *high to moderate quality evidence*. *Existing recommendation*).
- In countries with a high TB incidence, children aged under 5 years, adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB who are found not to have active TB by an appropriate clinical evaluation or according to national guidelines may be given TB preventive treatment (*Conditional recommendation*, *low quality evidence*. *New recommendation*).

**Costs/cost-effectiveness**

No information was provided in the application regarding the cost of this product.

**Availability**

The application stated that the product is available in Azerbaijan, Georgia, Kazakhstan, Kenya, Kyrgyzstan, Moldova, Namibia, Tajikistan, Turkmenistan, Uganda, Ukraine and Uzbekistan.

No information was provided on the regulatory status of this product. It does not appear to have current regulatory approval from a stringent regulatory authority (SRA).

Isoniazid oral liquid (any strength) is not currently included in the Stop TB Partnership/Global Drug Facility medicine catalogue.

### Other considerations

The application stated that the currently available 50 mg/mL oral liquid formulation is not available in many countries, and is less convenient than the proposed strength formulation, requiring a greater volume to deliver the prescribed dose.

The application stated that dispersible tablet formulations have limitations insofar as they cannot always meet weight-based dosing requirements as they cannot be divided.

A separate application from the Stop TB Partnership/Global Drug Facility requested listing of isoniazid 100 mg dispersible tablet. Unlike isoniazid oral liquid, quality-assured isoniazid dispersible tablet products are available through the GDF.

### Committee recommendations

The Expert Committee did not recommend the addition of a new strength formulation of isoniazid oral liquid to the core list of the EMLc for treatment and preventive therapy of tuberculosis in infants and children. The Committee considered that quality-assured dispersible tablet formulations of TB medicines represent a preferred treatment option to oral liquid formulations. The Committee considered that an additional strength oral liquid formulation of isoniazid would be unlikely to add value to patients or TB treatment programmes.

In addition, with the separate recommendation made at this meeting to add isoniazid 100 mg dispersible tablets to the EMLc, the Committee recommended that the existing isoniazid oral liquid formulation (50 mg/mL) could be considered for removal from the EMLc in 2021.

## References

1. Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2nd edition. Geneva: World Health Organization; 2014. Available from https://www.who.int/tb/publications/childtb_guidelines/en/, accessed 30 October 2019.
2. Global tuberculosis report 2018. Geneva: World Health Organization; 2018. Available from https://apps.who.int/iris/bitstream/handle/10665/274453/9789241565646-eng.pdf, accessed 30 October 2019.
3. Smieja MJ, Marchetti CA, Cook DJ, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. Cochrane Database Syst Rev. 2000(2):CD001363.

4. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva: World Health Organization; 2018.
5. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database Syst Rev. 2010(1):CD000171.
6. Zenner D, Beer N, Harris RJ, Lipman MC, Stagg HR, van der Werf MJ. Treatment of Latent Tuberculosis Infection: An Updated Network Meta-analysis. Ann Intern Med. 2017;167(4):248–55.

## 6.4 Antiviral medicines

### 6.4.2 Antiretrovirals

*Antiretrovirals – formulations for deletion – EML and EMLc*

**ARV formulations for deletion** **ATC Code: various**

**Proposal**

The application requested the deletion of various antiretroviral (ARV) formulations from the core list of the EML and EMLc.

**Applicant**

WHO HIV Department

**WHO Technical Department**

HIV Department

**EML/EMLc**

EML and EMLc

**Section**

6.4.2 Antiretrovirals

**Dose form(s) & strengths(s)**

Zidovudine: tablet (dispersible, scored) 60 mg

Abacavir + lamivudine: tablet (dispersible, scored) 60 mg (as sulfate) + 30 mg

Ritonavir: oral liquid 400 mg/5 mL

Raltegravir: tablet (chewable) 100 mg

**Core/Complementary**

Core

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Separate applications to the 2019 Expert Committee requested the inclusion of new formulations of ritonavir (oral powder 100 mg) and raltegravir (oral granules 100 mg).

**Public health relevance** (burden of disease)

N/A

**Summary of evidence: benefits** (from the application)

Recommendations were made by the WHO HIV Department to delete the antiretroviral formulations from the EML and EMLc in order to achieve alignment between the 2018 WHO interim guidelines for antiretroviral regimens (*1*), and *The 2018 optimal formulary and limited-use list for paediatric ARVs* (*2*).

Zidovudine (AZT) 60 mg dispersible scored tablet was removed from the latest limited-use list. Zidovudine 60 mg is available in dual fixed-dose combination formulations with lamivudine that can be combined with an abacavir 60 mg dispersible scored tablet to deliver a triple nucleoside regimen during TB treatment.

Abacavir + lamivudine (ABC/3TC) 60 mg + 30 mg dispersible scored tablet was removed from the latest optimal formulary. It has been replaced with ABC/3TC 120 mg + 60 mg dispersible scored tablet to minimize market fragmentation while decreasing pill burden for older children. The double strength formulation was included on the EML and EMLc in 2017.

Ritonavir oral liquid 400 mg/5 mL was removed from the latest limited-use List. Cold chain requirements, poor palatability and short shelf-life has limited use of this product. Alternative formulations of ritonavir are preferred.

Raltegravir 100 mg scored chewable tablets were replaced by the 25 mg strength on the latest optimal formulary in order to optimize dosing flexibility to provide raltegravir-based regimens across all weight bands for first- and second-line treatment.

**Summary of evidence: harms** (from the application)

N/A

**Additional evidence** (not in the application)

N/A

**WHO Guidelines**

The proposed deletions are in alignment with recommendations in the 2018 WHO guidelines and paediatric ARV formulary.

**Costs/cost-effectiveness**

N/A

**Availability**

N/A

**Other considerations**

- Zidovudine oral solution 50 mg/5 mL remains included on the Model Lists for postnatal prophylaxis or neonatal use.
- Zidovudine in fixed-dose combination with nevirapine and/or lamivudine remains included on the Model Lists.
- Abacavir + lamivudine 120 mg + 60 mg scored dispersible tablets remain included on the Model Lists.
- Ritonavir heat-stable tablets 25 mg and 100 mg remain included on the Model Lists. A separate recommendation was made at this meeting to add ritonavir 100 mg oral powder.
- Raltegravir tablets 400 mg and chewable tablets 25 mg remain included on the Model Lists. A separate recommendation was made at this meeting to add raltegravir 100 mg oral granules.

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**Committee recommendations**

The Committee recommended deletion of zidovudine 60 mg dispersible scored tablet and of abacavir + lamivudine 60 mg + 30 mg dispersible scored tablet from the EML and EMLc, noting they are no longer included in the current WHO guidelines for paediatric HIV treatment, and that suitable alternatives are already included on the Model Lists and available for use.

The Committee recommended that ritonavir oral liquid and raltegravir 100 mg chewable tablets be retained on the Model Lists at this time. The Committee considered that until the availability is well established of the alternative formulations of these medicines recommended in separate applications to this meeting, (i.e. ritonavir 100 mg oral powder and raltegravir 100 mg oral granules), deletion of the existing formulations could be premature.

The existing formulations could be flagged for deletion without further discussion in 2021 unless an application is received in support of their retention.

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**Committee recommendations**

The Committee recommended deletion of zidovudine 60 mg dispersible scored tablet and of abacavir + lamivudine 60 mg + 30 mg dispersible scored tablet from the EML and EMLc, noting they are no longer included in the current WHO guidelines for paediatric HIV treatment, and that suitable alternatives are already included on the Model Lists and available for use.

The Committee recommended that ritonavir oral liquid and raltegravir 100 mg chewable tablets be retained on the Model Lists at this time. The Committee considered that until the availability is well established of the alternative formulations of these medicines recommended in separate

applications to this meeting, (i.e. ritonavir 100 mg oral powder and raltegravir 100 mg oral granules), deletion of the existing formulations could be premature.

The existing formulations could be flagged for deletion without further discussion in 2021 unless an application is received in support of their retention.

## References

1. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines, supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. World Health Organization, Geneva. December, 2018. Available from https://apps.who.int/iris/bitstream/handle/10665/277395/WHO-CDS-HIV-18.51-eng.pdf?ua=1, accessed 26 September 2019.
2. The 2018 optimal formulary and limited-use list for paediatric ARVs. Geneva, Switzerland: World Health Organization; 2018. Available from http://apps.who.int/iris/bitstream/handle/10665/273153/WHO-CDS-HIV-18.15-eng.pdf?ua=1, accessed 26 September 2019.

### 6.4.2.3 *Protease inhibitors*

*Ritonavir – new formulation – EML and EMLc*

| Ritonavir | ATC Code: J05AE03 |
|---|---|

**Proposal**

The application requested the addition of a new formulation of ritonavir (RTV) to the core list of the EML and EMLc for the treatment of HIV infection.

**Applicant**

WHO HIV Department

**WHO Technical Department**

HIV Department

**EML/EMLc**

EML and EMLc

**Section**

6.4.2.3 Protease inhibitors

**Dose form(s) & strengths(s)**

Oral powder 100 mg in sachet

**Core/Complementary**

Core

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Single-agent ritonavir (RTV) has been included on the EMLc since 2007. Currently listed formulations are oral liquid 400 mg/5 mL and heat-stable tablets 25 mg and 100 mg.

In a separate application to the 2019 Expert Committee, ritonavir oral liquid was proposed for deletion from the EML and EMLc.

**Public health relevance** (burden of disease)

Despite an impressive reduction in mother-to-child transmission of HIV in recent years, 180 000 new paediatric infections occurred in 2017. There are now 1.8 million children living with HIV, the vast majority in sub-Saharan Africa (*1*).

Evidence shows that in the absence of antiretroviral therapy (ART), over 50% of HIV-infected infants progress to AIDS and death by the age of 2 years (*2*), but the introduction of paediatric ART has changed HIV infection in children from a life-threatening illness to a chronic but manageable infection. Despite recognition of the advantages of early treatment, paediatric treatment coverage still only reaches 52% of children eligible for treatment (*1*) and in 2017 an estimated 110 000 HIV/AIDS-related deaths occurred in children <15 years of age (*3*).

Children are at particular risk of acquiring TB, although good epidemiologic data has been difficult to collect. A 2016 systematic review and meta-analysis of opportunistic and other infections among HIV-infected children in LMICs confirmed a high incidence rate (12.3% in ART-naive and 8.8% in ART-exposed) of TB co-infection in this population (*4*). Among children with TB, the WHO estimates that HIV prevalence, in countries with moderate to high prevalence, ranges from 10 to 60% with the variation in rates depending on the background rates of HIV infection (*5*).

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**Summary of evidence: benefits** (from the application)

RTV is used only for pharmacologic boosting of other protease inhibitors (PI). The amount of RTV used depends on the PI used as the active ARV, but most PIs currently recommended as second- or third-line antiretroviral therapy (ART) require 100 mg of RTV combined with the adult dose of the PI. Paediatric patients may use differing amounts of RTV in boosted PI regimens based on their weight.

Evidence supporting the use of RTV as a pharmacologic booster for second- and third-line PIs has previously been accepted by the EML which notes: "Ritonavir is recommended for use in combination as a pharmacological booster, and not as an antiretroviral in its own right."

Since 2010, WHO has recommended the approach of 'super-boosting' LPV/r with additional ritonavir (RTV) (1:1 instead of 4:1 LPV/r ratio, i.e. equal doses of LPV and RTV) to manage rifampicin-based TB co-treatment in children on an LPV/r-based regimen (*6*). Although HIV therapy is life-long, the use of the RTV super-boosted LPV/r regimen is only used for the duration of TB treatment with rifampicin.

A retrospective review of ART regimens and outcomes in HIV/TB coinfected children younger than 2 years in South Africa suggested that super-boosted LPV/r led to better outcomes and less toxicity than earlier PI regimens (*7*). The adequacy of the super-boosted regimen was confirmed in a pharmacokinetic study conducted in South Africa, which demonstrated that LPV trough concentrations in children receiving super-boosted LPV/r and rifampicin were non-inferior to LPV concentrations in children off TB therapy (*8*).

RTV oral powder is currently listed as a limited use formulation on the optimal paediatric ARV formulary for superboosting of LPV/r during TB co-treatment and boosting non-coformulated PIs (*9*).

**Summary of evidence: harms** (from the application)

Evidence for the safety of ritonavir has been considered previously.

The adverse event profile of ritonavir observed during paediatric clinical trials has been reported as similar to that for adult patients. Vomiting, diarrhoea and skin rash/allergy were the only drug-related clinical adverse events of moderate to severe intensity observed in greater than or equal to 2% of paediatric patients enrolled in clinical trials. Grade 3–4 laboratory abnormalities occurring in greater than 3% of paediatric patients who received treatment with ritonavir either alone or in combination with reverse transcriptase inhibitors were neutropenia (9%), hyperamylasaemia (7%), thrombocytopenia (5%), anaemia (4%), and elevated aspartate aminotransferase (AST) (3%) (*10*).

The South African retrospective study evaluating PI-based ART in children younger than 2 years of age, also receiving TB treatment, concluded there were only few treatment interruptions due to toxicity. This suggests that the use of boosted LPV/r and TB treatment in this group was generally well tolerated. The authors also noted there were no significant differences in the proportions of children with Grade 3/4 alanine aminotransferase (ALT) elevations in the TB cotreatment groups while receiving TB treatment compared to children on LPV/r alone (*7*).

**Additional evidence** (not in the application)

N/A

**WHO Guidelines**

WHO guidelines for paediatric HIV treatment recommend the approach of 'super-boosting' LPV/r with additional RTV (1:1 instead of 4:1 LPV/r ratio, i.e. equal doses of LPV and RTV) to manage rifampicin-based TB cotreatment in children on an LPV/r-based regimen (*6*).

**Costs/cost-effectiveness**

No cost or cost-effectiveness information is currently publicly available for ritonavir oral powder.

The manufacturer has made a general commitment to employ market-specific pricing strategies as part of their commitment to access to medicines (*11*).

**Availability**

Ritonavir oral powder is available internationally from Abbvie Inc. Generic brands are not currently available.

**Other considerations**

N/A

**Committee recommendations**

The Expert Committee recommended the addition of the new formulation of ritonavir oral powder 100 mg to the core list of the EML and EMLc for the treatment of HIV infection, in line with recommendations in current WHO guidelines, noting the importance of the availability of quality, age-appropriate paediatric dosage forms of antiretroviral medicines.

## References


1. Global AIDS Update 2018 – Miles to Go, Breaking Barriers, Righting Injustices. Geneva: Joint United Nations Programme on HIV/AIDS; 2018. Available from http://www.unaids.org/sites/default/files/media_asset/miles-to-go_en.pdf, accessed 26 September 2019.
2. Newell ML, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. Lancet. 2004;364(9441):1236–43.
3. UNAIDS Core Epidemiology Slides. Geneva: Joint United Nations Programme on HIV/AIDS; 2018. Available from http://www.unaids.org/en/resources/documents/2018/core-epidemiology-slides, accessed 26 September 2019.
4. B. Lajoie MR, Drouin O, Bartlett G, Nguyen Q, Low A, Gavriilidis G, et al. Incidence and Prevalence of Opportunistic and Other Infections and the Impact of Antiretroviral Therapy Among HIV-infected Children in Low- and Middle-income Countries: A Systematic Review and Meta-analysis. Clin Infect Dis. 2016;62(12):1586–94.
5. Venturini E, Turkova A, Chiappini E, Galli L, de Martino M, Thorne C. Tuberculosis and HIV co-infection in children. BMC Infect Dis. 2014;14 Suppl 1:S5.
6. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach - Second edition. Geneva: World Health Organization; 2016. Available from http://www.who.int/hiv/pub/arv/arv-2016/en/, accessed 26 September 2019.
7. Frohoff C, Moodley M, Fairlie L, Coovadia A, Moultrie H, Kuhn L, et al. Antiretroviral therapy outcomes in HIV-infected children after adjusting protease inhibitor dosing during tuberculosis treatment. PLoS One. 2011;6(2):e17273.
8. Rabie H, Denti P, Lee J, Masango M, Coovadia A, Pillay S, et al. Lopinavir-ritonavir super-boosting in young HIV-infected children on rifampicin-based tuberculosis therapy compared with lopinavir-ritonavir without rifampicin: a pharmacokinetic modelling and clinical study. Lancet HIV. 2019;6(1):e32-e42
9. The 2018 optimal formulary and limited-use list for paediatric ARVs. Geneva, Switzerland: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO. Available from http://apps.who.int/iris/bitstream/handle/10665/273153/WHO-CDS-HIV-18.15-eng.pdf?ua=1, accessed 26 September 2019.
10. U.S. Food and Drug Administration. Norvir package insert, November 15, 2018. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209512s004lbl.pdf, accessed 26 September 2019.

11. Our commitment to access to medicines [website]. North Chicago: AbbVie. (https://www.abbvie.com/content/dam/abbvie-dotcom/uploads/PDFs/our-commitment-to-access-to-medicines-2.pdf, accessed 26 September 2019).

*Lopinavir + ritonavir – new formulation – EML and EMLc*

**Lopinavir + ritonavir** **ATC Code: J05AR10**

**Proposal**

The application requested addition of a new formulation of lopinavir + ritonavir (LPV/r) fixed-dose combination to the core list of the EMLc for the treatment of children with HIV infection.

**Applicant**

WHO HIV Department

**WHO Technical Department**

HIV Department

**EML/EMLc**

EMLc

**Section**

6.4.2.3 Protease inhibitors

**Dose form(s) & strengths(s)**

Oral granules: 40 mg + 10 mg in sachet

**Core/Complementary**

Core

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Fixed-dose combinations of LPV/r have been included on the EMLc since 2007. Currently listed formulations are oral liquid 400 mg +100 mg/5 mL, heat-stable tablets 100 mg + 25 mg and capsules containing oral pellets 40 mg + 10 mg.

**Public health relevance** (burden of disease)

Despite an impressive reduction in mother-to-child transmission of HIV in recent years, 180 000 new paediatric infections occurred in 2017. There are now 1.8 million children living with HIV, the vast majority in sub-Saharan Africa (*1*). Evidence shows that in the absence of ART, over 50% of HIV-infected infants

progress to AIDS and death by the age of 2 years (*2*), but the introduction of paediatric ART has changed HIV infection in children from a life-threatening illness to a chronic but manageable infection. Despite recognition of the advantages of early treatment, paediatric treatment coverage still only reaches 52% of children eligible for treatment (*1*) and in 2017 an estimated 110 000 HIV/AIDS-related deaths occurred in children <15 years of age (*3*).

**Summary of evidence: benefits** (from the application)

The effectiveness of LPV/r in HIV-infected adult and paediatric patients has been demonstrated in a variety of clinical settings and populations, and has been previously reviewed. The data supporting use of the oral pellets (also LPV/r 40 mg/10 mg) was considered by the Expert Committee in 2017. LPV/r oral granules are expected to be used in the same settings and for the same patient population as the LPV/r pellets.

Since the previous EML application for LPV/r pellets was submitted, additional data on this dosage form have been reported. The LIVING Study conducted in Kenya and Uganda evaluated use and acceptability of LPV/r pellets in 723 infants and young children from 3 kg to <25kg. As of the July 2018 report, 303 patients had reached week 48 of treatment; 266 had HIV RNA data available for the week 48 visit. At 48 weeks, 49–60% of patients across four age groups had HIV RNA <50 copies/mL (*4*). These data suggest that the oral granules will also be an acceptable formulation in young infants.

LPV/r oral pellets and oral granules are currently listed as optimal formulations and are listed collectively as a 'solid oral dosage form 40 mg/10 mg' on The 2018 optimal formulary and limited-use list for paediatric ARVs (5). These two formulations are listed to be used with two nucleoside reverse transcriptase inhibitors (NRTIs) for alternative first-line or second-line treatment for infants and children below 10 kg or unable to swallow 100 mg/25 mg tablets whole. The optimal paediatric ARV formulary was first developed in 2011 to address this challenge and now provides guidance to streamline the selection of paediatric ARV dosage forms to those that conform to a list of criteria, including dosing flexibility, user-friendliness, optimization of supply chain management, and availability of quality-assured products in resource-limited settings.

**Summary of evidence: harms** (from the application)

Evidence for the safety of LPV/r in paediatric patients has been previously evaluated. The LPV/r oral granules formulation is expected to have the same safety and tolerability as other LPV/r formulations.

**Additional evidence** (not in the application)

N/A

**WHO Guidelines**

Based on evidence from randomized controlled trials showing the superiority of LPV/r-based regimens over nevirapine (NVP)-based regimens for treating young children, the WHO 2013 guidelines first recommended the use of LPV/r-based treatment in children younger than 3 years (36 months) of age where feasible, regardless of NNRTI exposure (*6*).

In the WHO 2016 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*, LPV/r in combination with two NRTIs is recommended as the preferred regimen in infants and children younger than 3 years (*7*). The recommended NRTI backbone in this age group is either abacavir (ABC) or zidovudine (ZDV) plus lamivudine (3TC).

In the updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV published in 2018, WHO elevated the integrase inhibitors dolutegravir (DTG) and raltegravir (RAL) in combination with two NRTIs to first-line treatment for infants and children (*8*). However, LPV/r formulations remain alternate first-line treatment in patients younger than 3 years of age and as second-line therapy in older children who have received an integrase inhibitor. Lack of dosing recommendations for young infants (for DTG) and lack of availability (for RAL) of integrase inhibitors will likely mean continued use of LPV/r in young patients for several years.

**Costs/cost-effectiveness**

The application reported a price per patient per year (PPPY) for LPV/r oral granules of US$ 281 based on WHO dosing guidelines for the 3 to 9.9 kg weight band. This is similar to the PPPY for LPV/r oral pellets, but more expensive than LPV/r oral liquid.

It has previously been proposed that cost savings associated with freight and storage are associated with LPV/r oral pellets compared to oral liquid.

**Availability**

The US FDA granted tentative approval to Mylan's LPV/r 40 mg/10 mg oral granules in August 2018.

**Other considerations**

N/A

**Committee recommendations**

The Expert Committee recommended the addition of a new formulation of lopinavir + ritonavir (LPV/r) oral granules 40 mg + 10 mg fixed-dose combination to the core list of the EMLc for the treatment of children with HIV

infection, in line with recommendations in current WHO guidelines, noting the importance of the availability of quality, age-appropriate paediatric dosage forms of antiretroviral medicines.

The Committee recommended the new LPV/r oral granules and the existing LPV/r capsules containing oral pellets should be listed collectively as "solid oral dosage form", for consistency with the the 2018 optimal paediatric ARV formulary.

## References


1. Global AIDS Update 2018 – Miles to Go, Breaking Barriers, Righting Injustices. Geneva: Joint United Nations Programme on HIV/AIDS; 2018. Available from http://www.unaids.org/sites/default/files/media_asset/miles-to-go_en.pdf, accessed 29 September 2019.
2. Newell ML, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. Lancet. 2004;364(9441):1236–43.
3. UNAIDS Core Epidemiology Slides. Geneva: Joint United Nations Programme on HIV/AIDS; 2018. Available from http://www.unaids.org/en/resources/documents/2018/core-epidemiology-slides, accessed 29 September 2019.
4. Andrieux-Meyer I, Salami O, Omollo R, Egondi T, Waweru M, Odiambo S, et al. Pellets' formulation of Lopinavir/ritonavir in children: 48-week evolution of viral suppression across age categories in the LIVING study. Abstract WEAB0204. J Int AIDS Soc. 2018;21(S6):e25148.
5. The 2018 optimal formulary and limited-use list for paediatric ARVs. Geneva: World Health Organization; 2018. Available from http://apps.who.int/iris/bitstream/handle/10665/273153/WHO-CDS-HIV-18.15-eng.pdf?ua=1, accessed 29 September 2019.
6. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013. Available from http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf, accessed 29 September 2019.
7. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach - Second edition. Geneva: World Health Organization; 2016. Available from http://www.who.int/hiv/pub/arv/arv-2016/en/, accessed 29 September 2019.
8. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines, supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2018. Available from https://apps.who.int/iris/bitstream/handle/10665/277395/WHO-CDS-HIV-18.51-eng.pdf?ua=1, accessed 29 September 2019.

### 6.4.2.4 *Integrase inhibitors*

*Dolutegravir – addition – EMLc*

**Dolutegravir** **ATC Code: J05AX12**

**Proposal**

The application requested the addition of dolutegravir to the core list of the EMLc for treatment of HIV infection in paediatric patients weighing 25 kg or more.

**Applicant**

WHO HIV Department

**WHO Technical Department**

HIV Department

**EML/EMLc**

EMLc

**Section**

6.4.2.4 Integrase inhibitors

**Dose form(s) & strengths(s)**

Tablet 50 mg

**Core/Complementary**

Core

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Dolutegravir was added to the core list of the EML in 2017 for treatment of adult patients.

**Public health relevance** (burden of disease)

There are now 1.8 million children living with HIV, the vast majority in sub-Saharan Africa. Evidence shows that in the absence of ART, over 50% of HIV-infected infants progress to AIDS or death by the age of 2 years (*1*), but the introduction of paediatric ART has changed HIV infection in children from a life-threatening illness to a chronic but manageable infection. Despite recognition

of the advantages of early treatment, paediatric treatment coverage still only reaches 52% of children eligible for treatment (estimated 940 000) and in 2017 an estimated 110 000 HIV/AIDS-related deaths occurred in children <15 years of age (*2*).

Although there is limited clinical experience globally with use of dolutegravir (DTG) in children, it is recommended in this population based on extrapolation of efficacy from the larger, and more diverse adult studies (*3*). Regulatory and normative bodies including the WHO (and its paediatric working groups) and the US FDA have accepted the concept of extrapolation of efficacy of ARVs in paediatric patients based on bridging pharmacokinetic (PK) data and supporting safety information. Thus, the most recent WHO treatment guidelines for paediatric use of DTG are based primarily on aligning PK data collected in children receiving DTG in clinical trials to adult PK targets.

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**Summary of evidence: benefits** (from the application)

Dolutegravir has been shown to be effective in diverse adult patient populations enrolled in multiple clinical trials conducted internationally. The results of these adult clinical trials were reviewed in the dossier submitted to support inclusion of dolutegravir 50 mg as first-line ART in the EML in 2017 and are not reproduced here.

The paediatric data published to date comprises two ongoing clinical trials and several observational cohort reports. The trials on which WHO treatment and dosing recommendations are based include the IMPAACT P1093 study, sponsored by the U.S. National Institutes of Health, and the ODYSSEY study, sponsored by the Paediatric European Network for Treatment of AIDS-ID. PK and safety data from these trials have been reported and reviewed as new weight band cohorts have been completed. Both trials are evaluating paediatric patients as young as 4 weeks of age using a dispersible tablet, but data for the younger/smaller patients are not available at this time.

IMPAACT P1093 is an ongoing single-arm, open-label trial of DTG in children with HIV. FDA approval of DTG for use in children weighing as low as 40 kg was based on data from 23 treatment-experienced, integrase strand transfer inhibitor (INSTI)-naive adolescents (*4*). Intensive PK evaluations were performed on the first 10 participants, nine of whom weighed ≥40 kg and received dolutegravir 50 mg and one of whom weighed 37 kg and received DTG 35 mg. These doses resulted in exposures comparable to those seen in adults receiving 50 mg once daily. At 48 weeks, 61% of participants had achieved HIV RNA concentration <50 copies/mL. By week 144, 39% and 30% of participants had achieved HIV RNA concentrations <400 copies/mL and <50 copies/mL, respectively. All who experienced virologic failure were reported to be non-adherent. A younger cohort of children aged ≥6 to <12 years were also enrolled

in IMPAACT P1093, with those weighing ≥30 kg to <40 kg receiving the 35 mg dose and those weighing ≥40 kg receiving the 50 mg dose. At 48 weeks, data from 23 participants demonstrated a favourable safety profile, adequate PK and virologic efficacy, with HIV RNA concentrations of <50 copies/mL achieved in 74% of participants. These data led to FDA approval of the lower strength film-coated tablets (10 mg plus 25 mg) for children with HIV weighing at least 30 kg.

Using similar data, the European Medicines Agency (EMA) approved the lower strength film-coated tablets for children aged ≥6 years and weighing ≥15 kg based on population PK modelling and simulation analyses (*5*). The EMA approved doses of 20 mg for children weighing 15 kg to <20 kg and 25 mg doses for those weighing 20 kg to <30 kg. Because the available PK data in these weight bands were very limited and the observed trough concentrations ($C_{trough}$) were lower than expected, the FDA did not approve dosing for children weighing <30 kg.

The ODYSSEY trial is enrolling both treatment-naive and -experienced paediatric patients in the EU, Thailand and several African countries, and initially evaluated the EMA-approved doses for children weight > 15kg. A total of 674 children <18 years of age were enrolled; 282 starting dolutegravir as first-line therapy and 392 starting second-line therapy (*6*). Nested pharmacokinetic sub-studies within ODYSSEY are evaluating simplified paediatric dosing aligned with WHO-recommended weight bands. PK data have been reported from a cohort of children >25 kg switching to the 50 mg adult tablet (n=27). These children receiving the 50 mg film-coated tablet achieved exposures similar to those of adults. When given to children 14 to <25 kg, the DTG 25 mg film-coated tablet resulted in lower exposure than the adult target exposure, particularly $C_{trough}$. The lower $C_{trough}$ was more marked in the 20 to <25 kg group. Higher doses are currently under study in these weight bands and doses have been adjusted for lower weight bands (*7*, *8*).

After careful review and discussion, the WHO-convened Paediatric Antiretroviral Working Group endorsed the simplified dosing using the dolutegravir 50 mg tablet in children weighing >25kg.

In the adult clinical studies to date, dolutegravir-based regimens were either non-inferior or superior in efficacy to comparator regimens containing other integrase inhibitors, boosted protease inhibitors and NNRTIs, regardless of patient population. In patients initiating first-line treatment, successful virologic suppression occurred in more patients receiving DTG than the comparators. There are no comparative paediatric trials available but both the WHO working groups and multiple regulatory agencies (including the U.S. FDA and the EMA) endorse the concept of extrapolating efficacy from well-designed, adequately-powered adult trials on the basis of similar pharmacokinetic profile and supplemental safety data.

**Summary of evidence: harms** (from the application)

A French, retrospective, multicentre cohort study evaluated 50 adolescents who initiated dolutegravir-based ART. In this cohort, only one patient discontinued DTG-based treatment because of a significant adverse effects (dizziness and sleep disturbance) (*9*). Another cohort of adolescents reported from Barcelona received the fixed-dose combination product Triumeq (abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg). No serious safety concerns were reported, however, patients complained about the size of the tablet and six reported having to crush or split the tablet in order to swallow it, potentially contributing to adherence issues (*10*).

In the original clinical trials, patients on dolutegravir experienced significantly fewer incidences of nervous system disorders and psychiatric disorders than those receiving efavirenz, however, there have been post-marketing reports of neuropsychiatric events (such as insomnia or depression) among adults receiving DTG-based treatment since its approval. Causality for these events has been difficult to determine as many patients are reported to have a previous history of psychiatric symptoms.

In a surveillance study of birth outcomes among pregnant women on ART in Botswana, an increased rate of neural tube defects was observed among infants born to women who were receiving dolutegravir at the time of conception (*11*). As children and young adolescents mature, and before they become sexually active, paediatric and adolescent providers should discuss this potential risk with patients who are receiving or initiating dolutegravir and their caregivers. The WHO 2018 interim guidelines (*3*) note the following in their guidance on this topic:

- Dolutegravir appears to be safe when started later in pregnancy: after the period of risk of neural tube defects and after the first trimester.
- Adolescent girls and women of childbearing potential who do not currently want to become pregnant can receive DTG together with consistent and reliable contraception; hormonal contraception and DTG have no reported or expected drug–drug interactions although data are limited.

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**Additional evidence (not in the application)**

N/A

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**WHO Guidelines**

The WHO-recommended dose of DTG in integrase inhibitor treatment naive adults and paediatric patients weighing more than 25 kg is one tablet (50 mg) once daily (*3*). Dolutegravir should be given together with two NRTIs appropriate

for paediatric patients (i.e. abacavir plus lamivudine or zidovudine plus lamivudine). In addition, the WHO 2018 interim guidelines also recommend that DTG in combination with an optimized NRTI backbone is the preferred second-line regimen for children with approved DTG dosing for whom non-DTG-based regimens are failing.

**Costs/cost-effectiveness**

The indicative average price per patient per year (PPPY) for dolutegravir 50 mg tablets is approximately US$ 50 for children weighing between 25 and 35 kg. This price is lower than PPPY for other ARVs suitable for children.

In November 2015, the Clinton Health Access Initiative (CHAI), UNAIDS, and Unitaid announced a pricing agreement for DTG 50 mg single tablets that had been brokered with Aurobindo Pharma (*12*). Under the agreement, Aurobindo agreed to make generic DTG 50 mg tablets available at a price of US$ 44.00 PPPY (or US$ 3.67 per pack).

**Availability**

Dolutegravir 50 mg tablets are manufactured by multiple pharmaceutical companies, including generic and WHO prequalified manufacturers.

**Other considerations**

N/A

**Committee recommendations**

The Expert Committee recommended the addition of dolutegravir 50 mg tablets to the core list of the EMLc for treatment of HIV infection in paediatric patients weighing 25 kg or more, in combination with an optimized NRTI backbone regimen, in line with recommendations in current WHO guidelines.

The Committee acknowledged the important need to expand HIV treatment options for children. The Committee noted the available evidence for use of dolutegravir in children was largely limited to pharmacokinetic and safety data from two ongoing paediatric trials, but considered that extrapolation of efficacy from adult trials was acceptable.

## References

1. Newell ML, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. Lancet. 2004;364(9441):1236–43.
2. UNAIDS Core Epidemiology Slides. Geneva: Joint United Nations Programme on HIV/AIDS; 2018. Available from http://www.unaids.org/en/resources/documents/2018/core-epidemiology-slides, accessed 29 September 2019.

3. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines, supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2018. Available from https://apps.who.int/iris/bitstream/handle/10665/277395/WHO-CDS-HIV-18.51-eng.pdf?ua=1 with accompanying Annex 3: Dosages of ARV drugs. World Health Organization, Geneva. December, 2018. Available from https://www.who.int/hiv/pub/guidelines/ARV_Guidelines-2018-Annex3.pdf?ua=1. Both accessed 29 September 2019.
4. Viani RM, Alvero C, Fenton T, Acosta EP, Hazra R, Townley E et al. Safety, Pharmacokinetics and Efficacy of Dolutegravir in Treatment-experienced HIV-1 Infected Adolescents: Forty-eight-week Results from IMPAACT P1093. Pediatr Infect Dis J. 2015;34(11):1207–13.
5. Summary of Product Characteristics: Tivicay [website]. London: European Medicines Agency; 2014. (https://www.ema.europa.eu/documents/product-information/tivicay-epar-product-information_en.pdf, accessed 29 September 2019).
6. Moore C, Kekitinwa A, Kaudha E, Lugemwa A, Mujuru H, Cotton M et al. ODYSSEY: A randomised trial evaluating the efficacy and toxicity of dolutegravir-based antiretroviral therapy compared to standard of care in HIV-infected children starting first-line or second-line therapy: design, current status and baseline characteristics. Abstract 34. 10th International Working on HIV Pediatrics. 21–22 July 2018, Amsterdam, The Netherlands. Reviews in Antiviral Therapy & Infectious Diseases. 2018;8:37.
7. Bollen P, Turkova A, Mujuru H, Musiime V, Amuge P, Lugemwa A et al. Steady-state pharmacokinetics and early safety data in HIV-infected African children weighing 14 to <25kg on film-coated dolutegravir 25mg tablets in the ODYSSEY trial. Abstract 22. 10th International Working on HIV Pediatrics. 21–22 July 2018, Amsterdam, The Netherlands. Reviews in Antiviral Therapy & Infectious Diseases 2018;8:27.
8. Turkova A, Bollen P, Kaudha E, Chidziva E, Lugemwa A, Kekitiinwa A et al. Steady-state pharmacokinetics and early safety data in HIV-infected African children weighing ≥25kg after switching to 50mg film-coated dolutegravir tablets in the ODYSSEY trial. Abstract 3. 10th International Working on HIV Pediatrics. 21–22 July 2018, Amsterdam, The Netherlands. Reviews in Antiviral Therapy & Infectious Diseases. 2018;8:5.
9. Briand C, Dollfus C, Caseris M et al. Abstract: Dolutegravir-based cART in vertically HIV-1-infected adolescents, real-world setting." 24th Conference on Retroviruses and Opportunistic Infections. Seattle, WA. 2017.
10. Bossacoma Busquets F, Noguera-Julian A, Sanchez E, Fortuny C. Dolutegravir plus abacavir/lamivudine works in adolescents, but size matters. J Antimicrob Chemother. 2017;72(10):2958–60.
11. Zash R, Makhema J, Shapiro RL. Neural-Tube Defects with Dolutegravir Treatment from the Time of Conception. N Engl J Med. 2018;379(10):979–81.
12. Three new agreements announced with the potential to expand access to innovative HIV treatment in low- and middle-income countries [Press Release]. Harare/Geneva: UNAIDS; 2015. Available from http://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2015/november/20151130_PR_CHAI_UNITAID, accessed 29 September 2019.

*Raltegravir – new formulation – EML and EMLc*

**Raltegravir** **ATC Code: J05AX08**

**Proposal**

The application requested the addition of a new formulation of raltegravir to the core list of the EML and EMLc for the treatment of HIV infection.

**Applicant**

WHO HIV Department

**WHO Technical Department**

HIV Department

**EML/EMLc**

EML and EMLc

**Section**

6.4.2.4 Integrase inhibitors

**Dose form(s) & strengths(s)**

Granules for oral suspension 100 mg in sachet

**Core/Complementary**

Core

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Raltegravir was added to the Model Lists in 2017 for use in pregnant women and as a second-line treatment option for children in accordance with WHO guidelines. Currently listed formulations include 400 mg tablets and 25 mg and 100 mg chewable tablets.

In a separate application to the 2019 Expert Committee, raltegravir 100 mg chewable tablet formulation was proposed for deletion from the EML and EMLc.

**Public health relevance** (burden of disease)

Despite an impressive reduction in mother-to-child transmission of HIV in recent years, 180 000 new paediatric infections occurred in 2017. There are now

1.8 million children living with HIV, the vast majority in sub-Saharan Africa (*1*). Evidence shows that in the absence of ART, over 50% of HIV-infected infants progress to AIDS and death by the age of 2 years (*2*), but the introduction of paediatric ART has changed HIV infection in children from a life-threatening illness to a chronic but manageable infection. Despite recognition of the advantages of early treatment, paediatric treatment coverage still only reaches 52% of children eligible for treatment (*1*) and in 2017 an estimated 110 000 HIV/AIDS-related deaths occurred in children <15 years of age (*3*).

**Summary of evidence: benefits** (from the application)

Data supporting general effectiveness of raltegravir in adults has been considered previously. The application only presented evidence relevant to the use of raltegravir granules for oral suspension.

Data from IMPAACT P1066, a Phase I/II open-label multicentre trial to evaluate the pharmacokinetic profile, safety, tolerability and efficacy of RAL in HIV-infected children (*4*) have been considered previously, and are not reproduced here.

The safety and pharmacokinetics of raltegravir granules for oral suspension were evaluated in 42 full-term HIV-1-exposed neonates at high risk of acquiring HIV-1 infection in a Phase I, open-label, multicentre clinical study (IMPAACT P1110) (*5*). Cohort 1 neonates received 2 single doses of RAL powder for oral suspension: the first within 48 hours of birth and the second at 7 to 10 days of age. Cohort 2 neonates received daily dosing of RAL powder for oral suspension for 6 weeks: 1.5 mg/kg once daily starting within 48 hours of birth through Day 7 (week 1); 3 mg/kg twice daily on Days 8 to 28 of age (weeks 2 to 4); and 6 mg/kg twice daily on Days 29 to 42 of age (weeks 5 and 6). Sixteen neonates were enrolled in Cohort 1 and 26 in Cohort 2; all infants received a standard of care ARV drug regimen for prevention of mother-to-child HIV transmission. All enrolled neonates were followed for safety for a duration of 24 weeks. HIV-1 status was assessed by nucleic acid test at birth, week 6 and week 24 and all remained HIV-1 negative.

IMPAACT P1066 also enrolled HIV-infected infants and toddlers from 4 weeks to less than 2 years of age who had received prior antiretroviral therapy either as prophylaxis for prevention of mother-to-child transmission and/or as combination antiretroviral therapy for treatment of HIV infection. Raltegravir granules for oral suspension was administered in combination with an optimized background regimen, and without regard to food. None of the enrolled subjects were completely treatment naive (all had prenatal/*in utero* ARV exposure or postnatal prophylaxis or treatment). Of the 26 treated subjects, 24 subjects were included in the week 48 efficacy analyses. All 26 treated subjects were included for safety analyses. At week 48, 45% achieved HIV RNA <50 copies/mL and 67%

achieved HIV RNA <400 copies/mL. The mean CD4 count (percent) increase from baseline to week 48 was 527 cells/mm3 (7.3%) (*6*). A recent follow-up publication reports the outcomes of those patients receiving raltegravir at the final selected doses through 240 weeks of treatment. In this analysis, 13 of 15 infants receiving raltegravir oral granules for 240 weeks achieved virologic success (>1 log decrease in HIV RNA from baseline or HIV RNA <400 copies/mL) (*7*).

Raltegravir granules for oral suspension is currently listed as a limited use formulation on the optimal formulary and limited-use list for neonatal treatment only.

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**Summary of evidence: harms** (from the application)

Evidence of the safety and tolerability of raltegravir has been previously considered. The overall safety of raltegravir in paediatric patients, including neonates, was similar to that observed in adults.

Overall, the safety profile in paediatric patients, including neonates, is similar to that observed in adults. Raltegravir is metabolized primarily by UGT1A1 (the same metabolic pathway as bilirubin) and UGT1A1 activity is greatly reduced in neonates. Concerns regarding potential competition with bilirubin for albumin binding sites and resulting jaundice in infants have not been borne out. The dose recommended in neonates takes into consideration the rapidly increasing UGT1A1 activity and drug clearance in this age group (*5*).

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**Additional evidence** (not in the application)

N/A

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**WHO Guidelines**

The WHO 2018 updated recommendations on first- and second-line ARV regimens make the following recommendations in relation to raltegravir-based regimens in children:

- A raltegravir-based regimen may be recommended as an alternative first-line regimen for infants and children for whom approved dolutegravir dosing is not available (condition recommendation, low-certainty evidence).
- A raltegravir-based regimen is recommended as the preferred first-line regimen for neonates (conditional recommendations, very-low-certainty evidence).

Raltegravir-based regimens for neonates are recommended for use for no longer than three months, when transition to LPV/r solid formulations is possible (*8*).

### Costs/cost-effectiveness

The reported price per patient per year for raltegravir oral granules is US$ 260. No cost-effectiveness information for this formulation is currently available.

### Availability

Raltegravir granules for oral suspension are manufactured by Merck Sharp & Dohme Ltd.

### Other considerations

Raltegravir granules for oral suspension are not recommended in pre-term neonates or in paediatric patients weighing less than 2 kg.

### Committee recommendations

The Expert Committee recommended the addition of a new formulation of raltegravir granules for oral suspension 100 mg to the core list of the EML and EMLc for the treatment of HIV infection, in line with recommendations in current WHO guidelines. The Committee considered that this formulation of raltegravir could facilitate treatment of neonates and paediatric patients, and would be a suitable alternative for adult and paediatric patients for whom dolutegravir is not available or is not tolerated.

## References

1. Global AIDS Update 2018 – Miles to Go, Breaking Barriers, Righting Injustices. Geneva: Joint United Nations Programme on HIV/AIDS; 2018. Available from http://www.unaids.org/sites/default/files/media_asset/miles-to-go_en.pdf, accessed 29 September 2019.
2. Newell ML, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. Lancet. 2004;364(9441):1236–43.
3. UNAIDS Core Epidemiology Slides. Geneva: Joint United Nations Programme on HIV/AIDS; 2018. Available from http://www.unaids.org/en/resources/documents/2018/core-epidemiology-slides, accessed 29 September 2019.
4. Nachman S, Zheng N, Acosta EP, Teppler H, Homony B, Graham B et al. Pharmacokinetics, safety, and 48-week efficacy of oral raltegravir in HIV-1-infected children aged 2 through 18 years. Clin Infect Dis. 2014;58(3):413–22.
5. Isentress U.S. package insert. Silver Spring: U.S. Food and Drug Administration; 2018. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022145s038,205786s007,022003045s015lbl.pdf, accessed 29 September 2019.
6. Nachman S, Alvero C, Acosta EP, Teppler H, Homony B, Graham B et al. Pharmacokinetics and 48-Week Safety and Efficacy of Raltegravir for Oral Suspension in Human Immunodeficiency Virus Type-1-Infected Children 4 Weeks to 2 Years of Age. J Pediatric Infect Dis Soc 2015;4(4):e76–83.

7. Nachman S, Alvero C, Teppler H, Homony B, Rodgers AJ, Graham BL et al. Safety and efficacy at 240 weeks of different raltegravir formulations in children with HIV-1: a phase 1/2 open label, non-randomised, multicentre trial. Lancet HIV. 2018;5(12):e715–e22.

8. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines, supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2018. Available from https://apps.who.int/iris/bitstream/handle/10665/277395/WHO-CDS-HIV-18.51-eng.pdf?ua=1, accessed 29 September 2019.

### *Fixed-dose combinations*

*Dolutegravir + lamivudine + tenofovir disoproxil fumarate – addition – EML*

| **Dolutegravir + lamivudine + tenofovir disoproxil fumarate** | **ATC Code: to be assigned** |
|---|---|

**Proposal**

The application requested the addition of a fixed-dose combination formulation of dolutegravir, lamivudine and tenofovir disoproxil fumarate (TLD) to the core list of the EML for treatment of HIV infection in adults and adolescents.

**Applicant**

WHO HIV Department

**WHO Technical Department**

HIV Department

**EML/EMLc**

EML

**Section**

6.4.2 Antiretrovirals – fixed-dose combinations

**Dose form(s) & strengths(s)**

Tablet 50 mg + 300 mg + 300 mg (disoproxil fumarate equivalent to 245 mg tenofovir disoproxil)

**Core/Complementary**

Core

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

This fixed-dose combination (FDC) had not been previously considered by the Expert Committee for addition to the EML. The component medicines are all included individually on the EML.

**Public health relevance** (burden of disease)

In 2017, UNAIDS reported there were 36.9 million people living with HIV/AIDS globally, 1.8 million new HIV-1 infections, and 940 000 thousand HIV-

related deaths (*1*). Over 95% of infected people live in low- and middle-income countries (LMICs) with inadequate resources to effectively combat the epidemic. While some countries have achieved declines in new HIV infections among adults of 50% or more, global data show that many others have not made measurable progress and others have experienced worrying increases in new HIV infections. Overall, approximately 21.7 million people were receiving antiretroviral therapy (ART) in 2017, but this is estimated to represent only 59% of people living with HIV.

Early and effective ART not only significantly improves the health of those people living with HIV, but also reduces transmission of the disease as shown in the recently reported START study (*2*). For this reason, WHO released guidelines in 2015 calling for treatment for all people with HIV. Easy to administer, highly effective, safe treatment options remain desperately needed in many areas of the world to meet the UNAIDS '90-90-90' targets, which call for 90% of people living with HIV to know their status, 90% of those with known infection to be on ART, and 90% of those on ART to be virally suppressed (i.e. on successful therapy) by the year 2020 (*3*).

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**Summary of evidence: benefits** (from the application)

The efficacy of dolutegravir (DTG) has been demonstrated in ART-naive subjects in three randomized, controlled, multinational, Phase III studies: SPRING-2 (*4*), SINGLE (*5*) and FLAMINGO (*6*). The findings of these studies were evaluated in the 2017 consideration of dolutegravir by the Expert Committee and are not reproduced here.

The safety, tolerability and efficacy of a dolutegravir-based regimen was evaluated in a prospectively-enrolled, open-label cohort of 564 Indian adults receiving dolutegravir in combination with other ARVs (primarily tenofovir disoproxil fumarate (TDF) and lamivudine (3TC) or emtricitabine (FTC)) as either first- or second-line therapy. Among the treatment naive patients initiating DTG plus TDF/3TC or TDF/FTC, all had viral suppression at the 6 month follow-up, and overall, viral suppression occurred in 82.9% at six months (*7*).

The NAMSAL ANRS study randomized HIV-infected adults in Cameroon to receive either a dolutegravir-based regimen (TLD) (n=310) or an efavirenz-containing regimen (TLE-400) (n=303) for first-line treatment. Preliminary efficacy results at 48 weeks on treatment indicate the proportion of patients with HIV RNA <50 copies/mL was 74.5% in the TLD arm and 69% in the TLE-400 arm. Fewer patients with initial HIV RNA levels >100 000 copies/mL had virologic suppression to <50 copies/mL: 66.2% in the TLD arm and 61.5% in the TLE-400 arm. In this study, viral suppression with TLD was numerically higher but not statistically superior to TLE-400; NNRTI resistance was an important determinant of TLE-400 failure (*8*).

In the clinical studies to date, dolutegravir-based regimens were either non-inferior or superior in efficacy to comparator regimens containing other integrase inhibitors, boosted protease inhibitors and NNRTIs regardless of patient population. In patients initiating first-line treatment, successful virologic suppression occurred in more patients receiving dolutegravir than the comparators. A systematic review and meta-analysis conducted by WHO in 2016 concluded that among treatment-naive patients, treatment with an integrase inhibitor (particularly DTG) plus two NRTIs, had superior efficacy and tolerance to the current standard of care regimens of efavirenz plus two NRTIs (*9*).

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**Summary of evidence: harms** (from the application)

The overall safety profile of dolutegravir in adults compared favourably to other ARVs included in the clinical trials reported previously.

There have been multiple reports of neuropsychiatric events among patients receiving dolutegravir-based treatment since its approval. Although dolutegravir appears to result in fewer of these events compared to efavirenz in comparative clinical trials (*5*), some patients receiving dolutegravir experience episodes of insomnia or depression. Causality for these events has been difficult to determine as many patients are reported to have a previous history of psychiatric symptoms.

In the South Indian cohort of first- and second-line patients, dolutegravir-based regimens were well tolerated. Mean alanine aminotransferase (ALT) and aspartate aminotransferase (AST) decreased slightly in the cohort during the 6-month evaluation period, mean haemoglobin increased slightly, and kidney function remained stable. In this cohort, sleep disturbances and neuropsychiatric symptoms were not reported. The frequency of opportunistic infections decreased from 7.4% prior to starting DTG to 3.3% after six months follow up. None of the patients in this cohort discontinued DTG during the evaluation period. Four deaths were reported (two sepsis and two cytomegalovirus (CMV) encephalitis, considered unrelated to ARVs) (*7*).

A nationwide birth outcomes surveillance programme conducted in Botswana began collecting data in women initiating dolutegravir in 2014. An initial report of pregnant women who began taking either a dolutegravir- (n=1729) or efavirenz-based (n=4593) treatment regimen identified no difference in risk for adverse birth outcomes, even among those beginning treatment during the first trimester (i.e. post-conception ART) (*10*). However, an interim analysis of a second surveillance study of women becoming pregnant while already receiving ART (i.e. pre-conception ART) identified an excess number of neural tube defects among infants of women receiving a dolutegravir-based regimen. Neural tube defects were observed in 4 of 426 (0.94%) infants born to women receiving dolutegravir compared to 14 of 11 300 (0.12%) infants born to women receiving any other ART regimen and 61 of 66 057 (0.09%) infants

born to HIV-uninfected women. Although none of the affected women were receiving folate supplements, no other risk factors for neural tube defects have been identified (*11*). This study is ongoing and expects to have a final analysis in 2019. While awaiting the final study results and data from other sources, WHO recommends counselling for women of childbearing potential and access to effective contraception in those receiving dolutegravir. However, they also suggest that an efavirenz-based regimen remains safe and effective in women who plan to become pregnant (*12*).

The NRTI backbone of TDF/3TC has an extensive history of use in ART globally and has accumulated a favourable safety and tolerability profile. Initial concerns regarding potentially serious renal and bone toxicity due to the TDF component have not been borne out over years of clinical experience although it requires dose adjustment in patients with significant renal impairment and so is not generally used in this sub-group.

In addition, the potential risks and benefits of wide implementation of TLD were evaluated in a 2018 modelling exercise conducted by a group of independent researchers. The group used existing data to estimate HIV transmission and disease progression (taking into account drug resistance, drug potency, differential viral suppression and clinical outcomes) to compare outcomes of different ART regimens in various scenarios. In their model, the greatest number of disability-adjusted life-years was averted in the scenario providing TLD to all adult patients without restrictions over 20 years compared to adults based on intent to have children and/or dependent on documentation of viral suppression (*13*).

**Additional evidence** (not in the application)

N/A

**WHO Guidelines**

The 2016 WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* recommended TDF plus 3TC as a preferred nucleoside/tide backbone in first-line therapy and dolutegravir 50 mg in combination with TDF and 3TC as an alternative first-line regimen (*14*). In addition, these guidelines reiterate the WHO conclusion that FDCs and once-daily regimens are most preferred. At that time, TLD was not available as an FDC. In the most recent WHO treatment guidelines update (July 2018), a DTG-based regimen is recommended as a preferred first-line regimen for adults and adolescents living with HIV who are initiating antiretroviral therapy (*12*).

**Costs/cost-effectiveness**

Various sources indicate an average price per patient per year for the FDC of US$ 74. This price is comparable to other first-line regimens.

A pricing agreement was announced in July 2017 by the governments of South Africa and Kenya, together with UNAIDS, CHAI, the Bill & Melinda Gates Foundation, Unitaid, the UK Department for International Development, PEPFAR, USAID, and the Global Fund, with Aurobindo and Mylan.

Under the agreement, Aurobindo and Mylan agreed to offer TLD at approximately US$ 75 PPPY. This lower price is accessible to public sector purchasers in over 92 LMICs worldwide.

**Availability**

This product is currently available for procurement from multiple suppliers (including WHO prequalified manufacturers).

**Other considerations**

N/A

**Committee recommendations**

The Expert Committee recommended the addition of the fixed-dose combination formulation of dolutegravir + lamivudine + tenofovir disoproxil fumarate to the core list of the EML for treatment of HIV infection in adults and adolescents. The Committee noted the demonstrated efficacy and safety of DTG-based regimens in treatment-naive patients, and that DTG-based regimens are now recommended as preferred first-line therapy in WHO Guidelines for adults and adolescents initiating antiretroviral treatment.

The Committee also considered that the availability of fixed-dose combinations of antiretroviral therapies provides benefits to patients in terms of ease of administration and reduced pill burden, which can contribute to improved therapeutic adherence.

## References

1. Global AIDS Update 2018 – Miles to Go, Breaking Barriers, Righting Injustices. Geneva: Joint United Nations Programme on HIV/AIDS; 2018. Available from http://www.unaids.org/sites/default/files/media_asset/miles-to-go_en.pdf, accessed 29 September 2019.
2. Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, Sharma S et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med. 2015;373(9):795–807.
3. 90–90–90 - An ambitious treatment target to help end the AIDS epidemic. Geneva: Joint United Nations Programme on HIV/AIDS; 2017. Available from http://www.unaids.org/sites/default/files/media_asset/miles-to-go_en.pdf, accessed 29 September 2019.
4. Raffi F, Jaeger H, Quiros-Roldan E, Albrecht H, Belonosova E, Gatell JM et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. Lancet Infect Dis. 2013;13(11):927–35.

5. Walmsley SL, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutierrez F et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. N Engl J Med. 2013;369(19):1807–18.

6. Molina JM, Clotet B, van Lunzen J, Lazzarin A, Cavassini M, Henry K, et al. Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naive adults with HIV-1 infection (FLAMINGO): 96 week results from a randomised, open-label, phase 3b study. Lancet HIV. 2015;2(4):e127–36.

7. Kumarasamy N, Prabhu S, Chandrasekaran E, Poongulali S, Pradeep A, Chitra D et al. Safety, Tolerability, and Efficacy of Generic Dolutegravir-containing Antiretroviral Therapy Regimens Among South Indian Human Immunodeficiency Virus-infected Patients. Clin Infect Dis. 2019;68(6):1048-51.. Clin Infect Dis. 2019;68(6):1048–51

8. Cournil A, Kouanfack C, Eymard-Duvernay S, Lem S, Mpoudi-Ngole M, Omgba P et al. Dolutegravir versus an efavirenz 400 mg-based regimen for the initial treatment of HIV-infected patients in Cameroon: 48-week efficacy results of the NAMSAL ANRS 12313 trial. Abstract O342. J Int AIDS Soc. 2018;21(S8):16.

9. Kanters S, Vitoria M, Doherty M, Socias ME, Ford N, Forrest JI et al. Comparative efficacy and safety of first-line antiretroviral therapy for the treatment of HIV infection: a systematic review and network meta-analysis. Lancet HIV. 2016;3(11):e510–e20.

10. Zash R, Jacobson DL, Diseko M, Mayondi G, Mmalane M, Essex M et al. Comparative safety of dolutegravir-based or efavirenz-based antiretroviral treatment started during pregnancy in Botswana: an observational study. Lancet Glob Health. 2018;6(7):e804–e10.

11. Zash R, Makhema J, Shapiro RL. Neural-Tube Defects with Dolutegravir Treatment from the Time of Conception. N Engl J Med. 2018;379(10):979–81.

12. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines, supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2018. Available from https://apps.who.int/iris/bitstream/handle/10665/277395/WHO-CDS-HIV-18.51-eng.pdf?ua=1, accessed 29 September 2019.

13. Phillips AN, Venter F, Havlir D, Pozniak A, Kuritzkes D, Wensing A et al. Risks and benefits of dolutegravir-based antiretroviral drug regimens in sub-Saharan Africa: a modelling study. Lancet HIV. 2019;6(2):e116–e27.

14. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach - Second edition. Geneva: World Health Organization; 2016. Available from http://www.who.int/hiv/pub/arv/arv-2016/en/, accessed 29 September 2019.

### 6.4.4 Antihepatitis medicines

#### 6.4.4.2 *Medicines for hepatitis C*

*Glecaprevir + pibrentasvir – addition – EML*

**Glecaprevir + pibrentasvir** **ATC Code: J05AP57**

**Proposal**

The application requested addition of the fixed-dose combination of glecaprevir + pibrentasvir to the core list of the EML for the treatment of adult patients with chronic hepatitis C virus infection, genotypes 1 to 6.

**Applicant**

AbbVie Inc.

**WHO Technical Department**

WHO Global Hepatitis Programme

**EML/EMLc**

EML

**Section**

6.4.4.2.1 Pangenotypic direct-acting antiviral combinations

**Dose form(s) & strengths(s)**

Tablet 100 mg + 40 mg

**Core/Complementary**

Core

**Individual/Square box listing**

Individual

**Background**

Neither this fixed-dose combination (FDC) nor its individual components have been previously considered by the Expert Committee for addition to the EML.

**Public health relevance** (burden of disease)

Globally in 2015, it was estimated that 71 million persons were living with chronic HCV infection and nearly 400 000 died from cirrhosis or hepatocellular cancer.

The *Global health sector strategy on viral hepatitis* was endorsed by the World Health Assembly in 2016 and proposes the elimination of viral hepatitis as a public health threat by 2030 by achieving a 90% reduction in incidence and a 65% reduction in mortality. This requires 90% of infection persons to be diagnosed, and 80% of diagnosed persons to be treated (*1*).

**Summary of evidence: benefits** (from the application)

In Phase II and III registrational studies, glecaprevir + pibrentasvir has shown high sustained viral response rates at 12 weeks (SVR12) across all hepatitis C genotypes and in key patient sub-populations (patients with chronic kidney disease, organ transplant recipients, patients coinfected with HIV and patients with compensated cirrhosis).

The application described SVR12 rates greater than 95% for all treated genotypes:

| Genotype | Intervention | Proportion SVR12 (n/N) | 95%CI |
|---|---|---|---|
| GT1 | 12 weeks | 99.7% (331/332) | 99.1 to 100.0 |
| GT2 | 8 weeks | 98.5% (135/137) | 96.5 to 100.0 |
| GT2 | 12 weeks | 99.5% (195/196) | 98.5 to 100.0 |
| GT3 | 12 weeks | 95.3% (222/233) | 94.2 to 98.9 |
| GT4 | 12 weeks | 99.0% (95/96) | 94.3 to 99.8 |
| GT5 | 12 weeks | 100% (21/21) | 84.5 to 100.0 |
| GT6 | 12 weeks | 100% (30/30) | 88.6 to 100.0 |

Among all GT1–6-infected subjects who received the recommended duration of treatment with glecaprevir + pibrentasvir, regardless of renal function, cirrhosis status, presence of HIV co-infection, treatment naive or treatment experienced, 97.4% (1252/1287) achieved SVR12 (*2*).

High SVR12 rates were also reported for GT1–6-infected subjects in key patient sub-populations:

| Sub-population | Intervention | Proportion SVR12 (n/N) |
|---|---|---|
| Chronic kidney disease (CKD) (+/- haemodialysis) | 12 weeks | 98.1% (102/104) |
| Post liver/renal transplant | 12 weeks | 98.0% (98/100) |
| HCV/HIV-1 co-infection (with or without cirrhosis) | 12 or 8 weeks | 98.2% (165/168) |

Table *continued*

| Sub-population | Intervention | Proportion SVR12 (n/N) |
|---|---|---|
| Compensated cirrhosis | NR | 95.3% (222/233) |
| NS5A inhibitor (only) experienced | 16 weeks | 94.4% (17/18) |
| PI (only) experienced | 12 weeks | 100% (27/27) |
| Both NS5A and PI experienced | 16 weeks | 81.3% (13/16) |

The application described the findings of two randomized, Phase III, open-label studies that evaluated the safety and effectiveness of glecaprevir + pibrentasvir compared to sofosbuvir + ribavirin in Japanese patients with HCV GT2 (CERTAIN-2, Study M15-828) (*3*), and compared to sofosbuvir + daclatasvir in treatment-naive, non-cirrhotic HCV GT3 patients (ENDURANCE-3, Study M13-594) (*4*). In each study, glecaprevir + pibrentasvir was found to be non-inferior to the comparator treatments for the percentage of patients achieving SVR12.

Real-world data for glecaprevir + pibrentasvir also support the effectiveness demonstrated in the Phase 2 and 3 trials (*5*–*9*).

**Summary of evidence: harms** (from the application)

The application stated the safety assessment for glecaprevir + pibrentasvir in subjects with compensated liver disease (with or without cirrhosis) were derived from Phase II and III studies that evaluated 2369 subjects infected with GT 1, 2, 3, 4, 5 or 6 HCV who received treatment for 8, 12 or 16 weeks. The overall proportion of subjects who permanently discontinued treatment due to adverse reactions was 0.1%. The most common adverse reactions were reported as headache (13.2%), fatigue (11.4%) and nausea (7.6%). These adverse reactions occurred at a similar frequency in patients receiving placebo or sofosbuvir + daclatasvir. Seven deaths were reported in the Phase II and III analysis set, none of which were considered to be related to the study drug. No apparent differences were observed in adverse event profiles by sex, race, ethnicity or baseline body mass index (BMI). The incidence of serious adverse events and adverse events of Grade 3 or higher was higher in patients aged 65 years or older compared to patients under 65 years. No other differences by age in the proportion of subjects reporting any adverse event, discontinuations or deaths were observed.

Real-world data for glecaprevir + pibrentasvir also support the safety demonstrated in clinical trials (*5*–*9*).

**Additional evidence** (not in the application)

A systematic review of treatment options for chronic hepatitis C virus infection, genotypes 1–6 was conducted to inform the 2018 WHO *Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection* (*10*, *11*). The review found that the proportion of patients treated with glecaprevir + pibrentasvir who achieved SVR12 ranged from 83% to 98%. GRADE assessments of the quality of evidence were high for GT1–3 and very low for GT4–6. For safety outcomes, the review assessed discontinuations due to adverse events (DAEs), serious adverse events (SAEs) and mortality. The pooled proportions for DAEs, SAEs and mortality for glecaprevir + pibrentasvir was 1%, 2% and 1%, respectively. GRADE assessments of the quality of evidence were moderate for DAEs and high for SAEs and mortality.

**WHO Guidelines**

The 2018 WHO *Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection* (*1*) recommend:

- the use of pangenotypic direct-acting antiviral (DAA) regimens for the treatment of chronic HCV infection in persons aged 18 years and older (conditional recommendation, moderate quality evidence);
- glecaprevir + pibrentasvir as a pangenotypic treatment option for adults with or without compensated cirrhosis.

**Costs/cost-effectiveness**

In a 2017 cost-effectiveness analysis in the United States, glecaprevir + pibrentasvir was shown to be a dominant pan-genotypic treatment option compared to current standard practices providing most favourable health outcomes at lowest cost (*2*). Health outcomes included quality-adjusted life-years (QALYs) and number needed to treat (NNT) to achieve a QALY, SVR or avoid an adverse liver event. In this analysis, glecaprevir + pibrentasvir was compared to two treatment strategies: (i) sofosbuvir + ledipasvir for GTs 1 and 4, and sofosbuvir + velpatasvir for GTs 2, 3, 5 and 6; and (ii) grazoprevir + elbasvir for GTs 1 and 4, and sofosbuvir + velpatasvir for GTs 2, 3, 5 and 6. A 12-week regimen course of glecaprevir + pibrentasvir was assumed to cost US$ 27 929 USD (at 2017 wholesale acquisition drug costs). Cost-effectiveness results in other countries may vary based on the different pricing of glecaprevir + pibrentasvir and other DAAs.

**Availability**

Glecaprevir + pibrentasvir has marketing approval and is commercially available in 58 countries globally. AbbVie and the Medicines Patent Pool have entered into a royalty-free licensing agreement to accelerate access in 99 LMICs. Through

this agreement, AbbVie will allow WHO prequalified generic manufacturers to license, manufacture and supply generic versions. AbbVie is also considering the inclusion of glecaprevir + pibrentasvir on the WHO List of Prequalified Medicinal Products.

**Other considerations**

N/A

**Committee recommendations**

The Expert Committee recommended the addition of the fixed-dose combination of glecaprevir + pibrentasvir to the core list of the EML for the treatment of adult patients with chronic hepatitis C virus infection, based on evidence of pan-genotypic effectiveness and an acceptable safety profile. The Committee noted that this combination is one of three pan-genotypic combinations recommended in the current WHO guidelines for treatment of hepatitis C and is suitable for use in patients with or without compensated cirrhosis.

The Committee noted that the manufacturer and the Medicines Patent Pool (MPP) have entered into a licensing agreement for this product to accelerate access in 99 LMICs. However, the Committee noted with concern that some LMICs with a high burden of hepatitis C are not included in this agreement and encouraged the manufacturer and the MPP to address this issue to ensure patients in these high-burden countries have equitable access.

The Committee recommended that the hepatitis C medicines section of the Model List be amended to differentiate between pangenotypic (glecaprevir + pibrentasvir, sofosbuvir + daclatasvir and sofosbuvir + velpatasvir), non-pangenotypic direct acting antivirals, and other antivirals for hepatitis C. The pangenotypic regimens should be considered as therapeutically equivalent to facilitate selection and procurement by countries at national level.

The Expert Committee then considered whether it was appropriate to delete non-pangenotypic treatments for hepatitis C, and recommended the deletion of simeprevir, whose place in therapy was now superseded by the pan-genotypic options. The Committee recommended that other non-pangenotypic treatments could be considerd for deletion from the EML in the future.

## References

1. Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. Geneva: World Health Organization; 2018. Available from https://apps.who.int/iris/bitstream/handle/10665/273174/9789241550345-eng.pdf, accessed 29 September 2019.
2. Saab S, Parisé H, Virabhak S, Johnson S, Pinsky B, Sanchez Y. Pan-genotypic hepatitis C treatment with glecaprevir/pibrentasvir achieves greatest improvements in quality-adjusted life-years and lifetime risk reductions in liver-related morbidity and mortality vs standards of care: a cost-utility analysis. Poster Abstract 1578. Hepatology. 2017;66(S1):843A.

3. Abbvie - M15-828 Clinical Study Report – Final. A Randomized, Open-Label, Active Comparator, Multicenter Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Japanese Adults with Genotype 2 Chronic Hepatitis C Virus Infection (CERTAIN-2) [website]. (https://www.abbvie.com/content/dam/abbvie-dotcom/clinical-trials/glecaprevir_pibrentasvir_M15-828_Redacted.pdf, accessed 29 September 2019).
4. Abbvie - M13-594 Clinical Study Report - Final. A Randomized, Open-Label, Active-Controlled, Multicenter Study to Compare Efficacy and Safety of ABT-493/ABT-530 to Sofosbuvir Co-Administered with Daclatasvir in Adults with Chronic Hepatitis C Virus Genotype 3 Infection (ENDURANCE-3) [website]. (https://www.abbvie.com/content/dam/abbvie-dotcom/clinical-trials/glecaprevir_pibrentasvir_M13-594_Redacted.pdf, accessed 29 September 2019).
5. Belperio P, Shahoumian T, Loomis T, Mole L, Backus LI. Real-World Effectiveness of Glecaprevir/Pibrentasvir in 1,941 Patients with Hepatitis C Genotypes 1 through 4. Poster Abstract 703. Hepatology. 2018;68(S1):417A-418A.
6. Curry MP, Bacon BR, Flamm SL, Marks M, Milligan S, Tsai NCS et al. Preferences in Clinical Practice with Glecaprevir/Pibrentasvir (GLE-PIB), Ledipasvir/ Sofosbuvir (LDV-SOF), and Sofosbuvir/Velpatasvir (SOF-VEL); Data from the Trio Network. Poster Abstract 678. Hepatology. 2018;68(S1):402A.
7. D'Ambrosio R, Pasulo L, Puoti M, Vinci M, Schiavini M, Lazzaroni S et al. Real-world effectiveness and safety of glecaprevir/pibrentasvir in 723 patients with chronic hepatitis C. J Hepatol. 2019; 70(3):379–387.
8. Puigvehi M, Albillos A, Viu A, Hernandez Guerra MN, Fernandez I, Prieto M et al. Effectiveness and Safety of Glecaprevir/Pibrentasvir for the Pangenotypic Treatment of Chronic Hepatitis C: Results from a Spanish Cohort (Hepa-C). Poster Abstract 601. Hepatology. 2018;68(S1):657A.
9. Wiegand J, Naumann U, Stoehr A, Sick C, John C, Teuber G et al. Glecaprevir/Pibrentasvir for the Treatment of Patients with Chronic Hepatitis C Virus Infection: Updated Real-World Data from the German Hepatitis C-Registry. Poster Abstract 611. Hepatology. 2018;68(S1):364A.
10. Zoratti M. Web Annex 3.1. Adult hepatitis C virus treatment systematic review. In: Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. Geneva: World Health Organization; 2018. Available from https://apps.who.int/iris/bitstream/handle/10665/277215/WHO-CDS-HIV-18.36-eng.pdf, accessed 29 September 2019.
11. Zoratti M. Web Annex 3.2. Adult hepatitis C virus treatment systematic review: supporting evidence. In: Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. Geneva: World Health Organization; 2018. Available from https://apps.who.int/iris/bitstream/handle/10665/277216/WHO-CDS-HIV-18.37-eng.pdf, accessed 29 September 2019.

## 6.5 Antiprotozoal medicines

### 6.5.3 Antimalarial medicines

#### 6.5.3.2 *For chemoprevention*

*Sulfadoxine + pyrimethamine – new indication IPTi – EMLc*

**Sulfadoxine + pyrimethamine** **ATC Code: P01BD51**

**Proposal**

The application requested listing of sulfadoxine + pyrimethamine fixed-dose combination tablet on the core list of the EMLc for the new indication of intermittent preventive treatment (of malaria) in infancy (IPTi).

**Applicant**

WHO Global Malaria Programme

**WHO Technical Department**

Global Malaria Programme

**EML/EMLc**

EMLc

**Section**

6.5.3.2 Antimalarial medicines – For chemoprevention

**Dose form(s) & strengths(s)**

Tablet 250 mg + 12.5 mg

**Core/Complementary**

Core

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Sulfadoxine + pyrimethamine 500 mg + 25 mg tablets are currently included on the EML and EMLc for use in combination with artesunate 50 mg for the curative treatment of malaria.

**Public health relevance** (burden of disease)

Malaria is one of the leading causes of illness, death and lost economic productivity globally. In 2017, there were an estimated 219 million malaria cases worldwide, the majority of which occurred in the African region (92%, 200 million cases) (*1*). Of the 435 000 deaths due to malaria globally in 2017, 266 000 (61%) were in children under 5 years of age.

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**Summary of evidence: benefits** (from the application)

The application presented the findings of a pooled analysis of six randomized, placebo-controlled trials in 7930 infants that investigated the efficacy and safety of IPTi with sulfadoxine + pyrimethamine (IPTi-SP) in four African countries with moderate to high transmission of malaria, when administered to infants at the time of routine vaccination according to the WHO Expanded Programme on Immunization (EPI) (2).

From the pooled analysis, the combined estimate of protective efficacy of IPTi-SP against clinical malaria in infants aged up to 1 year of age was 30.3% (95%CI 19.8% to 39.4%, p<0.0001).

IPTi-SP was also associated with protective efficacy in infants up to 1 year of age for anaemia (21.3% (95%CI 8.3% to 32.5%, p=0.002)), all-cause hospital admissions (22.9% (95%CI 10.0% to 34.0%, p=0.001)), and hospital admissions associated with malaria parasitaemia (38.1% (95%CI 12.5% to 56.2%, p=0.007)).

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**Summary of evidence: harms** (from the application)

SP for intermittent preventive treatment in infancy is generally well tolerated.

Studies showed no evidence of any adverse effects of SP-IPTi on infants' serological responses to vaccines (e.g. DTP, polio, hepatitis B, Haemophilus influenzae B, yellow fever or measles). A rebound effect in terms of greater susceptibility to malaria after termination of SP-IPTi, although reported in some studies, was not found in the pooled analysis, where the pooled estimate of protective efficacy of IPTi-SP against clinical malaria for the potential rebound period was 9.5% (95%CI 0.3% to 17.8%, p=0.044) (*2*).

Surveillance of molecular markers of SP resistance should accompany SP-IPTi, in particular the distribution and prevalence of *Pfdhps* 540 mutations, which is a surrogate measure of SP efficacy.

Use pf IPTi-SP is contraindicated in individuals with known hypersensitivity to pyrimethamine, sulfonamides and related compounds and infants receiving a sulfa-based medication for treatment or prophylaxis, including co-trimoxazole (trimethoprim–sulfamethoxazole), which is widely used as prophylaxis against opportunistic infections in HIV-infected infants.

**Additional evidence** (not in the application)

A 2011 systematic review of the cost and the cost-effectiveness of malaria interventions found that the median financial cost of IPTi-SP for protecting one person for one year was US$ 0.60 (range US$ 0.48 to US$ 1.08) (*3*).

A study by Conteh et al of the cost-effectiveness of IPTi in sub-Saharan Africa found the cost per malaria episode averted for IPTi-SP was very low, US$ 1.36 to US$ 4.03 based on trial specific data (US$ 0.68 to US$ 2.27 on pooled analysis). The authors concluded that IPTi delivered with the EPI was a highly cost-effective intervention against clinical malaria (*4*).

**WHO Guidelines**

A 2010 WHO policy recommendation on IPTi-SP recommends the co-administration of SP-IPTi with DTP2, DTP3 and measles immunization to infants, through routine EPI in countries in sub-Saharan Africa, in areas with moderate-to-high malaria transmission (i.e. annual entomological inoculation rates ≥10), and where parasite resistance to SP is not high – defined as a prevalence of the pfdhps 540 mutation of ≤50% (*5*).

This recommendation was not re-evaluated during the guideline development process for the 2015 WHO Guidelines for the treatment of malaria (3rd edition). The same recommendation is included in the 2015 Guidelines, however the quality of evidence was not formally assessed (*6*).

**Costs/cost-effectiveness**

No information was provided in the application.

**Availability**

A paediatric formulation of sulfadoxine + pyrimethamine 250 mg + 12.5 mg is currently under assessment by the WHO Prequalification Programme.

The administered dose of IPTi-SP depends on the weight of the child:

- Children weighing less than 5 kg should be given 125 mg sulfadoxine and 6.25 mg pyrimethamine.
- Children weighing 5 kg or more should be given 250 mg sulfadoxine and 12.5 mg pyrimethamine.

**Other considerations**

The successful implementation of SP-IPTi requires that national malaria control and EPI programmes work together. WHO, working with UNICEF developed an implementation guide which provides the necessary technical and operational

information and tools for country-level policy-makers and programme managers to decide on how to include SP-IPTi with immunization services (*7*). In areas where SP-IPTi is implemented each child will be given SP three times in their first year of life when they receive routine vaccinations as follows:

- First SP-IPTi dose (SP-IPTi1) when DTP2/Penta2 (or combo) vaccination is given (i.e. 8-10 weeks of age)
- Second SP-IPTi dose (SP-IPTi2) when DTP3/Penta3 (or combo) vaccination is given (12-14 weeks of age)
- Third SP-IPTi dose (SP-IPTi3) at the time of measles vaccination (nine months)

The exact timing of the doses may vary according to the national immunization schedule for DTP and measles vaccination.

**Committee recommendations**

The Expert Committee recommended listing of sulfadoxine + pyrimethamine 250 mg + 12.5 mg fixed-dose combination tablet on the core list of the EMLc for the new indication of intermittent preventive treatment (of malaria) in infancy (IPTi) on the basis of demonstrated efficacy and acceptable safety, and in alignment with WHO malaria guideline recommendations.

The Expert Committee noted the lack of evidence of the impact of the use of SP-IPTi on antimicrobial resistance, and encouraged further assessment and monitoring in this regard within programme delivery.

## References

1. World Malaria Report 2018. Geneva: World Health Organization; 2018. Available from https://apps.who.int/iris/bitstream/handle/10665/275867/9789241565653-eng.pdf?ua=1, accessed 29 September 2019.
2. Aponte JJ, Schellenberg D, Egan A, Breckenridge A, Carneiro I, Critchley J et al. Efficacy and safety of intermittent preventive treatment with sulfadoxine-pyrimethamine for malaria in African infants: a pooled analysis of six randomised, placebo-controlled trials. Lancet. 2009;374(9700):1533–42.
3. White MT, Conteh L, Cibulskis R, Ghani AC. Costs and cost-effectiveness of malaria control interventions--a systematic review. Malar J. 2011;10:337.
4. Conteh L, Sicuri E, Manzi F, Hutton G, Obonyo B, Tediosi F et al. The cost-effectiveness of intermittent preventive treatment for malaria in infants in Sub-Saharan Africa. PLoS One. 2010; 5(6):e10313.
5. WHO Policy recommendation on Intermittent Preventive Treatment during infancy with sulphadoxine-pyrimethamine (SP-IPTi) for Plasmodium falciparum malaria control in Africa. Geneva: World Health Organization; 2010. Available from https://www.who.int/malaria/news/WHO_policy_recommendation_IPTi_032010.pdf, accessed 29 September 2019.

6. Guidelines for the treatment of malaria - 3rd edition. Geneva: World Health Organization; 2015. Available from http://apps.who.int/iris/bitstream/10665/162441/1/9789241549127_eng.pdf?ua=1&ua=1, accessed 29 September 2019.
7. Intermittent preventive treatment for infants using sulfadoxine-pyrimethamine (SP-IPTi) for malaria control in Africa: Implementation Field Guide. Geneva: World Health Organization; 2011. Available from https://apps.who.int/iris/bitstream/handle/10665/70736/WHO_IVB_11.07_eng.pdf, accessed 29 September 2019.

*Sulfadoxine + pyrimethamine – new indication IPTp – EML*

**Sulfadoxine + pyrimethamine** **ATC Code: P01BD51**

**Proposal**

The application requested listing of sulfadoxine + pyrimethamine (SP) fixed-dose combination tablet on the core list of the EML for the new indication of intermittent preventive treatment (of malaria) in pregnancy (IPTp).

**Applicant**

WHO Global Malaria Programme

**WHO Technical Department**

Global Malaria Programme

**EML/EMLc**

EML

**Section**

6.5.3.2 Antimalarial medicines - For chemoprevention

**Dose form(s) & strengths(s)**

Tablet 500 mg + 25 mg

**Core/Complementary**

Core

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Sulfadoxine + pyrimethamine 500 mg + 25 mg tablets are currently included on the EML and EMLc for use in combination with artesunate 50 mg for the curative treatment of malaria.

**Public health relevance** (burden of disease)

Malaria is one of the leading causes of illness, death, and lost economic productivity globally. While there has been successful scale up and use of critical commodities, malaria still resulted in over 219 million cases and more than 435 000 deaths in 2017; most of the deaths occurred in children under 5 years of age and pregnant women (*1*).

In sub-Saharan Africa (SSA), over 30 million pregnant women are annually exposed to infection from malaria (*2*). Of these, an estimated 10 000 pregnant women and up to 200 000 newborns die from malaria in pregnancy (MiP), primarily due to infection with *Plasmodium falciparum* (*3*). Furthermore, recent data indicate that up to 20% of stillbirths in SSA are attributable to MiP (*4*).

WHO recommends that IPTp-SP be given to all pregnant women at each antenatal care visit, starting as early as possible in the second trimester (i.e. not during the first trimester) (*5*). Each IPTp-SP dose should be given at least one month apart, with at least three doses during each pregnancy. The expected benefits of IPTp-SP include:

- Prevention of the adverse consequences of malaria on maternal and fetal outcomes, such as placental infection, clinical malaria, maternal anaemia, fetal anaemia, low-birth-weight and neonatal mortality (*6*).
- A cost-effective intervention for both prevention of maternal malaria and reduction of neonatal mortality in areas with moderate or high malaria transmission (*7*).
- Protection against both neonatal mortality (protective efficacy 18%) and low-birth-weight (21% reduction) under routine programme conditions (*8*).

To date, 39 African countries have adopted this policy. However, there is an unacceptably low proportion of eligible pregnant women receiving IPTp with quality-assured SP: only an estimated 22% of pregnant women received three doses of IPTp-SP in 2017 (*1*). It has been estimated that if all women with at least three antenatal care visits in Africa received IPTp-SP, that an additional 215 000 (95% credible interval (crI) 128 000 to 318 000) low-birth-weight deliveries could be prevented (*9*).

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**Summary of evidence: benefits** (from the application)

The application presented the findings of a systematic review of seven trials (6281 pregnancies) in which a direct comparison of two doses of IPTp-SP with three or more doses at least one month apart was evaluated (*10*). The trials were conducted in Burkina Faso, Kenya, Malawi, Mali and Zambia between 1996 and 2008. In comparison with two doses of SP, three or more doses was associated with:

- increased mean birth weight by an average of 56 g (95%CI 29 to 83; seven trials, 2190 participants, high quality evidence);
- fewer low-birth-weight infants by about 20% (relative risk (RR) 0.80; 95%CI 0.69 to 0.94; absolute risk reduction, 33 per 1000 (95%CI 10 to 52); NNT = 31; seven trials, 2190 participants, high quality evidence);

- reduced placental parasitaemia by about 50% (RR, 0.51; 95%CI 0.38 to 0.68; absolute risk reduction, 31 per 1000 (95%CI 20 to 39); six trials, 1436 participants, high quality evidence); and
- reduced maternal parasitaemia by about 33% (RR, 0.68; 95%CI 0.52 to 0.89; seven trials, 2096 participants, moderate quality evidence).

The reduction in risk for low-birth-weight was consistent for a wide range of levels of resistance to SP.

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**Summary of evidence: harms** (from the application)

There were no differences in rates of serious adverse events between treatment groups in the systematic review mentioned above (*10*).

IPTp-SP is generally very well tolerated. Mild and transient side-effects including nausea, vomiting, weakness and dizziness have been reported by some women, particularly with the first dose. Studies have demonstrated that side-effects tend to decrease with the administration of further doses (*11*, *12*).

The adverse effects reported are mainly those associated with sulfonamides, including gastrointestinal disturbances, headache, dizziness and skin reactions such as photosensitivity, rash, pruritus, urticaria and slight hair loss (*13*–*16*). Potentially fatal skin reactions, namely erythema multiforme, Stevens–Johnson syndrome and toxic epidermal necrolysis, have also been reported.

Demonstrated drug–drug interactions have been observed between SP and high doses (>5 mg) folic acid resulting in reduced efficacy of SP (*17*). Concurrent use with trimethoprim, alone or in combination with sulfamethoxazole should be avoided due to increased risk of severe cutaneous reactions (*18*).

There is limited evidence of potential teratogenicity when SP is used during the first trimester of pregnancy (*13*, *19*). Use of SP during the first trimester is not recommended.

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**Additional evidence** (not in the application)

N/A

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**WHO Guidelines**

The 2015 *WHO Guidelines for the treatment of malaria* (*5*) make the following recommendation regarding IPTp-SP:

In malaria-endemic areas in Africa, provide IPTp-SP to all women in their first or second pregnancy as part of antenatal care. Dosing should start in the second trimester and doses should be given at least one month apart, with the objective of ensuring that at least three doses are received (strong recommendation, high quality evidence).

### Costs/cost-effectiveness

SP is an inexpensive medicine, and most countries already have a delivery system for IPTp-SP in place, which is often integrated into a comprehensive focused antenatal care (FANC) package.

In comparison to placebo, in Mozambique, delivery of two doses of IPTp-SP has been estimated to cost US$ 41.46 (95%CI 20.50 to 96.70) per maternal outpatient visit averted. This same study estimated an incremental cost effectiveness ratio (ICER) of US$ 1.08 (95%CI 0.43 to 3.48) per disability-adjusted life-year (DALY) averted (*7*). Additionally, using data from seven countries, the incremental cost-effectiveness of three or more doses of IPTp-SP (compared to two doses) has been estimated at US$ 7.28 (*20*).

The WHO recommendations on intermittent screening and treatment in pregnancy and the safety of ACTs in the first trimester (*21*) state that IPTp-SP remains highly cost-effective in preventing the adverse consequences of malaria on maternal and fetal outcomes, and should therefore be actively scaled up in line with the current WHO recommendations. The threshold level of malaria transmission below which IPTp-SP is no longer cost-effective has not been identified. Therefore, in areas where IPTp-SP is implemented and transmission has been reduced to low levels as a result of successful control strategies, WHO recommends continued IPTp-SP implementation until the area approaches interruption of transmission.

### Availability

Quality assured sulfadoxine + pyrimethamine 500 mg + 25 mg tablets are available from Guilin Pharmaceuticals (China) with WHO prequalification status. Quality-assured sulfadoxine + pyrimethamine 500 mg/25 mg tablets are also available from Remedica Pharmaceuticals (Cyprus).

### Other considerations

Starting as early as possible in the second trimester, IPTp-SP is recommended for all pregnant women at each scheduled antenatal care visit until the time of delivery, provided that the doses are given at least one month apart. IPTp-SP should ideally be administered as directly observed therapy (DOT) of three tablets sulfadoxine + pyrimethamine 500 mg + 25 mg giving the total required dosage of 1500 mg + 75 mg SP.

### Committee recommendations

The Expert Committee recommended the listing of sulfadoxine + pyrimethamine 500 mg + 25 mg fixed-dose combination tablet on the core list of the EML for the new indication of intermittent preventive treatment of malaria in pregnancy (IPTp) on the basis of demonstrated efficacy in terms of improved outcomes

for mothers and newborns, and acceptable safety, and in alignment with WHO malaria treatment guidelines.

The Expert Committee noted the lack of evidence of the impact of the use of SP-IPTp on antimicrobial resistance, and encouraged further assessment and monitoring in this regard within programme delivery.

## References


1. World Malaria Report 2018. Geneva: World Health Organization; 2018. Available from https://apps.who.int/iris/bitstream/handle/10665/275867/9789241565653-eng.pdf?ua=1, accessed 29 September 2019.
2. Dellicour S, Tatem AJ, Guerra CA, Snow RW, ter Kuile FO. Quantifying the number of pregnancies at risk of malaria in 2007: a demographic study. PLoS Med. 2010;7(1):e1000221.
3. The contribution of malaria control to maternal and newborn health. Progress and impact series: Number 10, July 2014. Geneva: World Health Organization and Roll Back Malaria Partnership. Available from https://apps.who.int/iris/bitstream/handle/10665/126340/9789241507219_eng.pdf, accessed 29 September 2019.
4. Lawn JE, Blencowe H, Waiswa P, Amouzou A, Mathers C, Hogan D et al. Stillbirths: rates, risk factors, and acceleration towards 2030. Lancet. 2016;387(10018):587-603.
5. Guidelines for the treatment of malaria - 3rd edition. Geneva: World Health Organization; 2015. Available from: http://apps.who.int/iris/bitstream/10665/162441/1/9789241549127_eng.pdf, accessed 29 September 2019.
6. Menendez C, Bardaji A, Sigauque B, Sanz S, Aponte JJ, Mabunda S et al. Malaria prevention with IPTp during pregnancy reduces neonatal mortality. PLoS One. 2010;5(2):e9438.
7. Sicuri E, Bardaji A, Nhampossa T, Maixenchs M, Nhacolo A, Nhalungo D et al. Cost-effectiveness of intermittent preventive treatment of malaria in pregnancy in southern Mozambique. PLoS One. 2010;5(10):e13407.
8. Eisele TP, Larsen DA, Anglewicz PA, Keating J, Yukich J, Bennett A et al. Malaria prevention in pregnancy, birthweight, and neonatal mortality: a meta-analysis of 32 national cross-sectional datasets in Africa. Lancet Infect Dis. 2012;12(12):942–9.
9. Walker PG, Floyd J, Ter Kuile F, Cairns M. Estimated impact on birth weight of scaling up intermittent preventive treatment of malaria in pregnancy given sulphadoxine-pyrimethamine resistance in Africa: A mathematical model. PLoS Med. 2017;14(2):e1002243.
10. Kayentao K, Garner P, van Eijk AM, Naidoo I, Roper C, Mulokozi A et al. Intermittent preventive therapy for malaria during pregnancy using 2 vs 3 or more doses of sulfadoxine-pyrimethamine and risk of low birth weight in Africa: systematic review and meta-analysis. JAMA. 2013;309(6):594–604.
11. Clerk CA, Bruce J, Affipunguh PK, Mensah N, Hodgson A, Greenwood B et al. A randomized, controlled trial of intermittent preventive treatment with sulfadoxine-pyrimethamine, amodiaquine, or the combination in pregnant women in Ghana. J Infect Dis. 2008;198(8):1202–11.
12. Tagbor H, Bruce J, Browne E, Randal A, Greenwood B, Chandramohan D. Efficacy, safety, and tolerability of amodiaquine plus sulphadoxine-pyrimethamine used alone or in combination for malaria treatment in pregnancy: a randomised trial. Lancet. 2006;368(9544):1349–56.

13. Peters PJ, Thigpen MC, Parise ME, Newman RD. Safety and toxicity of sulfadoxine/pyrimethamine: implications for malaria prevention in pregnancy using intermittent preventive treatment. Drug Saf. 2007;30(6):481–501.
14. Luntamo M, Kulmala T, Mbewe B, Cheung YB, Maleta K, Ashorn P. Effect of repeated treatment of pregnant women with sulfadoxine-pyrimethamine and azithromycin on preterm delivery in Malawi: a randomized controlled trial. Am J Trop Med Hyg. 2010;83(6):1212–20.
15. Maokola W, Chemba M, Hamisi Y, Mrisho M, Shirima K, Manzi F et al. Safety of sulfadoxine/pyrimethamine for intermittent preventive treatment of malaria in infants: evidence from large-scale operational research in southern Tanzania. Int Health. 2011;3(3):154–9.
16. Mutabingwa TK, Muze K, Ord R, Briceno M, Greenwood BM, Drakeley C et al. Randomized trial of artesunate+amodiaquine, sulfadoxine-pyrimethamine+amodiaquine, chlorproguanal-dapsone and SP for malaria in pregnancy in Tanzania. PLoS One. 2009;4(4):e5138.
17. Ouma P, Parise ME, Hamel MJ, Ter Kuile FO, Otieno K, Ayisi JG et al. A randomized controlled trial of folate supplementation when treating malaria in pregnancy with sulfadoxine-pyrimethamine. PLoS Clin Trials. 2006;1(6):e28.
18. Gimnig JE, MacArthur JR, M'Bang'ombe M, Kramer MH, Chizani N, Stern RS et al. Severe cutaneous reactions to sulfadoxine-pyrimethamine and trimethoprim-sulfamethoxazole in Blantyre District, Malawi. Am J Trop Med Hyg. 2006;74(5):738–43.
19. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Folic acid antagonists during pregnancy and the risk of birth defects. N Engl J Med. 2000;343(22):1608–14.
20. Fernandes S, Sicuri E, Kayentao K, van Eijk AM, Hill J, Webster J et al. Cost-effectiveness of two versus three or more doses of intermittent preventive treatment for malaria during pregnancy in sub-Saharan Africa: a modelling study of meta-analysis and cost data. Lancet Glob Health. 2015;3(3):e143–53.
21. Recommendations on intermittent screening and treatment in pregnancy and the safety of ACTs in the first trimester. Geneva: World Health Organization; 2015. Available from https://www.who.int/malaria/publications/atoz/istp-and-act-in-pregnancy.pdf, accessed 29 September 2019.

*Amodiaquine with sulfadoxine + pyrimethamine – addition – EMLc*

| **Amodiaquine with sulfadoxine + pyrimethamine** | **ATC Code: P01BA06, P01BD51** |
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**Proposal**

The application requested the addition of co-packaged amodiaquine with sulfadoxine + pyrimethamine to the core list of the EMLc for seasonal malaria chemoprevention (SMC) in children.

**Applicant**

WHO Global Malaria Programme

**WHO Technical Department**

Global Malaria Programme

**EML/EMLc**

EMLc

**Section**

6.5.3.2 Antimalarial medicines - For chemoprevention

**Dose form(s) & strengths(s)**

Co-packaged amodiaquine dispersible tablet 76.5 mg (as hydrochloride) [3 tablets] and sulfadoxine + pyrimethamine dispersible tablet 250 mg + 12.5 mg [1 tablet]

Co-packaged amodiaquine dispersible tablet 153 mg (as hydrochloride) [3 tablets] and sulfadoxine + pyrimethamine dispersible tablet 5000 mg + 25 mg [1 tablet]

**Core/Complementary**

Core

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Amodiaquine and sulfadoxine + pyrimethamine are both listed on the EMLc for use in combination with artesunate for the curative treatment of malaria. These medicines have not previously been considered for use in malaria prophylaxis/ prevention.

**Public health relevance** (burden of disease)

Malaria is one of the leading causes of illness, death and lost economic productivity globally. In 2017, there were an estimated 219 million malaria cases worldwide, the majority of which occurred in the African region (92%, 200 million cases) (*1*). Of the 435 000 deaths due to malaria globally in 2017, 266 000 (61%) were in children under 5 years of age.

Across the Sahel sub-region in Africa, most childhood morbidity and mortality from malaria occurs during the rainy season, which is generally short. Giving effective antimalarial medicines – at full treatment doses and at appropriate intervals during this period – has been shown to prevent illness and death from malaria in children.

The interventions currently recommended by WHO for the control of malaria are use of long-lasting insecticidal mosquito nets and/or indoor residual spraying for vector control, prompt access to diagnostic testing of suspected cases and treatment of confirmed cases with effective artemisinin-based combination therapy. In addition to these, other interventions recommended for specific high-risk groups in areas of high transmission include intermittent preventive treatment in pregnancy (IPTp) and infancy (IPTi). With the changing epidemiology of malaria, there has been a progressive shift from a 'one size fits all' approach to targeting malaria control strategies to specific populations and/or locations for maximal effectiveness. In line with this approach and on the basis of new evidence, WHO recommends an additional intervention against *Plasmodium falciparum* malaria: seasonal malaria chemoprevention (SMC). The objective of preventive treatment is to prevent malarial illness by maintaining therapeutic drug levels in the blood throughout the period of greatest risk (*2*).

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**Summary of evidence: benefits** (from the application)

A 2012 Cochrane systematic review of seven trials (12 589 participants) evaluated the effects of seasonal malaria chemoprophylaxis compared with no prophylaxis in children aged 6 years or less living in areas of West Africa with seasonal malaria transmission (*3*). In three studies, amodiaquine (AQ) and sulfadoxine + pyrimethamine (SP) was administered monthly at full treatment doses, two studies used SP every two months, and one study used SP and artesunate monthly, during the malaria transmission season.

In comparison with no chemoprophylaxis, SMC was associated with markedly reduced clinical malaria episodes (rate ratio (RR) 0.26, 95%CI 0.17 to 0.38) and serious malaria episodes (RR 0.17, 95%CI 0.1 to 0.76). SMC may also be associated with a reduction in mortality (RR 0.66, 95%CI 0.31 to 1.39) and a reduction in moderately severe anaemia (RR 0.71, 95%CI 0.52 to 0.98). The findings were consistent in trials in which there was high (>90%) use of insecticide-treated bednets (*3*).

**Summary of evidence: harms** (from the application)

AQ + SP are safe and well tolerated when used at the recommended doses and regimens. Both drugs have been used for decades for malaria treatment, and SP is currently used for intermittent preventive treatment of malaria in pregnancy and in infancy.

Both AQ and SP are also used in combination with artesunate as artemisinin-based combination therapy, which is used for the treatment of uncomplicated malaria in many endemic countries.

In Senegal, where nearly 800 000 treatment courses of SP + AQ within SMC have been given to children, no serious adverse events attributable to these drugs were observed during intensive pharmacovigilance based on spontaneous reporting (*4*).

AQ + SP is generally well tolerated in children. Mild side-effects may occur, of which the most common is vomiting associated with intake of AQ. No serious adverse events attributable to AQ + SP have been reported in trials involving children (*5–7*).

SMC with AQ + SP is contraindicated in children receiving sulfa-based medication for treatment or prophylaxis, including sulfamethoxazole + trimethoprim, which is widely used as prophylaxis against opportunistic infections in HIV-infected infants.

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**Additional evidence** (not in the application)

N/A

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**WHO Guidelines**

The 2015 WHO *Guidelines for the treatment of malaria* recommend SMC with monthly AQ + SP for all children aged less than 6 years during each transmission season in areas with highly seasonal malaria transmission in the sub-Sahel region of Africa (strong recommendation, high quality evidence) (*8*).

The guideline recommendation was informed by the Cochrane systematic review mentioned above (*3*).

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**Costs/cost-effectiveness**

Evaluation of the cost of delivering SMC in large field trials shows that the greatest costs are associated with delivering the drugs and the incentives paid to health workers. In Gambia, the cost of SMC delivery by village health workers was estimated to be US$ 1.63 per child per year (*9*). In Senegal, where SMC was delivered by community health workers paid a daily rate and supervised by the health post nurse, the overall cost at 46 health posts was estimated to be US$ 0.5 per child per month, or approximately US$ 1.50 per child per year (*10*). The cost of SMC is similar to those of other malaria control interventions (*11*).

### Availability

Co-packaged sulfadoxine + pyrimethamine and amodiaquine tablets are currently available on the market from three manufacturers and have been prequalified by the WHO Prequalification Programme.

### Other considerations

N/A

### Committee recommendations

The Expert Committee recommends the addition of co-packaged amodiaquine with sulfadoxine + pyrimethamine to the core list of the EMLc for seasonal malaria chemoprevention in children on the basis of acceptable safety and demonstrated benefits for reducing clinical malaria episodes, serious malaria episodes and reduced rates of mortality and anaemia, and in alignment with WHO malaria guidelines.

The Expert Committee noted the lack of evidence of the impact of the use of amodiaquine with sulfadoxine + pyrimethamine for SMC on antimicrobial resistance, and encouraged further assessment and monitoring in this regard within programme delivery.

## References

1. World Malaria Report 2018. Geneva: World Health Organization; 2018. Available from https://apps.who.int/iris/bitstream/handle/10665/275867/9789241565653-eng.pdf, accessed 29 September 2019.
2. World Health Organization. WHO Policy Recommendation: Seasonal malaria chemoprevention (SMC) for Plasmodium flaciparum malaria control in highly seasonal transmission areas of the Sahel sub-region in Africa. March 2012. Available from https://www.who.int/malaria/mpac/feb2012/smc_policy_recommendation.pdf, accessed 29 September 2019.
3. Meremikwu MM, Donegan S, Sinclair D, Esu E, Oringanje C. Intermittent preventive treatment for malaria in children living in areas with seasonal transmission. Cochrane Database Syst Rev. 2012(2):CD003756.
4. Cisse B, Ba EH, Sokhna C, JL ND, Gomis JF, Dial Y et al. Effectiveness of Seasonal Malaria Chemoprevention in Children under Ten Years of Age in Senegal: A Stepped-Wedge Cluster-Randomised Trial. PLoS Med. 2016;13(11):e1002175.
5. Dicko A, Diallo AI, Tembine I, Dicko Y, Dara N, Sidibe Y et al. Intermittent preventive treatment of malaria provides substantial protection against malaria in children already protected by an insecticide-treated bednet in Mali: a randomised, double-blind, placebo-controlled trial. PLoS Med. 2011;8(2):e1000407.
6. Konate AT, Yaro JB, Ouedraogo AZ, Diarra A, Gansane A, Soulama I et al. Intermittent preventive treatment of malaria provides substantial protection against malaria in children already protected by an insecticide-treated bednet in Burkina Faso: a randomised, double-blind, placebo-controlled trial. PLoS Med. 2011;8(2):e1000408.

7. Sokhna C, Cisse B, Ba el H, Milligan P, Hallett R, Sutherland C et al. A trial of the efficacy, safety and impact on drug resistance of four drug regimens for seasonal intermittent preventive treatment for malaria in Senegalese children. PLoS One. 2008;3(1):e1471.

8. Guidelines for the treatment of malaria - 3rd edition. Geneva: World Health Organization; 2015. Available from http://apps.who.int/iris/bitstream/10665/162441/1/9789241549127_eng.pdf, accessed 29 September 2019.

9. Bojang KA, Akor F, Conteh L, Webb E, Bittaye O, Conway DJ et al. Two strategies for the delivery of IPTc in an area of seasonal malaria transmission in the Gambia: a randomised controlled trial. PLoS Med. 2011;8(2):e1000409.

10. Pitt C, Ndiaye M, Conteh L, Sy O, Hadj Ba E, Cisse B et al. Large-scale delivery of seasonal malaria chemoprevention to children under 10 in Senegal: an economic analysis. Health Policy Plan. 2017;32(9):1256–66.

11. Seasonal malaria chemoprevention with sulfadoxine-pyrimethamine plus amodiaquine in children: a field guide. Geneva: World Health Organization; 2013. Available from https://apps.who.int/iris/bitstream/handle/10665/85726/9789241504737_eng.pdf, accessed 29 September 2019.

## 6.5.5 Antitrypanosomal medicines

### 6.5.5.1 *African trypanosomiasis*

*Fexinidazole – addition – EML and EMLc*

**Fexinidazole** **ATC Code: P01CA03**

**Proposal**

The application requested listing of fexinidazole on the core list of the EML and EMLc for treatment of human African trypanosomiasis due to Trypanosoma brucei gambiense infection.

**Applicant**

Sanofi-aventis groupe

**WHO Technical Department**

Comments on the application were received from the WHO Department of Neglected Tropical Diseases. The technical unit advised that it supported the inclusion of fexinidazole on the Model Lists and considered that its introduction could result in important advantages in the management of human African trypanosomiasis.

**EML/EMLc**

EML and EMLc

**Section**

6.5.5.1 African trypanosomiasis

**Dose form(s) & strengths(s)**

Tablet 600 mg

**Core/Complementary**

Core

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Fexinidazole had not previously been considered for inclusion on the Model Lists.

The Model Lists currently include pentamidine and suramin sodium for treatment of 1st stage African trypanosomiasis and eflornithine, melarsoprol and nifurtimox for treatment of 2nd stage African trypanosomiasis (*1*).

**Public health relevance** (burden of disease)

Human African trypanosomiasis (HAT), or sleeping sickness, is one of the most neglected tropical diseases (NTDs). Without diagnosis and treatment, HAT is usually fatal as the parasites multiply in the body, cross the blood–brain barrier and invade the central nervous system at the late stage of the disease.

Human African trypanosomiasis takes two forms, depending on the parasite involved: *Trypanosoma brucei gambiense* HAT and *Trypanosoma brucei rhodesiense* HAT. *T. b. rhodesiense* causes an acute, rapidly progressive and fatal disease and is present in 3% of HAT cases. *T. b. gambiense* is responsible for 97% of HAT cases (*2*) and evolves to a fatal outcome between two and three years after infection (*3*).

As of October 2012, 7106 annual cases of *T. b. gambiense* HAT had been reported worldwide. With the increased efforts of control programmes and availability of combination therapy with eflornithine and nifurtimox (NECT) therapy, only 1420 gambiense HAT cases worldwide were reported to WHO in 2017, the lowest level since the start of the systematic global data collection 75 years ago (*4*). However, the incidence is suspected to be under reported due to different elements. The Democratic Republic of Congo (DRC) bears the majority of disease burden (83–84% of the reported cases in 2012, 2015 and 2016 (*4*).

In view of the success in control of the disease, *T. b. gambiense* was included in the WHO 'roadmap' for elimination and control of neglected tropical diseases. A target date was set for global elimination of HAT as a public health problem (<1 case/10 000 inhabitants in at least 90% of endemic areas) by 2020 with complete interruption of transmission in Africa targeted for 2030 (*5*).

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**Summary of evidence: benefits** (from the application)

Evidence of efficacy is based on data from three (yet to be published) clinical efficacy and safety studies (DNDiFEX004, DNDiFEX005, and DNDiFEX006), using data from 749 patients with HAT (from study sites in DRC and Central African Republic), 619 of which were treated with fexinidazole. FEX006 included 125 paediatric patients aged between 6 and 15 years weighing 20 kg or more.

FEX004 compared fexinidazole and NECT in 394 adult patients (aged ≥15 years) with late stage 2 HAT. The success rate was 91.2% for fexinidazole and 97.6% for the NECT combination. The primary objective of the study was met. Fexinidazole was considered an acceptable treatment as the difference in response compared to NECT was <13% in favour of NECT at 18 months after the end of treatment (EOT). In the primary analysis, the difference in success rate between groups remained within the margin of acceptable difference (−6.4%, 97.06% CI −11.2% to −1.6%). However, in the sub-population of patients with cerebrospinal fluid white blood cell count (CSF-WBC) >100 /μL the efficacy was 86.9% in the fexinidazole arm versus 98.7%% in the NECT arm, and therefore

the risk of failure was higher in this sub-group with fexinidazole. The follow-up analysis of the success rate at 24 months on the complete population (n=389) yielded similar findings to those with partial data for 24 months at the primary analysis timepoint (n=345) with only two new failures (one in each group).

FEX005 was an open-label single-arm cohort study of efficacy and safety of fexinidazole in 230 adult patients with stage 1 or early stage 2 HAT. The success rate with fexinidazole at 12 months after the EOT (98.7%; 95%CI 96.2% to 99.7%), was greater than an unacceptable rate of 80%. No difference was seen in efficacy at 12 months according to the stage of the disease. The success rate at 18 months improved slightly between the initial and follow-up analysis due to the inclusion of the additional 69 patients in the follow-up analysis (all successes): 97.8% (95%CI 95.0 to 99.3) vs 96.9% (95%CI 92.9 to 99.0) in the initial analysis.

FEX006 was an open-label single-arm prospective study of efficacy and safety of fexinidazole in 125 children aged ≥6 years and <15 years weighing over 20 kg with any stage HAT. The success rate with fexinidazole at 12 months after the EOT (97.6%; 95%CI 93.1% to 99.5%) was greater than an unacceptable rate of 80% and compatible with a target rate of 92%. The success rate at 18 months improved slightly between the initial and follow-up analysis due to the inclusion of the additional 40 patients in the follow-up analysis (all successes): 98.4% (95%CI 94.3 to 99.8), vs 97.6% (95%CI 91.8% to 99.7%) in the initial 12-month analysis.

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**Summary of evidence: harms** (from the application)

Pooled analyses of data from FEX004, FEX005 and FEX006, revealed findings consistent with observations from the individual study analyses, with regard to the incidence of treatment emergent adverse events (TEAEs), TEAEs that occurred between baseline and end of hospitalization (EOH), TEAEs that occurred after EOH, and TEAEs that were considered by the Investigator as possibly related to treatment. A total of 577 of 619 (93%) patients experienced TEAEs. Overall, 506 of 619 (82%) patients reported a total of 2026 possibly related TEAEs between initiation of treatment and EOT, with most being mild or moderate. In study FEX004 in patients with late stage 2 disease, the overall incidence of TEAEs was comparable between treatment groups (93.6% with fexinidazole vs 92.3% with NECT).

The most commonly reported TEAEs across all fexinidazole-treated patients (≥10% of patients) were vomiting (42%), headache (37%), nausea (35%), asthenia (27%), insomnia (23%), tremor (22%), decreased appetite (20%), dizziness (19%), dyspepsia (14%) and feeling hot (10%).

Comparing overall TEAEs between fexinidazole and NECT in late stage 2 patients, there were notable differences between treatment groups; these included higher rates in the NECT arm of pyrexia, chills, hyperkalaemia, convulsions and procedural pain; and higher rates in the fexinidazole arm of

insomnia, tremor, headache, asthenia, nausea, dizziness, hypocalcaemia, feeling hot, hypoalbuminaemia, abdominal pain (upper), chest pain and dyspepsia. Vomiting was reported in a similar percentage of patients. All other TEAEs occurred with similar frequency with NECT and fexinidazole in late stage 2 HAT patients, suggesting that the AEs were related to the underlying disease or that both treatments were associated with increased risk of the events to similar extents.

With regard to risk of QT prolongation, fexinidazole has been associated with QTcF interval increases and its use is contraindicated in patients at risk of QT prolongation, uncorrected electrolyte abnormalities, symptomatic cardiac arrhythmia, clinically relevant bradycardia, severe congestive cardiac failure or family history of sudden death.

Central nervous system/psychiatric events as well as emesis/vomiting were observed with fexinidazole treatment. Asymptomatic reversible neutropenia and elevated liver enzymes that were found at different dose regimens in Chagas disease patients were not reported in HAT patients with the treatment regimen used in the HAT studies.

**Additional evidence (not in the application)**

N/A

**WHO Guidelines**

Fexinidazole received a positive opinion by the European Medicines Agency (EMA) under Article 58 on 15 November 2018. It is not yet included in the WHO guidelines or any other national guidelines. However, WHO sleeping sickness treatment guidelines will be under revision in order to consider integration of fexinidazole as part of the therapeutic options to treat gambiense HAT.

**Costs/cost-effectiveness**

Drugs for HAT are provided free of charge to the WHO via a public–private partnership between WHO/Sanofi (pentamidine, melarsoprol and eflornithine) and WHO/Bayer AG (suramin, nifurtimox).

Under a signed agreement between Sanofi and WHO, drugs are donated to WHO, to be used exclusively for the treatment of HAT. Requests for supplies are made to WHO by governments of disease-endemic countries and organizations working in association with these governments. Stock control and shipment of the drugs are undertaken by Médecins sans Frontières-Logistique according to the agreement. Transport costs to countries are paid by Sanofi through its partnership with WHO.

Similar to NECT and other HAT drugs, fexinidazole will be distributed free of charge through the WHO Neglected Tropical Diseases Department to

national sleeping sickness control programmes (NSSCPs) and from there to treatment centres. The product will not be available through wide logistics of pharmacies or out of the predefined distribution system. No return on investment is expected.

With NECT, indirect costs including transport to hospital, food and hospitalization costs are born by the patients. They should be significantly reduced with fexinidazole when patients are not hospitalized and can be treated close to their home.

### Availability

Fexinidazole is a new oral treatment for sleeping sickness disease and is not yet distributed.

An application for fexinidazole was submitted to European Medicines Agency (EMA) through Article 58 of Regulation (EC) No 726/2004. Article 58 is a mechanism whereby the EMA may give a scientific opinion, in cooperation with the WHO, for the evaluation of medicinal products intended to prevent or treat diseases of major public interest and exclusively intended for markets outside the European Community. A positive opinion from EMA was given on 15 November 2018 for the following indication:

"Fexinidazole Winthrop is indicated for the treatment of both the first-stage (haemo-lymphatic) and the second-stage (meningo-encephalitic) of human African trypanosomiasis (HAT) due to *Trypanosoma brucei gambiense* in adults and children ≥6 years old and weighing ≥20 kg. Fexinidazole should be used in line with official recommendations"

However, lower efficacy of fexinidazole as compared to NECT has been seen in a sub-group of patients. Patients with cerebrospinal fluid white blood count (CSF-WBC) >100/μL should only be treated with fexinidazole if no other adequate treatment (e.g. NECT) is available or tolerated.

Registrations in DRC and Uganda are also scheduled. Further registrations in other endemic African countries are not planned due to the specific registration regulatory picture for human African trypanosomiasis products and related distribution systems.

### Other considerations

Since 2009, NECT has become the first-line therapy for stage 2 HAT due to *T. b. gambiense* and has improved the prognosis of treated patients (*6*), replacing monotherapy with eflornithine. NECT treatment requires a minimum health infrastructure and personnel to administer two slow infusions every day for seven days, on top of an oral treatment every 8 hours for 10 days, requiring systematic hospitalization, as well as being resource consuming for skilled health staff in the environment in which HAT patients live (remote, poor

areas with little health infrastructure). NECT is not recommended for early stage disease, instead, patients are treated with pentamidine administered via intramuscular injections.

Second line-therapy for stage 2 HAT due to *T. b. gambiense* includes melarsoprol, an organoarsenic compound, which is highly toxic and to which resistance has developed (*7*). Intravenous injections of melarsoprol are painful and can cause phlebitis. The drug has been administered by use of lengthy and complicated dosing schedules, however, an abbreviated 10-day regimen of melarsoprol has been developed.

The limitations associated with current HAT therapy include mandatory hospitalization and need for equipment and skilled and trained health staff to administer IV infusions and/or injections. The repeated infusions needed with current HAT therapy are not only painful but increase the risk of infection for the patient.

The distribution of treatment to remote health facilities due to heavy components (38 kg per box which includes four treatments comprising drugs, solvents and equipment), is also a costly logistical challenge (*8*).

Fexinidazole is orally administered once daily with food for 10 days. Recommended dosage regimens are according to body weight.

**Committee recommendations**

The Expert Committee recommended the listing of fexinidazole on the core list of the EML and EMLc for treatment of human African trypanosomiasis due to *Trypanosoma brucei gambiense* infection.

The Committee noted that fexinidazole was demonstrated in clinical trials to have success rates within acceptable margins compared to NECT, and acceptable safety. The Committee acknowledged that as an orally administered treatment, use of fexinidazole may offer both patient and health system advantages compared to parenteral administration of other medicines for this disease.

The Committee noted that fexinidazole would be provided free of charge through the WHO NTD department to national sleeping sickness control programmes and treatment centres, and could contribute to the goal of disease eradication, particularly in areas where access to health facilities is limited.

## References:

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2017. (WHO Technical Report Series, No. 1006). Available from https://apps.who.int/iris/bitstream/handle/10665/259481/9789241210157-eng.pdf, accessed 30 October 2019.
2. Franco JR, Cecchi G, Priotto G, Paone M, Diarra A, Grout L et al. Monitoring the elimination of human African trypanosomiasis: Update to 2014. PLoS Negl Trop Dis. 2017;11(5):e0005585.

3. Simarro PP, Diarra A, Ruiz Postigo JA, Franco JR, Jannin JG. The human African trypanosomiasis control and surveillance programme of the World Health Organization 2000-2009: the way forward. PLoS Negl Trop Dis. 2011;5(2):e1007.
4. Global Health Observatory data repository - Number of new reported cases (T.b. gambiense) - Data by country [website]. Last updated 20 September 2016. Geneva: World Health Organization; 2016. (http://apps.who.int/gho/data/node.main.A1636, accessed 30 October 2019).
5. Control and surveillance of human African trypanosomiasis: report of a WHO Expert Committee 2013. WHO Technical Report Series, No. 984. Geneva: World Health Organization; 2013.
6. Simarro PP, Franco J, Diarra A, Postigo JA, Jannin J. Update on field use of the available drugs for the chemotherapy of human African trypanosomiasis. Parasitology. 2012;139(7):842–6.
7. Bisser S, N'Siesi FX, Lejon V, Preux PM, Van Nieuwenhove S, Miaka Mia Bilenge C et al. Equivalence trial of melarsoprol and nifurtimox monotherapy and combination therapy for the treatment of second-stage Trypanosoma brucei gambiense sleeping sickness. J Infect Dis. 2007;195(3):322–9.
8. Simarro PP, Cecchi G, Franco JR, Paone M, Diarra A, Ruiz-Postigo JA, et al. Mapping the capacities of fixed health facilities to cover people at risk of gambiense human African trypanosomiasis. Int J Health Geogr. 2014;13:4.

## 6.6 Medicines for ectoparasitic infections

*Ivermectin – new indication scabies – EML and EMLc*

**Ivermectin** **ATC Code: P02CF01**

**Proposal**

The application requested listing of ivermectin on the core list of the EML and EMLc for the new indication of treatment of scabies.

**Applicant**

International League of Dermatological Societies
International Alliance for the Control of Scabies
WHO Department of Control of Neglected Tropical Diseases

**WHO Technical Department**

Department of Control of Neglected Tropical Diseases

**EML/EMLc**

EML and EMLc

**Section**

6.6 Medicines for ectoparasitic infections

**Dose form(s) & strengths(s)**

Tablet (scored) 3 mg

**Core/Complementary**

Core

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Ivermectin is currently included on the EML and EMLc as an intestinal anthelminthic and antifilarial treatment.

Only topical therapies for scabies (benzyl benzoate and permethrin) are currently included on the Model Lists.

**Public health relevance** (burden of disease)

Scabies is seen in all countries. In many resource-poor settings, prevalence rates of infestation can exceed 20% of the population and the most vulnerable members of society, children (*1*) and the elderly, are at highest risk.

In 2015, the global prevalence of scabies was over 200 million (*2*). Globally, scabies was responsible for 0.21% of disability-adjusted life-years (DALYs) from all conditions studied by the *Global Burden of Disease Study 2015* (*2*).

A major complication of scabies with lasting consequences for health, seen most in resource-poor settings, is symptomatic acute glomerulonephritis (AGN), which was reported in 10% of children in a survey in northern Australia, while 24% had microscopic haematuria (3). AGN was closely linked to skin sores due to streptococcal infection, and scabies was identified as the principal cause. Scabies infestation is also an epidemiological risk factor for rheumatic fever and there is a strong association with scabies-associated streptococcal infections (*4*). One study has identified a possible link between scabies and bacterial sepsis caused by *Staphylococcus aureus* in infants in the Gambia (*5*).

Household economic loss due to scabies is also a major problem in resource-poor communities. A study in rural Mexico indicated that families were spending a significant part of their household income on ineffective topical treatment of scabies (US$ 24) over each 3-month period, impacting the ability to purchase other commodities, including food (*6*).

Scabies in resource-poor environments is therefore both a potential cause of serious morbidity and a source of financial burden. Its high prevalence places a huge burden on stretched health care resources.

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**Summary of evidence: benefits** (from the application)

The application presented the results of a 2018 Cochrane systematic review of 15 studies (1896 participants) comparing topical permethrin, systemic ivermectin or topical ivermectin for treatment of scabies (*7*).

The response to oral ivermectin was found to be equivalent to the response to topical permethrin, two and four weeks after treatment. 200 µg/kg oral ivermectin (was associated with slightly lower rates of complete clearance after one week compared to permethrin 5% cream. Using the average clearance rate of 65% in the trials with permethrin, the illustrative clearance with ivermectin was 43% (RR 0.65, 95%CI 0.54 to 0.78; 613 participants, six studies; low certainty evidence).

After two weeks, there was no significant difference (illustrative clearance of permethrin 74% compared to ivermectin 68%; RR 0.91, 95%CI 0.76 to 1.08; 459 participants, five studies; low certainty evidence). In this review, there did not appear to be any advantage in repeated treatments in conventional

cases of scabies. Hence treatment with one to three doses of ivermectin or one to three applications of permethrin led to little or no difference in rates of complete clearance after four weeks follow-up (illustrative cures with one to three applications of permethrin 93% and with one to three doses of ivermectin 86%; RR 0.92, 95%CI 0.82 to 1.03; 581 participants, five studies; low certainty evidence).

Seven days after treatment with oral ivermectin 200 µg/kg or one application of permethrin 5% lotion, there was little or no difference in complete clearance rates (illustrative cure rates: permethrin 73%, ivermectin 68%; RR 0.93, 95%CI 0.74 to 1.17; 120 participants, one study; moderate certainty evidence). After two weeks, one initial dose of systemic ivermectin compared to one application of permethrin lotion produced similar complete clearance rates (extrapolated cure rates: 67% in both groups; RR 1.00, 95%CI 0.78 to 1.29; 120 participants, one study; low certainty evidence).

The application also presented the findings of numerous individual studies of ivermectin versus various topical agents for scabies that supported the comparative effectiveness of oral ivermectin (*8–18*).

The application presented evidence of the effectiveness of ivermectin for treating scabies when delivered through mass drug administration programmes. Studies in Solomon Islands (*19*, *20*), Australia (*21*), Brazil (*22*) and Fiji (*23*) all showed mass drug administration of ivermectin to be an effective public health intervention.

There is some evidence from case reports and case series that oral ivermectin (with or without topical scabicides) is effective in the treatment of crusted scabies (*24–28*). Crusted scabies is a hyper-transmissible form of scabies where patients are infected with very large populations of scabies mites. It is mainly seen in those who are immunocompromised including HIV-infected individuals, transplant recipients and those on high doses immuno-modulating drugs or biologic agents; it may also occur in endemic settings in apparently healthy individuals. It is rare but can cause a major problem with transmission to susceptible populations.

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**Summary of evidence: harms** (from the application)

Evidence for the safety of ivermectin has been evaluated when it was considered for listing on the EML for other indications.

In terms of safety of oral ivermectin for treatment of scabies, the Cochrane systematic review reported moderate certainty evidence of no withdrawals due to adverse events in either the oral ivermectin or topical permethrin treatment groups. There was moderate certainty evidence of little or no difference between treatment groups for the proportion of participants who experienced at least one adverse event two weeks after initiation of

treatment. After four weeks, ivermectin was associated with a larger proportion of participants with at least one adverse event (RR 1.30, 95%CI 0.35 to 4.83; 502 participants, four studies; low certainty evidence).

Most side-effects reported in other studies were transient and mild. Loose stool, fatigue and headache were most frequently reported, and the incidence among the randomized control trials of all side-effects was highest in the studies involving children.

When ivermectin is administered to subjects with high Loa loa microfilariaemia, severe adverse reactions such as neurological signs, encephalopathy and coma have been reported (*29*). In Loa loa endemic countries, potential coinfection with this parasite has to be considered prior to using ivermectin.

There were a total of 1656 reports for ivermectin in VigiBase (out of a total of over 14 million reports in the database). Reports in males and females were of similar proportions. The majority of reports were in adults aged 18 years and older. The most commonly reported adverse drug reactions (ADRs) for ivermectin alone and ivermectin co-administered with albendazole included pruritus, headache, dizziness, vomiting, rash, urticarial and diarrhoea. Most reported ADRs were considered to be minor and transient.

Safety of ivermectin in pregnant women or children under 15 kg body weight has not been established.

**Additional evidence** (not in the application)

N/A

**WHO Guidelines**

WHO guidelines on the treatment of skin and oral HIV-associated conditions in children and adults (*30*) recommend treatment with oral ivermectin (200 µg/kg) for mild/moderate scabies in HIV-infected children and adults if topical permethrin treatment is not feasible or there is a poor response (Strong recommendation, low quality evidence). The guidelines also recommend two doses of oral ivermectin for treatment of HIV-infected children ≥15 kg and adults with severe or crusted scabies.

**Costs/cost-effectiveness**

The application stated that no cost-benefit analyses on the use of ivermectin in scabies have been undertaken, but proposes that effective interventions with ivermectin may reduce personal, institutional and governmental expenditure.

**Availability**

Ivermectin has wide market availability. Generic brands are available.

**Other considerations**

N/A

**Committee recommendations**

The Expert Committee recommended listing of ivermectin on the core list of the EML and EMLc for the new indication of treatment of scabies. The Committee noted that oral ivermectin treatment is associated with comparable effectiveness to topical therapies and has acceptable safety. The Committee also noted the effectiveness of ivermectin as a public health intervention when delivered via mass drug administration programmes.

The Committee considered that the ease of oral administration compared to topical administration may also represent an advantage for patients in terms of compliance.

## References


1. Kearns T, Clucas D, Connors C, Currie BJ, Carapetis JR, Andrews RM. Clinic attendances during the first 12 months of life for Aboriginal children in five remote communities of northern Australia. PLoS One. 2013;8(3):e58231.
2. Karimkhani C, Colombara DV, Drucker AM, Norton SA, Hay R, Engelman D et al. The global burden of scabies: a cross-sectional analysis from the Global Burden of Disease Study 2015. Lancet Infect Dis. 2017;17(12):1247–54.
3. Streeton CL, Hanna JN, Messer RD, Merianos A. An epidemic of acute post-streptococcal glomerulonephritis among aboriginal children. J Paediatr Child Health. 1995;31(3):245–8.
4. McDonald M, Currie BJ, Carapetis JR. Acute rheumatic fever: a chink in the chain that links the heart to the throat? Lancet Infect Dis. 2004;4(4):240–5.
5. Mulholland EK, Ogunlesi OO, Adegbola RA, Weber M, Sam BE, Palmer A et al. Etiology of serious infections in young Gambian infants. Pediatr Infect Dis J. 1999;18(10 Suppl):S35–41.
6. Hay RJ, Estrada Castanon R, Alarcon Hernandez H, Chavez Lopez G, Lopez Fuentes LF, Paredes Solis S et al. Wastage of family income on skin disease in Mexico. BMJ. 1994;309(6958):848.
7. Rosumeck S, Nast A, Dressler C. Ivermectin and permethrin for treating scabies. Cochrane Database Syst Rev. 2018;4:CD012994.
8. Chhaiya SB, Patel VJ, Dave JN, Mehta DS, Shah HA. Comparative efficacy and safety of topical permethrin, topical ivermectin, and oral ivermectin in patients of uncomplicated scabies. Indian J Dermatol Venereol Leprol. 2012;78(5):605–10.
9. Mushtaq A, Khurshid K, Pal SS. Comparison of efficacy and safety of oral ivermectin with topical permethrin in treatment of scabies. JPAD. 2010;20:227–31.
10. Rohatgi V, S. Reddy N, Vagge D. A prospective, randomized, open labelled, comparative study of efficacy and cost effectiveness of permethrin and ivermectin in 5-15 years age group patients with scabies in a tertiary care hospital. Indian J Pharmacol. 2013;45:S45.
11. Manjhi PK, Sinha RI, Kumar M, Sinha KI. Comparative study of efficacy of oral ivermectin versus some topical antiscabies drugs in the treatment of scabies. J Clin Diagn Res. 2014;8(9):Hc01–4.
12. Bachewar NP, Thawani VR, Mali SN, Gharpure KJ, Shingade VP, Dakhale GN. Comparison of safety, efficacy, and cost effectiveness of benzyl benzoate, permethrin, and ivermectin in patients of scabies. Indian J Pharmacol. 2009;41(1):9–14.

13. Ly F, Caumes E, Ndaw CA, Ndiaye B, Mahe A. Ivermectin versus benzyl benzoate applied once or twice to treat human scabies in Dakar, Senegal: a randomized controlled trial. Bull World Health Organ. 2009;87(6):424–30.
14. Brooks PA, Grace RF. Ivermectin is better than benzyl benzoate for childhood scabies in developing countries. J Paediatr Child Health. 2002;38(4):401–4.
15. Goldust M, Rezaee E, Raghifar R, Naghavi-Behzad M. Ivermectin vs. lindane in the treatment of scabies. Ann Parasitol. 2013;59(1):37–41.
16. Goldust M, Rezaee E, Raghifar R. Comparison of oral ivermectin versus crotamiton 10% cream in the treatment of scabies. Cutan Ocul Toxicol. 2014;33(4):333–6.
17. Madan V, Jaskiran K, Gupta U, Gupta DK. Oral ivermectin in scabies patients: a comparison with 1% topical lindane lotion. J Dermatol. 2001;28(9):481–4.
18. Sule HM, Thacher TD. Comparison of ivermectin and benzyl benzoate lotion for scabies in Nigerian patients. Am J Trop Med Hyg. 2007;76(2):392–5.
19. Lawrence G, Leafasia J, Sheridan J, Hills S, Wate J, Wate C et al. Control of scabies, skin sores and haematuria in children in the Solomon Islands: another role for ivermectin. Bull World Health Organ. 2005;83(1):34–42.
20. Marks M, Taotao-Wini B, Satorara L, Engelman D, Nasi T, Mabey DC et al. Long Term Control of Scabies Fifteen Years after an Intensive Treatment Programme. PLoS Negl Trop Dis. 2015; 9(12):e0004246.
21. Kearns TM, Speare R, Cheng AC, McCarthy J, Carapetis JR, Holt DC et al. Impact of an Ivermectin Mass Drug Administration on Scabies Prevalence in a Remote Australian Aboriginal Community. PLoS Negl Trop Dis. 2015;9(10):e0004151.
22. Worth C, Heukelbach J, Fengler G, Walter B, Liesenfeld O, Hengge U et al. Acute morbidity associated with scabies and other ectoparasitoses rapidly improves after treatment with ivermectin. Pediatr Dermatol. 2012;29(4):430–6.
23. Romani L, Whitfeld MJ, Koroivueta J, Kama M, Wand H, Tikoduadua L et al. Mass Drug Administration for Scabies Control in a Population with Endemic Disease. N Engl J Med. 2015; 373(24):2305–13.
24. Nofal A. Variable response of crusted scabies to oral ivermectin: report on eight Egyptian patients. J Eur Acad Dermatol Venereol. 2009;23(7):793–7.
25. Ortega-Loayza AG, McCall CO, Nunley JR. Crusted scabies and multiple dosages of ivermectin. J Drugs Dermatol. 2013;12(5):584–5.
26. Roberts LJ, Huffam SE, Walton SF, Currie BJ. Crusted scabies: clinical and immunological findings in seventy-eight patients and a review of the literature. J Infect. 2005;50(5):375–81.
27. Sandre M, Ralevski F, Rau N. An elderly long-term care resident with crusted scabies. Can J Infect Dis Med Microbiol. 2015;26(1):39–40.
28. Yee BE, Carlos CA, Hata T. Crusted scabies of the scalp in a patient with systemic lupus erythematosus. Dermatol Online J. 2014;20(10).
29. WHO African Programme for Onchocerciasis Control (WHO/APOC). Programme for the Elimination of Neglected Diseases in Africa (PENDA): Strategic Plan of Action and Indicative Budget 2016–2025 Ouagadougou: APOC; 2013. Available from http://www.who.int/apoc/en_apoc_strategic_plan_2013_ok.pdf, accessed 29 September 2019.
30. Guidelines on the treatment of skin and oral HIV-associated conditions in children and adults. Geneva: World Health Organization; 2014. Available from https://apps.who.int/iris/bitstream/handle/10665/136863/9789241548915_eng.pdf, accessed 30 October 2019.

# Section 7: ANTIMIGRAINE MEDICINES

## 7.1 For treatment of acute attack

*Sumatriptan – addition – EML*

**Sumatriptan** **ATC Code: N02CC01**

**Proposal**

The application requested the addition of sumatriptan to the core list of the EML for the treatment of adult patients with acute migraine.

**Applicant**

Medicines and Medical Devices Area, Health Care and Welfare Directorate, Community Care Service, Emilia-Romagna Region

WHO Collaborating Centre in Evidence-Based Research Synthesis and Guideline Development, Emilia Romagna Health Care and Welfare Directorate

**WHO Technical Department**

Department of Mental Health and Substance Abuse

**EML/EMLc**

EML

**Section**

7.1 Antimigraine medicines – For treatment of acute attack

**Dose form(s) & strengths(s)**

Tablet 50 mg

**Core/Complementary**

Core

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

An application requesting addition of sumatriptan to the EML was considered by the Expert Committee in 2007. The Committee considered that the application was generally of poor quality and provided only a limited review of the evidence. Overall, the evidence provided in the application did not support the public

health need or comparative effectiveness, safety and cost-effectiveness of sumatriptan. The Committee therefore recommended that sumatriptan not be added to the Model List (*1*).

The EML currently lists acetylsalicylic acid tablets and paracetamol tablets for treatment of acute migraine attacks.

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**Public health relevance** (burden of disease)

Headache disorders are a public health concern given the associated disability and financial costs to society. As headache disorders are most troublesome in the productive years (i.e. late teens to 50s), estimates of their financial cost to society – mainly from lost working hours and reduced productivity – are massive. In the United Kingdom, for example, some 25 million working- or school-days are lost every year because of migraine alone (*2*).

The main source of data about the burden of migraine worldwide is the *Global Burden of Disease (GBD) Study* (2016), although its estimates refer mainly to a selected population of high-income countries, while data from important and populous low- and middle-income countries, such as Bangladesh, Democratic Republic of Congo, Egypt, Indonesia, Viet Nam, South Africa and several other countries in sub-Saharan Africa, are lacking.

According to the GBD study, 1.04 billion (95% uncertainty interval [UI] 1.00 to 1.09) people were estimated to have a migraine in 2016 (*3*).

Migraine has a profound effect on well-being and general functioning, not only during the acute attack, but also in terms of work performance, family and social relationships, and school achievement. Migraine carries a substantial individual, societal and economic burden, ranking as the second cause of disability (*4*).

According to the GBD study, in 2016 migraine was estimated to have caused 45.1 million (95%UI 29.0 to 62.8) years of life lived with disability (YLDs), and in 2017 overall 5.54% (95%CI 3.91 to 7.5) of total YLDs were attributed to migraine (*5*).

Even though the burden of migraine worldwide is considerable, accurate diagnosis, quality of care and rates of drug utilization are still insufficient across countries and settings. Worldwide, only 40% of people with migraine are professionally diagnosed (*6*).

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**Summary of evidence: benefits** (from the application)

The application identified clinical evidence on efficacy of sumatriptan in adults and children and adolescents with acute migraine attack from systematic reviews (SR) and randomized controlled trials (RCT) and ongoing studies. Clinical practice guideline recommendations were also presented.

### *Children and adolescents*

A 2016 Cochrane systematic review of 27 trials involving 7630 participants compared any pharmacological intervention by any route of administration for symptomatic acute treatment of a migraine attack in children (under 12 years of age) and adolescents (12 to 17 years of age). Acceptable comparators included placebo or other active drug treatments. The primary outcome was the percentage of pain-free participants at two hours (*7*). Most data on triptans in children and adolescents came from treatment with sumatriptan. Only intranasal sumatriptan has been studied in clinical trials in children.

A pooled estimate of six studies of oral sumatriptan in adolescents with acute migraine showed no difference between oral sumatriptan and placebo in reaching pain freedom at 2 hours. In absolute terms, the proportion of patients that were pain-free at two hours with sumatriptan was 21.7% vs 20% with placebo (risk difference (RD) 1.7%, 95%CI −4.3 to 7.1).

For studies involving sumatriptan via any route of administration, for the primary outcome of pain-free at two hours, clinical trials in adolescents show superiority of sumatriptan vs placebo, while in children the estimate does not reach statistical significance. Absolute estimates show that 49.3% of children on (intranasal) sumatriptan vs and 23.6% with placebo were pain-free at two hours (RD 25.7%, 95%CI 10.0 to 39.6), while 34.8% of adolescents on sumatriptan vs 25.1% on placebo (RD 9.7%, 95%CI 4.8 to 14.4).

Triptans considered as a class (regardless of the formulation) showed superiority vs placebo in reaching the primary outcome both among children (RD 16.3, 95%CI 6.2 to 25.9) and adolescents (RD 7.6%, 95%CI 5.4 to 9.7).

### *Adults*

Two systematic reviews provided evidence for the efficacy and safety of sumatriptan in adults.

An analysis of pooled data from 18 studies showed 50 mg oral sumatriptan to be more effective than placebo for the pain-free outcome at two hours for any pain intensity at baseline. Similarly, pooled data from 21 studies of 100 mg oral sumatriptan showed slightly higher estimates. Numbers needed to treat (NNT) ranged from 3 to 6.1. The certainty in the estimates was rated as high, according to GRADE. Results for outcomes of sustained pain freedom at 24 hours and use of rescue medicine also showed clinically meaningful differences and NNTs in favour of sumatriptan (*8*).

Compared to active comparators, efficacy of sumatriptan was comparable to that of other triptans except for eletriptan 40 mg an 80 mg, which showed significantly greater efficacy. Four studies compared sumatriptan 50 mg and 100 mg with effervescent acetylsalicylic acid (ASA) 1000 mg (two studies, 726 participants) and ASA 900 mg + metoclopramide 10 mg (two studies, 575 participants), respectively. The pooled analysis of the former comparison showed

no statistically significant differences relative to the pain-free outcome at two hours, while in the latter a significant difference in favour of sumatriptan 100 mg was observed. In absolute terms, 32.3% of patients treated with sumatriptan 50 mg and 26.4% of those on ASA 1000 mg were pain-free at two hours (RD 15% in favour of sumatriptan). Sumatriptan 100 mg was compared to paracetamol 1000 mg + metoclopramide 10 mg relative to the outcome headache relief at two hours (two studies, 1035 participants), showing no difference (*8*).

A network meta-analysis (NMA) by the Canadian Agency for Drugs and Technologies in Health (CADTH) compared the relative efficacy, effectiveness and safety of triptans alone or in combination with other drugs, all administration routes, any dose, compared with other triptans, non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (ASA), paracetamol, ergots, opioids in the treatment of acute migraine attacks in adults (>18 years of age) (*9*). Overall, considering all administration routes, freedom from pain at two hours was achieved in 18% to 50% of patients with acute migraine taking standard dose triptans. Sumatriptan 50 mg provided pain freedom at two hours in 27.7% (95%CI 24.6 to 31%) of patients, compared with 10.60% (95%CI 10.0 to 11.3%) for placebo. Triptans showed to be effective in the largest proportion of patients on the outcome "headache relief at two hours": 42% to 76% of patients, compared to 26.70% (95%CI 25.7% to 27.7%) for placebo. Fifty percent of patients taking sumatriptan 50 mg (95%CI 46.3% to 53.1%) had a headache relief at two hours (*9*).

Two additional RCTs not included in the systematic reviews provided data that did not change the conclusions of the SRs (*10*, *11*).

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**Summary of evidence: harms** (from the application)

The application identified safety data of sumatriptan in adults and children and adolescents from systematic reviews and RCTs and one observational study.

*Children and adolescents*

No safety data were available on oral sumatriptan in children. Overall, triptans in children did not show a higher frequency of adverse events (AEs) compared to placebo. For intranasal sumatriptan, the risk difference for any AEs was statistically higher than placebo. The overall frequency of any AEs in adolescents taking triptans was higher than placebo although most were considered mild *(7)*.

*Adults*

Among 20 049 patients treated with oral sumatriptan (25 mg to 300 mg), only two treatment-related serious AEs were reported: one after treating with sumatriptan 85 mg (heart palpitations), one after treating with sumatriptan 300 mg (chest tightness and pressure). Withdrawals due to AEs were uncommon: in placebo-controlled studies, excluding those using high doses of sumatriptan

(>100 mg), the rate of AE withdrawal among patients treated with sumatriptan was equivalent to that of placebo (0.71% (45/6349) and 0.65% (19/2926), respectively). Any AEs were more common in patients treated with sumatriptan (particularly at the 100 mg dose) than placebo (*8*).

Pooled estimates of comparisons of sumatriptan versus other triptans did not show significant differences for any AEs. Sumatriptan 100 mg was associated with a higher frequency of AEs compared to ASA and paracetamol in combination with metoclopramide (*8*).

An industry-funded SR and NMA assessed the tolerability of treatments administered by oral route in adults (>18 years of age) with acute migraine. The SR included 141 RCTs evaluating triptans, NSAIDs or barbiturates in any combination, without any other limitation regarding sample size or treatment concealing (*12*). The quality of the included studies was not formally assessed and the results should be interpreted with caution.

Data from direct comparisons were available for sumatriptan versus. placebo (39 studies), naproxen (six studies), naproxen + sumatriptan (four studies), selective cox-inhibitors (one study), ergotamine (one study), paracetamol (one study), eletriptan (three studies), rizatriptan (eight studies), naratriptan (two studies), zolmitriptan (four studies) and almotriptan (two studies).

Sumatriptan showed a significantly higher incidence of any AEs than placebo (OR 1.80, 95%CI 1.57 to 2.05), as well as sumatriptan + naproxen, zolmitriptan and rizatriptan. Sumatriptan, sumatriptan + naproxen zolmitriptan, rizatriptan, eletriptan and paracetamol showed a higher frequency of treatment-related AEs vs placebo (sumatriptan OR 2.23, 95%CI 1.86 to 2.70).

Serious adverse events (SAEs) show estimates with wide CIs (SAEs are uncommon, many trials reported zero events in at least one arm, and the definition of SAE varied among trials).

A meta-analysis of six observational studies assessed the risk of pregnancy outcomes (major congenital malformations (MCM), prematurity and spontaneous abortion) of women with migraine prenatally exposed to triptans, comparing them with those of women with migraine not taking triptans and with healthy women (*13*). Pooled analysis showed that the rate of MCM and prematurity was not increased among women with migraine taking triptans during pregnancy when compared with women with migraine not taking triptans. Women exposed to triptans during pregnancy showed a higher rate of spontaneous abortion. Women with migraine not taking triptans compared to healthy controls showed a higher risk of MCM, however this difference was observed on a relatively small sample of triptan-exposed women (n=178). The estimates should be interpreted with caution as they were not adjusted for potential confounders and the overall certainty was rated as very low.

A systematic review by the UK National Clinical Guideline Centre found conflicting evidence of very low quality regarding pregnancy outcomes from

a pooled analysis of three observational studies that compared women with migraine who took triptans during pregnancy and women with migraine who did not (*14*). The guideline panel concluded that the evidence reviewed, although inconclusive, did not indicate an increased risk of triptan use during pregnancy.

The Sumatriptan, Naratriptan and Treximet Pregnancy Registry is a prospective, observational, uncontrolled, international study sponsored by GlaxoSmithKline. The registry collected pregnancy data of women exposed at any time during their pregnancy to sumatriptan, naratriptan or the combination of sumatriptan and naproxen sodium from health care providers enrolled on a voluntary basis in 18 countries. Data were gathered during 16 years of observation, including a total of 904 exposed pregnant women, with 689 pregnancy outcomes. Six-hundred-and-ten women (67%) with 626 pregnancy outcomes (91%) had been exposed to sumatriptan. The frequency of major birth defects following any trimester of exposure to sumatriptan was 4.2% (24/576; 95%CI 2.7 to 6.2). The same frequency was observed considering 528 pregnancy outcomes after exposure during the first trimester (4.2% 95%CI 2.6% to 6.5%). The authors compared these data with those from other observational studies, showing birth defect frequencies of 4–5% among migraineurs, concluding that there is no signal of teratogenicity associated with major birth defects for sumatriptan (*15*). These results should be interpreted with caution, due to numerous limitations. Certainty in the estimates was rated very low using GRADE.

Triptans can induce vasoconstriction that may potentially increase the risk of cardiovascular events. A meta-analysis of four observational studies assessed the risk of severe cardiovascular events among persons with migraine taking triptans or ergotamine. The authors distinguished the risk of cardiovascular events and stroke associated with the intensity (number of prescribed/dispensed doses) and with the recency of migraine-specific use. Pooled analysis showed no significant differences in the overall risk of cardiovascular events of patients with migraine treated with triptans (intensity of treatment) as compared with controls (OR 0.86; 95%CI 0.52 to 1.43, $I^2$ 24.5%). Due to the high heterogeneity of results of the included studies, pooled analysis of the risk of cardiovascular events and stroke in relation to recency was not performed (*16*). Certainty in the estimates was rated as low using GRADE.

**Additional evidence** (not in the application)

N/A

**WHO Guidelines**

In 2007, WHO in collaboration with Lifting the Burden and with the European Headache Federation published guidance on the management of common headache disorders in primary care (*17*). This guidance recommended stepped

management of acute migraine attacks, treating three attacks at each step before proceeding to the next, starting from common analgesics (such as acetylsalicylic acid, ibuprofen, diclofenac, ketoprofen, naproxen or – where these are contraindicated – paracetamol) followed, if needed, by antiemetics (such as domperidone or metoclopramide). Triptans were recommended at the second step, among specific drugs, to be offered to all patients failing step one. The starting recommended formulation was oral, subcutaneous sumatriptan was suggested when all other triptans are ineffective. Analgesics only were recommended for children.

Sumatriptan (50 mg or 100 mg) is recommended as the first-line monotherapy treatment in adults by the SIGN guideline, with the suggestion of trying other triptans in case of failure (*18*).

The NICE guideline recommends an oral triptan in monotherapy or combined with NSAID or paracetamol in adults and children. In young subjects (12–17 years of age) nasal triptan is preferred (*14*).

The Canadian Headache Society guideline recommends sumatriptan, or another triptan, for moderate–severe migraine attacks in adults. If triptan in monotherapy is insufficient, it is recommended the association with naproxen sodium 500 mg (*19*).

According to SIGN and NICE guidelines, triptans can be used for treatment of acute migraine during pregnancy and in women in childbearing age.

**Costs/cost-effectiveness**

Cost-effectiveness modelling suggested that common analgesics (acetylsalicylic acid in particular) are the most cost-effective strategy for managing acute episodic migraine (*20*).

A triptan in combination with acetylsalicylic acid or paracetamol are potentially cost-effective interventions, although with a higher absolute cost, that however would be largely offset by savings in terms of gained health (*14*).

All triptans are available as generic drugs, but sumatriptan has the lowest price in most countries, including LMICs. Oral eletriptan shows superiority to oral sumatriptan relative to all relevant outcomes. However, eletriptan is, on average, substantially more expensive than sumatriptan even considering the non-proprietary name preparations.

**Availability**

Sumatriptan is available globally in branded and generic forms.

**Other considerations**

Sumatriptan was not proposed for inclusion in the EMLc by the applicant because:

- oral sumatriptan is not licensed in children and has not been studied in RCTs;
- oral sumatriptan has been studied in adolescents 12 to 17 years of age with episodic migraine showing no superiority versus placebo in reaching pain freedom at two hours;
- intranasal sumatriptan has been studied in adolescents 12 to 17 years of age showing to be more effective than placebo and is licensed in such patients by some regulatory agencies in high-income countries. However, since the intranasal inhalation of the drug needs patient training, the effectiveness of this preparation observed in clinical trials may not be directly applicable in settings where training is impractical or not possible. Moreover, the cost-effectiveness of intranasal sumatriptan is substantially lower than oral sumatriptan.

**Committee recommendations**

The Committee did not recommend the addition of sumatriptan to the core list of the EML for the treatment of adult patients with acute migraine.

The Committee noted that the available evidence supported the superior effectiveness of sumatriptan compared to placebo, but that evidence comparing sumatriptan with currently listed analgesics (aspirin and paracetamol) showed varying results, including no difference in effect.

However, the Committee also noted that sumatriptan is recommended as first-line therapy for migraine in many international guidelines, and would welcome a future review of additional data of the role of sumatriptan in the context of other migraine therapies.

## References

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2007 (including the 15th Model List of Essential Medicines) (WHO Technical Report Series No. 946). Geneva: World Health Organization; 2007.
2. Headache disorders (WHO fact sheets). Available from http://www.who.int/news-room/fact-sheets/detail/headache-disorders, accessed 29 September 2019.
3. GBD 2016 Headache Collaborators. Global, regional and national burden of migraine and tension-type headache, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018;17(11):954–76.
4. Steiner TJ, Stovner LJ, Vos T, Jensen R, Katsarava Z. Migraine is first cause of disability in under 50s: will health politicians now take notice? J Headache Pain. 2018;19(1):17.
5. Global Burden of Disease Study 2016 data portal [website]. Seattle: Institute for Health Metrics and Evaluation, University of Washington; 2017. (https://vizhub.healthdata.org/gbd-compare/, accessed 29 September 2019).

6. Saylor D, Steiner TJ. The Global Burden of Headache. Semin Neurol. 2018;38(02):182–90.
7. Richer L, Billinghurst L, Linsdell MA, Russell K, Vandermeer B, Crumley ET et al. Drugs for the acute treatment of migraine in children and adolescents. Cochrane Database Syst Rev. 2016;4:CD005220.
8. Derry CJ, Derry S, Moore RA. Sumatriptan (subcutaneous route of administration) for acute migraine attacks in adults. Cochrane Database Syst Rev. 2012(2):CD009665.
9. Cameron C, Kelly S, Hsieh SC, Murphy M, Chen L, Kotb A et al. Triptans in the Acute Treatment of Migraine: A Systematic Review and Network Meta-Analysis. Headache. 2015;55 Suppl 4:221–35.
10. Tepper SJ, Cady RK, Silberstein S, Messina J, Mahmoud RA, Djupesland PG et al. AVP-825 breath-powered intranasal delivery system containing 22 mg sumatriptan powder vs 100 mg oral sumatriptan in the acute treatment of migraines (The COMPASS study): a comparative randomized clinical trial across multiple attacks. Headache. 2015;55(5):621–35.
11. Pini LA, Guerzoni S, Cainazzo M, Ciccarese M, Prudenzano MP, Livrea P. Comparison of tolerability and efficacy of a combination of paracetamol + caffeine and sumatriptan in the treatment of migraine attack: a randomized, double-blind, double-dummy, cross-over study. J Headache Pain. 2012;13(8):669–75.
12. Thorlund K, Toor K, Wu P, Chan K, Druyts E, Ramos E et al. Comparative tolerability of treatments for acute migraine: A network meta-analysis. Cephalalgia. 2017;37(10):965–78.
13. Marchenko A, Etwel F, Olutunfese O, Nickel C, Koren G, Nulman I. Pregnancy outcome following prenatal exposure to triptan medications: a meta-analysis. Headache. 2015;55(4):490–501.
14. Headaches in over 12s: diagnosis and management (Clinical guideline CG150) [website]. London: National Institute for Health and Care Excellence; 2015. (https://www.nice.org.uk/guidance/CG150, accessed 29 September 2019).
15. Ephross SA, Sinclair SM. Final results from the 16-year sumatriptan, naratriptan, and treximet pregnancy registry. Headache. 2014;54(7):1158–72.
16. Roberto G, Raschi E, Piccinni C, Conti V, Vignatelli L, D'Alessandro R et al. Adverse cardiovascular events associated with triptans and ergotamines for treatment of migraine: systematic review of observational studies. Cephalalgia. 2015;35(2):118–31.
17. Steiner TJ, Paemeleire K, Jensen R, Valade D, Savi L, Lainez MJ et al. European principles of management of common headache disorders in primary care. J Headache Pain. 2007;8 Suppl 1:S3–47.
18. Scottish Intercollegiate Guidelines Network S. Pharmacological management of migraine. 2018.
19. Worthington I, Pringsheim T, Gawel MJ, Gladstone J, Cooper P, Dilli E et al. Canadian Headache Society Guideline: acute drug therapy for migraine headache. Can J Neurol Sci. 2013;40(5 Suppl 3):S1–S80.
20. Linde M, Steiner TJ, Chisholm D. Cost-effectiveness analysis of interventions for migraine in four low- and middle-income countries. J Headache Pain. 2015;16:15.

# Section 8: IMMUNOMODULATORS AND ANTINEOPLASTICS

## 8.1 Immunomodulators for non-malignant disease

*Medicines for multiple sclerosis – addition – EML and EMLc*

| | |
|---|---|
| **Glatiramer acetate** | **ATC Code: L03AX13** |
| **Fingolimod** | **ATC Code: L04AA27** |
| **Ocrelizumab** | **ATC Code: L04AA36** |

**Proposal**

The application requested the addition of glatiramer acetate, fingolimod and ocrelizumab to the complementary list of the EML and EMLc for use in the treatment of multiple sclerosis.

**Applicant**

Multiple Sclerosis International Federation (MSIF)

**WHO Technical Department**

Department of Mental Health and Substance Abuse

**EML/EMLc**

EML and EMLc

**Section**

8.1 Immunomodulators for non-malignant disease

**Dose form(s) & strengths(s)**

Glatiramer acetate: injection 20 mg/mL, 40 mg/mL
Fingolimod: capsule 0.25 mg, 0.5 mg
Ocrelizumab: injection 300 mg/10 mL in 10 mL vial

**Core/Complementary**

Complementary

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

In 2015, the Expert Committee reviewed an application requesting addition of azathioprine to the EML for the treatment of multiple sclerosis (MS). The Committee acknowledged the significant public health burden of MS

but noted the availability of a number of well-established and more recent immunomodulating medicines for this condition. The Committee therefore recommended that a comprehensive review be undertaken of all medicines used for the management of relapsing–remitting and other forms of MS for future consideration (*1*).

The Multiple Sclerosis International Federation (MSIF) is a non-state actor in official relations with WHO. They convened a taskforce of global experts in MS research and care to submit an application for disease-modifying therapies (DMTs) for the treatment of MS to be included on the EML. All approved DMTs used for the treatment of MS were summarized by comparative effectiveness in a variety of clinical settings based on the recently published ECTRIMS/EAN (European Committee for Treatment and Research for Multiple Sclerosis/European Association of Neurology) *Guideline on the pharmacological treatment of people with MS* (*2*). A comparison was also made with the American Academy of Neurology guidelines on DMTs in MS (*3*).

Of the multiple therapies used for treating MS, the application prioritized three medications to be included on the EML. Prioritization was based on their efficacy/safety profiles, tolerability/liveability, monitoring needs, route of administration, licensed use in paediatric-onset and primary progressive MS, safety profile in pregnancy, and availability of generic and/or biosimilar substitutes.

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**Public health relevance** (burden of disease)

Multiple sclerosis is an immune-mediated disorder of the central nervous system (grey and white matter) characterized by inflammation, demyelination and degenerative changes including neuroaxonal loss and progressive brain and spinal cord atrophy. Approximately 85% of those with MS initially experience relapses and remissions of neurological symptoms, (relapsing–remitting MS, RRMS), with relapses often associated with new areas of central nervous system inflammation. Gradual worsening in this population, with or without additional inflammatory events, is known as secondary progressive MS. Progressive changes can occur at any time in the disease course, but usually become more prominent over time. Approximately 15% of people diagnosed with MS have a progressive course from disease onset (primary progressive MS). Some with primary progressive MS may have typical relapses later in their disease course, after a progressive course has been established (*4*, *5*).

In 2013, there were more than 2.3 million people with MS worldwide (*6*, *7*). The incidence and prevalence of MS are rising, with studies showing significantly larger numbers than was previously estimated (*8*–*15*). Women are disproportionally affected, with prevalence in females two to three times that in males (*7*, *16*). Although the cause is not fully understood, MS is considered to have complex causality blending genetic risk and environmental factors. People

can be diagnosed throughout the age range, though MS is most often diagnosed between the ages of 20 and 50 years. Onset may also occur in childhood, and it is estimated that 3% to 10% of all individuals with MS experience their first attack prior to age 18 years (*17*). The incidence of paediatric-onset MS in North American and European studies has been reported to be between 0.13 to 0.6 cases per 100 000 children (*18*).

Symptoms of MS negatively impact functional abilities and quality of life, and often include overwhelming fatigue, mood and cognitive changes, mobility impairment, sensory impairment, visual disturbances, sexual dysfunction, and impaired bowel and bladder control. People with MS report lower health-related quality of life compared to other populations – including those with other chronic illnesses. The prevalence of depression is estimated to be 70% in people with MS (*19*).

The goal of treatment is to reduce the long-term burden of the disease, i.e. to delay disability progression and to prevent secondary progressive MS (*20*). Quality of life and the socioeconomic burden of MS are closely linked to disability, therefore, delaying and preventing disability worsening will have a major impact for individuals with the disease and for society (*21*).

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**Summary of evidence: benefits** (from the application)

***Glatiramer acetate***

Three trials (3217 patients) compared glatiramer acetate with placebo in patients with RRMS with follow up ranging from 52 to 104 weeks (*22–24*). Compared to placebo, glatiramer acetate lowered annualized relapse rates for follow ups of 52–96 weeks (mean difference (MD) −0.14, 95%CI −0.21 to −0.06, moderate quality evidence, n=2117, two studies) and resulted in more patients free from relapse at one to two years follow up (RR 1.17, 95%CI 1.10 to 1.24, moderate quality evidence, n=2360, three studies). Glatiramer acetate was also shown to result in a lower number of cumulative gadolinium-enhancing (GAD) lesions (MD −0.73, 95%CI −1.15 to −0.31, high quality evidence, n=1325, one study) and new or newly enlarging T2 lesions at 6 and 12 months follow up (MD −1.94, 95%CI −3.03 to −0.85, high quality evidence, n=1325, one study)). Low quality evidence showed a non-statistically significant effect on disability at two years follow up (RR 0.86, 95%CI 0.66 to 1.11, n=964, two studies).

Four trials compared glatiramer acetate to interferon in patients with RRMS (*25–28*). At two years' follow up, the number of participants free from relapse did not significantly differ (RR 0.98, 95%CI 0.90 to 1.06, moderate quality evidence, n=2175, 3 studies), nor did extent of disability worsening (RR 1.07, 95%CI 0.83 to 1.31, one study).

One trial (970 patients) compared glatiramer acetate to placebo for patients with primary-progressive MS (*29*). There was a non-significant effect on

the number of participants with disability worsening (RR 0.87, 95%CI 0.75 to 1.02) and longer time to disability worsening (HR 0.87, 95%CI 0.71 to 1.07) in the glatiramer acetate group.

### *Fingolimod*

Two trials compared fingolimod with placebo in patients with RRMS, with two years follow up (*30*, *31*). A larger proportion of patients were free from relapse at two years in the fingolimod arm (RR 1.44, 95%CI 1.28 to 1.63, moderate quality evidence, n=2355). The annualized relapse rate was also lower in the fingolimod arm (MD −0.21, 95%CI −0.25 to −0.16, moderate quality evidence). Fingolimod-treated patients had a lower risk of disability worsening compared to placebo (RR 0.71, 95%CI 0.56 to 0.90, moderate quality evidence, n=2355). Patients also had fewer new or newly enlarged T2 lesions (RR 2.16, 95%CI 1.77 to 2.63, moderate quality evidence, n=1192) and fewer GAD lesions (MD −0.87, 95%CI −1.10 to −0.64, moderate quality evidence, n=1216, two studies) at two years follow up. According to one study, fingolimod reduced percent change in brain volume at one to two years follow up (MD 0.3, 95%CI 0.16 to 0.44, moderate quality evidence, n=685).

One trial compared fingolimod with interferon in patients with RRMS (*32*). Moderate quality evidence showed that participants in the fingolimod arm had lower annualized relapse rates (MD −0.17, 95%CI −0.26 to −0.08, n=860), and more participants were free from relapse at one year (RR 1.19, 95%CI 1.11 to 1.29, n=860) than the interferon group. Fingolimod was also associated with fewer new or newly enlarged T2 lesions (MD −0.90, 95%CI −1.62 to −0.18, n=733) and GAD lesions (MD −0.28, 95%CI −0.50 to −0.06, n=728). There was no significant difference in extent of disability progression between fingolimod and interferon in the trial.

A Phase III trial investigated the safety and efficacy of fingolimod versus interferon beta-1a, in 215 children and adolescents (ages 10 to 17) with MS. Fingolimod significantly reduced annualized relapse rates by 82% (absolute difference, 0.55; 95%CI 0.36 to 0.74; relapses RR 0.18, 95%CI 0.11 to 0.30) over a period of up to two years compared to interferon beta-1a; reduced the number of new or newly enlarged T2 lesions up to 24 months by 53% (RR 0.47, 95%CI 0.36 to 0.62) and reduced the average number of gadolinium-enhancing T1 (Gd+) lesions per scan at 24 months by 66.0% (RR 0.34, 95%CI 0.22 to 0.54). Fingolimod was associated with a higher rate of serious adverse events (16.8% vs 6.5%) (*33*).

One trial (970 participants) compared fingolimod with placebo in patients with primary-progressive MS (*34*). There was no difference in disability progression at 156 weeks follow up between fingolimod or placebo (RR 0.93, 95%CI 0.80 to 1.08, moderate quality evidence). The adjusted annualized relapse rate was 0.12 with fingolimod and 0.67 with interferon beta-1a (absolute

difference, 0.55 relapses; relative difference, 82%; P<0.001). The key secondary end point of the annualized rate of new or newly enlarged lesions on T2-weighted magnetic resonance imaging (MRI) was 4.39 with fingolimod and 9.27 with interferon beta-1a (absolute difference, 4.88 lesions; relative difference, 53%; P<0.001). Adverse events, excluding relapses of multiple sclerosis, occurred in 88.8% of patients who received fingolimod and 95.3% of those who received interferon beta-1a. Serious adverse events occurred in 18 patients (16.8%) in the fingolimod group and included infection (in four patients) and leukopenia (in two patients). Six patients had convulsions. Serious adverse events occurred in seven patients (6.5%) in the interferon beta-1a group and included infection (in two patients) and supraventricular tachycardia (in one patient).

### *Ocrelizumab*

A Phase II trial compared ocrelizumab (low and high dose) and placebo in patients with RRMS. At the end of the 24 weeks participants in both ocrelizumab groups had lower numbers of active brain lesions compared to the placebo group (89%, 95%CI 68 to 97, lower in low dose ocrelizumab group and 96%, 95%CI 89 to 99, lower in high dose ocrelizumab group). Annualized relapse rates over the 24 weeks were 0.13 (95%CI 0.03 to 0.29) in the low dose ocrelizumab group and 0.17 (95%CI 0.05 to 0.35) in the high dose ocrelizumab group compared to the 0.64 rate (95%CI 0.43 to 0.94) of the placebo group. Findings also showed that both doses of ocrelizumab were effective in reducing MRI and clinical disease activity (*35*).

Two Phase III clinical trials, OPERA I and OPERA II, compared the effects of ocrelizumab (600 mg every 24 weeks) with interferon beta-1b (44 µg three times a week) for 96 weeks. Clinical outcomes from 1656 participants show significantly reduced annualized relapse rates with ocrelizumab compared to interferon beta-1a at two years (MD −0.13, 95%CI −0.18 to −0.08) thus meeting its primary endpoint. Secondary outcomes showed ocrelizumab had lower rate of disability progression. For the total trial period of 96 weeks, the rate of disability progression at 24 weeks was 6.9% vs 10.5% in the ocrelizumab and interferon beta-1a groups, respectively (HR 0.60; 95%CI 0.43 to 0.84). Patients in the ocrelizumab group also had fewer GAD lesions (*36*).

One trial compared ocrelizumab to placebo in patients with primary progressive MS. The ocrelizumab group had a greater time to disability progression at 120 weeks follow up when confirmed at both 12 weeks (HR 0.76, 95%CI 0.59 to 0.98, high quality evidence, n=732) and 24 weeks (HR 0.75, 95%CI 0.58 to 0.97, high quality evidence, n=732) (*37*).

### *Rituximab*

A 2013 Cochrane systematic review found one trial comparing rituximab to placebo in 104 adult patients with RRMS (*38*). The mean number of total GAD

lesions, the primary endpoint of this double-blind Phase II trial, was significantly decreased in patients receiving rituximab after 12, 16, 20 and 24 weeks (−5.0, 95%CI −9.99 to −0.01). The proportion of patients with relapses was significantly reduced in the rituximab group, both after 24 weeks (14.5% vs 34.3% in the placebo group; p=0.02) and 48 weeks (20.3% vs 40.0%, p=0.04) (*39*). A Phase II open-label study of 26 patients with RRMS receiving rituximab at baseline and six months found that mean annualised relapse rate reduced from 1.27 to 0.23, and mean number of GAD lesions reduced from 1.31 to 0.05 at week 48 and 0.0 at week 72. Mean number of new or newly enhancing T2 lesions also decreased from 0.92 at week 4 to 0.0 at week 72 (*40*).

A randomized controlled trial (439 participants) compared rituximab versus placebo in patients with primary progressive MS (*41*). Patients were randomized (2:1) to receive two intravenous doses (two weeks apart) of rituximab (n=292) or placebo (n=147) infusions every 24 weeks, for 96 weeks. Results showed that fewer in the rituximab group (30.2%) experienced 12 weeks confirmed disease progression during 96 weeks compared to 38.5% in the placebo group, but the difference did not reach statistical significance (p=0.14). However, in a predefined sub-analysis, rituximab showed a significant effect in patients with active MRI lesions or aged less than 51 years. This effect was comparable with the effect seen in the ocrelizumab trial, which only included patients below the age of 55.

Real-world data on treatment with rituximab in MS was available from a study that examined the disease course of 822 MS patients, 557 with RRMS, 198 with secondary progressive MS and 67 with primary progressive MS, who were followed for a mean duration of 22 months (*42*). RRMS patients treated with rituximab had a yearly relapse rate of 0.044 during the study period. In total, 5.2% of the patients stopped treatment because of side-effects or disease activity. The ratio of GAD lesions per MRI dropped significantly from approximately three months after treatment initiation, and was in total 0.054, present in 2.2% of MRIs. Moreover, the registry data suggest that the treatment efficacy of rituximab in RRMS could exceed the effect of fingolimod, dimethyl fumarate and beta-interferons. In addition, adherence was higher and side-effects were comparable to all other drugs (*43*, *44*).

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**Summary of evidence: harms** (from the application)

The application presented a summary description of adverse events associated with glatiramer acetate, fingolimod and ocrelizumab, and their associated frequencies, as reported in the respective approved prescribing information documents.

Common and very common adverse events associated with glatiramer acetate include injection site reactions, lipoatrophy, vasodilation, rash, dyspnoea, chest pain and lymphadenopathy.

Common and very common adverse events associated with fingolimod include headache, influenza, diarrhoea, back pain, elevated liver enzymes, cough, first-dose bradycardia, macular oedema, lymphopenia and bronchitis.

Common and very common adverse events associated with ocrelizumab include infusion reactions and infections. Ocrelizumab has also been associated with a possible increased risk of malignancies.

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**Additional evidence** (not in the application)

*Glatiramer acetate*

A 2016 Cochrane systematic review of six trials (2904 participants) compared the safety and efficacy of glatiramer acetate and beta-interferons (*45*). Both medicines showed similar clinical efficacy at 24 months (three studies) for number of participants with relapse (RR 1.04, 95%CI 0.87 to 1.24) or confirmed progression (RR 1.11, 95%CI 0.91 to 1.35). At 36 months, results from a single study suggested that relapse rates were higher in the IFN group than in the GA group (RR 1.40, 95%CI 1.13 to 1.74). However, greater and faster reduction in MRI lesion load accrual was observed in IFN-treated compared with GA-treated participants with MS (MD for T2 weighted lesion volume −0.58, 95%CI −0.99 to −0.18). Reviewers interpretation of overall evidence quality was cautious: the number of studies and participants was limited, the heterogeneity among studies was high and the clinical relevance of scales to measure disease progression was considered doubtful. The number of participants who withdrew from or dropped out of the study because of adverse events was available for four studies (2685 participants; 93%). No differences were found between the two treatment groups (RR 0.95, 95%CI 0.64 to 1.40). Results were similar for severe adverse events (RR 0.99, 95%CI 0.63 to 1.56).

A 2018 network meta-analysis including direct and indirect evidence, including 24 trials published between 1987 and 2015, yielded a more precise estimate of effectiveness for both interferon beta-1a once a week versus placebo (HR 0.73, 95%CI 0.53 to 1.00) and glatiramer acetate (HR 0.76, 95%CI 0.60 to 0.97) at three months (*46*). There was little evidence of superiority of one drug over another but ranking of the medicines suggested that interferon beta-1a three times weekly had the highest cumulative probability of superiority. Interpretation of these findings should take into consideration the short length of follow up, the high risk of bias across studies, and the potential differences among trials that may act as effect modifiers and introduce bias in the network meta-analysis. This review also considered discontinuation due to adverse events, at different follow up times. Evidence that one medicine was more likely to lead to discontinuation than another was limited, as the confidence intervals were wide: more discontinuation were observed with interferon beta-1a three times weekly versus placebo (RR 2.49, 95%CI 0.89 to 6.95) and with glatiramer acetate (RR 2.36, 95%CI 0.74 to 7.53).

### *Fingolimod*

A 2016 Cochrane systematic review of six trials (5512 participants) compared the safety and efficacy of fingolimod versus placebo or other disease modifying treatment for RRMS (*47*). Compared to placebo, fingolimod at 24 months increased the probability of being relapse-free (RR 1.44, 95%CI 1.28 to 1.63); moderate quality of evidence), little or no difference in preventing disability progression was observed (RR 1.07, 95%CI 1.02 to 1.11; primary clinical endpoints; low quality evidence). Benefit was observed for other measures of inflammatory disease activity including annualized relapse rate and GAD lesions. No significant increased risk of discontinuation due to adverse events was observed for fingolimod at recommended dose compared to placebo at six and 24 months. No significant increased risk of discontinuation due to serious adverse events was observed for fingolimod 0.5 mg compared to placebo at six and 24 months. A significant increased risk of discontinuation due to serious adverse events was found for fingolimod 5.0 mg (RR 2.77, 95%CI 1.04 to 7.38) compared to placebo at six months.

Compared to intramuscular interferon beta-1a, there was moderate quality evidence fingolimod 0.5 mg at one year slightly increased the number of participants free from relapse (RR 1.18, 95%CI 1.09 to 1.27) or from GAD lesions (RR 1.12, 95%CI 1.05 to 1.19), and decreased the relapse rate (rate ratio 0.48, 95%CI 0.34 to 0.70). There was no observed advantage for preventing disability progression (RR 1.02, 95%CI 0.99 to 1.06; low quality evidence).

There was a greater likelihood of participants discontinuing fingolimod, compared to other DMTs, due to adverse events at six months (RR 3.21, 95%CI 1.16 to 8.86), but there was no significant difference versus interferon beta-1a at 12 months (RR 1.51, 95%CI 0.81 to 2.80; moderate quality evidence). A higher incidence of adverse events was suggestive of the lower tolerability rate of fingolimod compared to interferon-beta 1a.

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**WHO Guidelines**

None available.

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**Costs/cost-effectiveness**

The cost-effectiveness of disease modifying treatments for MS have been assessed in multiple systematic reviews involving studies conducted in high-income countries in Europe and North America (*48–51*). The studies reported that DMTs (including glatiramer acetate, fingolimod, ocrelizumab and rituximab) were potentially cost-effective but several studies reported costs that were likely to be above particular countries' willingness to pay thresholds. Limitations of these studies noted in these reviews included the lack of head-to-head comparisons between different DMTs, variation in time-horizons, and variation in end-points. There were no cost-effectiveness studies identified from LMICs.

Though there is significant variance globally, a North American study suggested that approximately 60% of people with MS are unemployed (*52*), accounting for about one third of the total economic burden of MS (*53*). In addition to a loss in productivity, people with MS will have additional care needs with advancing age and disease severity. The economic burden of MS per patient and year ranges from approximately US$ 24 666 to US$ 51 678 (*54*). These amounts represent direct costs, which include in and out patient care, medications, medical procedures and social services as well as indirect costs related to loss of employment, disability benefits, early pension plans, and loss of productivity for spouses or family members providing informal care and death. Given the most frequent age of presentation (young adults), it is important to note that MS has both physical and cognitive impact, and also impacts the family development of the patients, as well as, determines a socioeconomic impact on society as a whole.

### Availability

Glatiramer acetate has marketing approval in many countries. Generic versions of glatiramer acetate are available in some countries – for example, in India, the Russian Federation and the United States. Secondary patents concerning glatiramer acetate are active in some jurisdictions.

Fingolimod also has marketing approval in many countries. Price and availability of fingolimod vary globally. Generic versions are available. The main product patent on fingolimod appears not to have been filed in the LMIC jurisdictions surveyed and expires between 2016 and 2018 in some European countries and 2019 in the United States.

Ocrelizumab has marketing approval in 68 high- and middle-income countries. Ocrelizumab is protected by a product patent expiring in 2023 in many jurisdictions. It is likely that biosimilar ocrelizumab cannot enter the market where this patent has been granted before 2023.

Rituximab has marketing approval for indications other than multiple sclerosis in high-, middle- and low-income countries. Biosimilar versions of rituximab have been approved in numerous countries, including Australia, Bolivia, Chile, India, Peru, the Republic of Korea, and the European Union.

### Other considerations

Use in pregnancy

A pregnancy registry maintained by the marketing company of branded glatiramer acetate captured over 7000 pregnancies exposed to glatiramer acetate. It did not find an increase in spontaneous abortions, premature births, neonatal complications or birth defects (*55*). No significant differences were observed in birth weight of babies born to mothers exposed to glatiramer during pregnancy

compared with mothers not exposed to glatiramer acetate during pregnancy. Evidence supports the use of branded glatiramer acetate in pregnant women who are recommended to remain on treatment to manage disease activity.

Fingolimod is a teratogen class C agent and should be considered an absolute contraindication in pregnancy and breastfeeding based on its known teratogenicity in animal studies and post-marketing data.

Ocrelizumab is known to cross the placental barrier and is recommended to be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the fetus. There are no adequate data on the developmental risk associated with use of ocrelizumab in pregnant women.

For rituximab, a large cohort study found that out of 153 pregnancies, 90 resulted in live births (*56*). Twenty-two infants were born prematurely; with one neonatal death at six weeks. Eleven neonates had haematologic abnormalities; none had corresponding infections. Two congenital malformations were identified.

The European League Against Rheumatism (EULAR) considered use of rituximab before pregnancy and during pregnancy (*57*). Based on a systematic literature and consensus among experts, the recommendation considered that rituximab should be replaced by other medication before conception. It should be used during pregnancy only when no other pregnancy-compatible drug can effectively control maternal disease.

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**Committee recommendations**

The Expert Committee acknowledged the important public health burden of MS and the need for effective and affordable treatments and noted the large number of supporting letters that were received in relation to the application.

The Committee appreciated the approach taken in the application to propose a limited number of essential medicines for MS, but noted that the superiority of the presented medicines over other therapeutic options in terms of benefits, harms and affordability did not clearly emerge.

The Committee noted that some commonly used treatments were not included (e.g. azathioprine, natalizumab, dimethyl fumarate, cladribine) or were not given full consideration (rituximab) and the reasons for their exclusion were not clear. The Committee also noted ongoing development in international MS guidelines and would welcome a revised application for EML inclusion in the future that considers the relative roles of all available medicines for MS.

In particular, the Committee noted the evidence presented in the application in relation to rituximab. The Committee agreed that rituximab could have a relevant clinical role in treatment of MS, and recommended that any future application should include evidence for rituximab versus active comparators, not just placebo.

The Committee, therefore, did not recommend the addition of glatiramer acetate, fingolimod and ocrelizumab to the Model Lists at this time, and would welcome a revised application which comprehensively reviews the relative roles of relevant available medicines for MS.

## References


1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children) (WHO Technical Report Series, No. 994). Geneva: World Health Organization; 2015. Available from https://apps.who.int/iris/bitstream/handle/10665/189763/9789241209946_eng.pdf, accessed 30 October 2019.
2. Montalban X, Gold R, Thompson AJ, Otero-Romero S, Amato MP, Chandraratna D et al. ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis. Mult Scler. 2018;24(2):96–120.
3. Rae-Grant A, Day GS, Marrie RA, Rabinstein A, Cree BAC, Gronseth GS et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2018;90(17):777–88.
4. Lublin FD. New multiple sclerosis phenotypic classification. Eur Neurol. 2014;72 Suppl 1:1–5.
5. Frischer JM, Bramow S, Dal-Bianco A, Lucchinetti CF, Rauschka H, Schmidbauer M et al. The relation between inflammation and neurodegeneration in multiple sclerosis brains. Brain. 2009;132(Pt 5):1175–89.
6. Browne P, Chandraratna D, Angood C, Tremlett H, Baker C, Taylor BV et al. Atlas of Multiple Sclerosis 2013: A growing global problem with widespread inequity. Neurology. 2014;83(11):1022–4.
7. Atlas of MS 2013: mapping multiple sclerosis around the world. London: Multiple Sclerosis International Federation; 2013. Available from: http://www.msif.org/about-us/advocacy/reports-and-resources/, accessed 29 September 2019.
8. Marrie RA, Yu N, Blanchard J, Leung S, Elliott L. The rising prevalence and changing age distribution of multiple sclerosis in Manitoba. Neurology. 2010;74(6):465–71.
9. Mackenzie IS, Morant SV, Bloomfield GA, MacDonald TM, O'Riordan J. Incidence and prevalence of multiple sclerosis in the UK 1990-2010: a descriptive study in the General Practice Research Database. J Neurol Neurosurg Psychiatry. 2014;85(1):76–84.
10. Benito-Leon J. Multiple sclerosis: is prevalence rising and if so why? Neuroepidemiology. 2011;37(3-4):236–7.
11. Amankwah N, Marrie RA, Bancej C, Garner R, Manuel DG, Wall R et al. Multiple sclerosis in Canada 2011 to 2031: results of a microsimulation modelling study of epidemiological and economic impacts. Health Promot Chronic Dis Prev Can. 2017;37(2):37–48.
12. Sahraian MA, Sahebkar M, Dehghani R, Derakhshan-Jazari M, Kazami-Moghaddam V, Kouchaki E. Multiple sclerosis-A disease on a dramatically rising trend in Iran: Review of possible reasons. Iran J Neurol. 2017;16(1):34–40.
13. Chinea A, Rios-Bedoya CF, Vicente I, Rubi C, Garcia G, Rivera A et al. Increasing Incidence and Prevalence of Multiple Sclerosis in Puerto Rico (2013-2016). Neuroepidemiology. 2017;49(3-4):106–12.
14. Brola W, Sobolewski P, Flaga S, Fudala M, Jantarski K. Increasing prevalence and incidence of multiple sclerosis in Poland. Neurol Neurochir Pol. 2017;51(1):82–5.

15. Bezzini D, Policardo L, Profili F, Meucci G, Ulivelli M, Bartalini S et al. Multiple sclerosis incidence in Tuscany from administrative data. Neurol Sci. 2018;39(11):1881–5.

16. Ascherio A, Munger KL. Epidemiology of Multiple Sclerosis: From Risk Factors to Prevention-An Update. Semin Neurol. 2016;36(2):103–14.

17. Chitnis T. Disease-modifying therapy of pediatric multiple sclerosis. Neurotherapeutics. 2013; 10(1):89–96.

18. Waldman A, Ghezzi A, Bar-Or A, Mikaeloff Y, Tardieu M, Banwell B. Multiple sclerosis in children: an update on clinical diagnosis, therapeutic strategies, and research. Lancet Neurol. 2014;13(9):936–48.

19. Marrie RA, Fisk JD, Tremlett H, Wolfson C, Warren S, Tennakoon A et al. Differences in the burden of psychiatric comorbidity in MS vs the general population. Neurology. 2015;85(22):1972–9.

20. Giovannoni G, Butzkueven H, Dhib-Jalbut S, Hobart J, Kobelt G, Pepper G et al. Brain health: time matters in multiple sclerosis. Mult Scler Relat Disord. 2016;9 Suppl 1:S5–s48.

21. Kobelt G, Thompson A, Berg J, Gannedahl M, Eriksson J. New insights into the burden and costs of multiple sclerosis in Europe. Mult Scler. 2017;23(8):1123–36.

22. Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology. 1995;45(7):1268–76.

23. Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med. 2012;367(12):1087–97.

24. Khan O, Rieckmann P, Boyko A, Selmaj K, Zivadinov R. Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis. Ann Neurol. 2013;73(6):705–13.

25. Mikol DD, Barkhof F, Chang P, Coyle PK, Jeffery DR, Schwid SR et al. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. Lancet Neurol. 2008;7(10):903–14.

26. Cadavid D, Wolansky LJ, Skurnick J, Lincoln J, Cheriyan J, Szczepanowski K et al. Efficacy of treatment of MS with IFNbeta-1b or glatiramer acetate by monthly brain MRI in the BECOME study. Neurology. 2009;72(23):1976–83.

27. Calabrese M, Bernardi V, Atzori M, Mattisi I, Favaretto A, Rinaldi F et al. Effect of disease-modifying drugs on cortical lesions and atrophy in relapsing-remitting multiple sclerosis. Mult Scler. 2012;18(4):418–24.

28. O'Connor P, Filippi M, Arnason B, Comi G, Cook S, Goodin D et al. 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. Lancet Neurol. 2009;8(10):889–97.

29. Wolinsky JS, Narayana PA, O'Connor P, Coyle PK, Ford C, Johnson K et al. Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial. Ann Neurol. 2007;61(1):14–24.

30. Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med. 2010;362(5):387–401.

31. Calabresi PA, Radue EW, Goodin D, Jeffery D, Rammohan KW, Reder AT et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 2014;13(6):545–56.

32. Cohen JA, Barkhof F, Comi G, Hartung HP, Khatri BO, Montalban X et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med. 2010;362(5):402–15.
33. Chitnis T, Arnold DL, Banwell B, Bruck W, Ghezzi A, Giovannoni G et al. Trial of Fingolimod versus Interferon Beta-1a in Pediatric Multiple Sclerosis. N Engl J Med. 2018;379(11):1017–27.
34. Lublin F, Miller DH, Freedman MS, Cree BAC, Wolinsky JS, Weiner H et al. Oral fingolimod in primary progressive multiple sclerosis (INFORMS): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet. 2016;387(10023):1075–84.
35. Kappos L, Li D, Calabresi PA, O'Connor P, Bar-Or A, Barkhof F et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. Lancet. 2011;378(9805):1779–87.
36. Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med. 2017;376(3):221–34.
37. Montalban X, Hauser SL, Kappos L, Arnold DL, Bar-Or A, Comi G et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. N Engl J Med. 2017;376(3):209–20.
38. He D, Guo R, Zhang F, Zhang C, Dong S, Zhou H. Rituximab for relapsing-remitting multiple sclerosis. Cochrane Database Syst Rev. 2013(12):CD009130.
39. Hauser SL, Waubant E, Arnold DL, Vollmer T, Antel J, Fox RJ et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N Engl J Med. 2008;358(7):676–88.
40. Bar-Or A, Calabresi PA, Arnold D, Markowitz C, Shafer S, Kasper LH et al. Rituximab in relapsing-remitting multiple sclerosis: a 72-week, open-label, phase I trial. Ann Neurol. 2008;63(3):395–400.
41. Hawker K, O'Connor P, Freedman MS, Calabresi PA, Antel J, Simon J et al. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. Ann Neurol. 2009;66(4):460–71.
42. Salzer J, Svenningsson R, Alping P, Novakova L, Bjorck A, Fink K et al. Rituximab in multiple sclerosis: A retrospective observational study on safety and efficacy. Neurology. 2016;87(20):2074–81.
43. Granqvist M, Boremalm M, Poorghobad A, Svenningsson A, Salzer J, Frisell T et al. Comparative Effectiveness of Rituximab and Other Initial Treatment Choices for Multiple Sclerosis. JAMA Neurol. 2018;75(3):320–7.
44. Alping P, Frisell T, Novakova L, Islam-Jakobsson P, Salzer J, Bjorck A et al. Rituximab versus fingolimod after natalizumab in multiple sclerosis patients. Ann Neurol. 2016;79(6):950–8.
45. La Mantia L, Di Pietrantonj C, Rovaris M, Rigon G, Frau S, Berardo F et al. Interferons-beta versus glatiramer acetate for relapsing-remitting multiple sclerosis. Cochrane Database Syst Rev. 2016;11:CD009333.
46. Melendez-Torres GJ, Armoiry X, Court R, Patterson J, Kan A, Auguste P et al. Comparative effectiveness of beta-interferons and glatiramer acetate for relapsing-remitting multiple sclerosis: systematic review and network meta-analysis of trials including recommended dosages. BMC Neurol. 2018;18(1):162.
47. La Mantia L, Tramacere I, Firwana B, Pacchetti I, Palumbo R, Filippini G. Fingolimod for relapsing-remitting multiple sclerosis. Cochrane Database Syst Rev. 2016;4:CD009371.
48. Sharac J, McCrone P, Sabes-Figuera R. Pharmacoeconomic considerations in the treatment of multiple sclerosis. Drugs. 2010;70(13):1677–91.
49. Hawton A, Shearer J, Goodwin E, Green C. Squinting through layers of fog: assessing the cost effectiveness of treatments for multiple sclerosis. Appl Health Econ Health Policy. 2013; 11(4):331–41.

50. Thompson JP, Abdolahi A, Noyes K. Modelling the cost effectiveness of disease-modifying treatments for multiple sclerosis: issues to consider. Pharmacoeconomics. 2013;31(6):455–69.

51. Hernandez L, O'Donnell M, Postma M. Modeling Approaches in Cost-Effectiveness Analysis of Disease-Modifying Therapies for Relapsing-Remitting Multiple Sclerosis: An Updated Systematic Review and Recommendations for Future Economic Evaluations. Pharmacoeconomics. 2018; 36(10):1223–52.

52. Dobrescu A, Dinh T, Stonebridge C. Multiple Sclerosis in the Workplace: Making the Case for Enhancing Employment and Income Supports. Ottawa: The Conference Board of Canada; 2018. Available from https://www.conferenceboard.ca/e-library/abstract.aspx?did=9611, accessed 29 September 2019.

53. Dinh T, Astles P, Turpin K. Multiple Sclerosis in the Workplace: Supporting Successful Employment Experiences. Ottawa: The Conference Board of Canada, 2016. Available from: https://www.conferenceboard.ca/e-library/abstract.aspx?did=7921, accessed 29 September 2019.

54. Ernstsson O, Gyllensten H, Alexanderson K, Tinghog P, Friberg E, Norlund A. Cost of Illness of Multiple Sclerosis - A Systematic Review. PLoS One. 2016;11(7):e0159129.

55. Sandberg-Wollheim M, Neudorfer O, Grinspan A, Weinstock-Guttman B, Haas J, Izquierdo G et al. Pregnancy Outcomes from the Branded Glatiramer Acetate Pregnancy Database. Int J MS Care. 2018;20(1):9–14.

56. Chakravarty EF, Murray ER, Kelman A, Farmer P. Pregnancy outcomes after maternal exposure to rituximab. Blood. 2011;117(5):1499–506.

57. Gotestam Skorpen C, Hoeltzenbein M, Tincani A, Fischer-Betz R, Elefant E, Chambers C et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis. 2016;75(5):795–810.

*TNF-alfa inhibitors for chronic inflammatory diseases – addition – EML and EMLc*

| | |
|---|---|
| **Etanercept** | **ATC Code: L04AB01** |
| **Infliximab** | **ATC Code: L04AB02** |
| **Adalimumab** | **ATC Code: L04AB04** |
| **Certolizumab pegol** | **ATC Code: L04AB05** |
| **Golimumab** | **ATC Code: L04AB06** |

**Proposal**

The application requested the addition of anti-tumour necrosis factor (TNF) biologic medicines etanercept, infliximab and adalimumab (and biosimilars) to the EML and EMLc and of certolizumab pegol and golimumab to the EML for the treatment of severe chronic inflammatory autoimmune disorders: rheumatoid arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and Crohn disease.

**Applicant**

Centre for Global Health - University of Ottawa

**WHO Technical Department**

Management of NCDs, Disability, Violence & Injury Prevention

**EML/EMLc**

EML and EMLc

**Section**

8.1 Immunomodulators for non-malignant disease

**Dose form(s) & strengths(s)**

Etanercept (ETN): injection 25 mg/mL, 50 mg/mL
Infliximab (IFX): powder for injection 100 mg
Adalimumab (ADA): injection 40 mg/0.8 mL, 40 mg/0.4 mL
Certolizumab pegol (CZP): injection 200 mg/mL
Golimumab (GOL): injection 50 mg/0.5 mL, 100 mg/mL

**Core / Complementary**

Complementary

**Individual / Square box listing**

Square box

**Background** (if relevant, eg. resubmission, previous EC consideration)

Anti-TNF biologic medicines had not previously been considered for inclusion on the Model Lists.

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**Public health relevance** (burden of disease)

**Rheumatoid arthritis** (RA) is a chronic autoimmune disease that can affect multiple joints, connective tissues, muscles, tendons and fibrous tissues. It is a chronic disabling condition causing severe pain and deformity. The global prevalence of RA in 2017 was 0.27%. Countries from all income levels are affected (*1*).

**Ankylosing spondylitis** (AS) is a type of chronic inflammatory arthritis that primarily affects the spine and sacroiliac joints and ligaments. Individuals with AS have increased risk for developing articular and extra-articular manifestations that further compound the negative health outcomes and prognosis (*2*). The pooled global prevalence of AS has been estimated at 0.18%, with the highest prevalence seen in Europe, North America (*3*) and in individuals who are human leukocyte antigen (HLA)-B27 positive with a family member with the disease (*4*).

**Juvenile idiopathic arthritis** (JIA) is the most common rheumatic disease affecting children under the age of 16 years. There are limited epidemiological data for JIA, likely due to lack of standard diagnostic criteria (*5*, *6*). However, recent estimates indicate that the prevalence varies from 3.8 to 400/100 000 and after directly standardizing for age and gender, the pooled prevalence is 70.2 [62.9 to 78.1]/100 000 (*6*).

**Crohn disease** is a chronic autoimmune disorder characterized by severe inflammation of any part of the gastrointestinal tract, but most commonly occurs in the lower part of the small intestine and the colon. Crohn disease is a lifelong systemic condition with deliberating symptoms that negatively affect an individual's quality of life. Most people will need surgery and/or drug treatment. As such, it is associated with high morbidity, mortality, and substantial costs to the health care system. Although the incidence is the highest in western nations, it is greatly accelerating in Asia, South America and Africa (*7*). The overall burden of Crohn disease remains high with prevalence exceeding 0.3% in North America, Oceania, and many countries in Europe (*7*). The prevalence has especially risen in the paediatric population in the past 15 years (*8*).

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**Summary of evidence: benefits** (from the application)

***Early RA***

A systematic review of 16 RCTs (6908 participants) compared anti-TNF biologics to conventional synthetic disease modifying anti-rheumatic drugs (csDMARD) as monotherapy (n=13) or combination therapy (n=3). One RCT compared TNF

and non-TNF biologic therapies. The majority of the included studies were rated as medium risk of bias (ROB) (*9*).

Overall, the results of a network meta-analysis revealed that when anti-TNF biologics were combined with methotrexate (MTX), patients achieved higher response rates (as measured by ACR50 (50% change in RA activity measures)) compared to MTX alone: ETN + MTX relative risk (RR) 1.49, 95%CI 1.27 to 1.74; moderate strength of evidence; ADA + MTX RR 1.35, 95%CI 1.15 to 1.59; low strength of evidence; CZP + MTX RR 1.20, 95%CI 1.04 to 1.38; low strength of evidence; IFX + MTX RR 1.57, 95%CI 1.30 to 1.88; insufficient strength of evidence (*9*).

Results also indicated that the combination of anti-TNF biologics plus MTX were favoured in comparison to biologic monotherapy. The ACR50 response rate was significantly higher for ADA + MTX than ADA monotherapy (RR 1.52, 95%CI 1.28 to 1.80; moderate evidence) and ETN + MTX than ETN monotherapy (RR 1.57, 95%CI 1.23 to 2.02) (*9*).

Anti-TNF combinations were also associated with benefits compared to MTX monotherapy for the outcome measures of remission, radiographic changes or functional capacity (*9*).

#### *Advanced RA*

A systematic review of 98 RCTs evaluated the comparative efficacy of different treatment options for advanced RA. Of these, 61 studies were included to determine the efficacy of anti-TNF biologics. Of the 88 studies assessed for risk of bias, half were judged to have a high ROB and only 10 were considered to have a low ROB overall; the rest (39%) had an unclear ROB overall (*10*).

ETN + MTX (odds ratio (OR) 3.95, 95% credible interval (CrI) 2.29 to 7.51), IFX + MTX (OR 3.00, 95%CrI 1.78 to 5.08), ADA + MTX (OR 3.99, 95%CrI 2.84 to 5.62), CZP + MTX (OR 5.35, 95%CrI 3.42 to 8.67) and GOL + MTX (OR intravenous (IV) 2.90, 95%CrI 1.21 to 7.12; OR subcutaneous (SC) 6.00, 95%CrI 3.27 to 11.35) all produced greater ACR 50 responses when compared to MTX monotherapy. Anti-TNF biologics in combination with MTX were also associated with greater odds of achieving ACR 50 response compared to MTX in combination with another conventional synthetic disease-modifying anti-rheumatic drug (csDMARD). With the exception of Infliximab, all the anti-TNF biologics in combination with MTX produced a comparable ACR 50 response to csDMARD triple therapy (*10*).

There were no significant differences in radiographic progression for any anti-TNFs in combination with MTX compared to csDMARD double or triple therapy. There were statistically significant higher odds of achieving remission among those who were treated with anti-TNF biologics in combination with MTX compared to MTX. Anti-TNF biologics in combination with MTX also

produced more favourable odds of remission compared to a csDMARD plus MTX (*10*).

CZP + MTX, achieved a statistically significant improvement in the DAS28 (Disease Activity Score 28) compared to MTX monotherapy. IFX, ADA, CZP and GOL (IV and SC) all in combination with MTX produced a significantly lower disability score and higher physical health-related quality of life scores compared to MTX monotherapy. Intravenous GOL and CZP both in combination with MTX produced higher mental health-related quality of life than MTX. Patients treated with ETN, ADA or CZP all in combination with MTX had lower pain scores than MTX monotherapy. CZP + MTX produced a significantly lower fatigue score than MTX monotherapy (*10*).

### *Ankylosing spondylitis*

A systematic review of 21 short-term RCTs involving 3308 participants assessed the benefits and harms of anti-TNF biologics in comparison with placebo, other drugs or usual care in the treatment of AS. Most included studies had low or unclear risk of bias (*4*).

Patients receiving anti-TNF biologics were found to be three to four times more likely to achieve an Assessment in SpondyloArthritis International Society (ASAS) 40 response by six months compared to placebo (ETN RR 3.31, 95%CrI 2.38 to 4.53; IFX RR 4.07, 95%CrI 2.80 to 5.74; ADA RR 3.53, 95%CrI 2.49 to 4.91; GOL RR 2.90, 95%CrI 1.90 to 4.23) (high strength of evidence). The number needed-to-treat (NNT) to receive this response ranged from 3 to 5. No significant difference was found for ASAS 40 response between the anti-TNF biologics (*4*). Moderate strength evidence found that patients receiving anti-TNF biologics were also significantly more likely than placebo to achieve ASAS partial remission. The NNT to detect a minimally clinically important difference of 0.7 points for physical functioning ranged from 2 to 4. There was high strength evidence that ETN, IFX, ADA and GOL all had significantly lower BASFI (Bath Ankylosing Spondylitis Functional Index) scores compared to placebo. Low to moderate strength evidence suggested that anti-TNF biologics have a small impact on reducing spinal inflammation, however the clinical relevance of this was not clear (*4*).

### *Juvenile idiopathic arthritis*

A systematic review of 100 full-text articles and conference abstracts (67 RCTs) evaluating the efficacy and safety of interventions for JIA included eight RCTs comparing anti-TNF biologics (*11*).

This review found that patients receiving ETN 0.4 mg/kg were more likely to maintain a disease response measured by the American College of Rheumatology (ACR) Pediatric (PEDI) 30 compared to patients receiving placebo (RR 1.91, 95%CrI 1.28 to 2.59). No other anti-TNF biologics showed

statistically significant differences compared to placebo for this outcome. There were no significant differences between anti-TNF biologics and methotrexate in combination with placebo. Indirect estimates of the head-to-head comparisons of anti-TNF biologics did not demonstrate statistically significant differences (*11*).

The number of active joints decreased for 0.2 mg/kg and 0.4 mg/kg ETN (mean difference (MD) −11.23, 95%CrI −18.16 to −4.59 and MD −11.01, 95% CrI −14.59 to −7.52, respectively) and the number of joints with limited range of motion decreased for 0.4 mg/kg ETN only (MD −5.15, CrI −9.5 to −0.8) (*11*).

### *Crohn disease*

A systematic review comparing the efficacy of therapies for induction and maintenance of remission in adult patients with Crohn disease included 15 trials involving anti-TNF therapies (IFX: one for induction and two for maintenance; ADA: four for induction and three for maintenance; CZP: four for induction and one for maintenance) and five additional studies evaluating combination therapies with IFX (12). All but one study assessed remission using the Crohn Disease Activity Index (CDAI) less than 150. Most of the included studies were assessed to have unclear risk of bias. Other limitations of this study have been identified in the literature that may limit the applicability of the results (*13*). However, additional network meta-analyses have found similar effectiveness of anti-TNFs against placebo in the induction and maintenance of remission for Crohn disease even after accounting for these differences (*14–16*).

Compared to placebo, IFX (odds ratio (OR) 2.8, 95%CrI 1.4 to 7.2), IFX plus azathioprine (OR 4.3, 95%CrI 2.0 to 9.8) and ADA (OR 2.9, 95%CrI 1.6 to 5.5) all had over 99% probability of being superior at inducing remission in Crohn patients. These same drugs also proved to be superior to azathioprine/6-mercaptopurine (OR 2.3, 95%CrI 1.3 to 5.0, OR 3.4, 95%CrI 1.9 to 6.3, and OR 3.4, 95%CrI 1.9 to 6.3). IFX plus azathioprine was 2.7 times more likely to induce remission compared to methotrexate (95%CrI 1.9 to 6.3). IFX + azathioprine (OR 3.1, 95%CrI 1.4 to 7.7) and ADA (OR 2.1, 95%CrI 1.0 to 4.6) were found to be superior to CZP for inducing remission (*12*).

For maintenance of remission, IFX (OR 2.8, 95%CrI 1.8 to 4.5), IFX plus azathioprine (OR 5.2, 95%CrI 2.8 to 11), ADA (OR 5.1, 95%CrI 3.3 to 8.1) and CZP (OR 2.0, 95%CrI 1.4 to 3.0) all had over 99% probability of being superior to placebo. ADA (OR 2.9, 95%CrI 1.6 to 5.1), IFX (OR 1.6, 95%CrI 1.0 to 2.5) and IFX plus azathioprine (OR 3.0, 95%CrI 1.7 to 5.5) all had greater odds at achieving maintenance of remission compared to azathioprine/6-mercaptopurine). IFX + azathioprine (OR 2.6, 95%CrI 1.3 to 6.0) and ADA (OR 2.5, 95%CrI 1.4 to 4.6) were found to be superior to CZP for maintenance of remission. IFX plus azathioprine was superior to IFX monotherapy for maintenance of remission (OR 1.8, 95%CrI 1.0 to 3.8) (*12*).

A systematic review comparing efficacy of pharmacologic interventions for preventing relapse of Crohn disease after surgery found that anti-TNF monotherapy was the most effective therapy for post-operative prophylaxis, with large effect sizes relative to all other strategies including antibiotics, immunomodulator monotherapy, immunomodulators with antibiotics, budesonide (clinical relapse: RR, 0.02 to 0.20; endoscopic relapse: RR, 0.005 to 0.04) (*17*).

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**Summary of evidence: harms** (from the application)

Uncommon yet serious adverse events for anti-TNF biologics include serious infection, malignancy and lymphoma, neurologic effects and cardiac failure.

A 2011 Cochrane Systematic Review assessed the potential adverse effects of anti-TNF biologics: etanercept (39 RCTs), infliximab (40 RCTs), adalimumab (22 RCTs), certolizumab pegol (six RCTs) and golimumab (eight RCTs) alone or in combination with other therapies. This review found that compared to control, CZP was associated with a higher odds of serious adverse effects (OR 1.57, 95%CI 1.06 to 2.32) and serious infections (OR 4.75, 95%CI 1.52 to 18.45) and IFX was associated with higher odds of total adverse events (OR 1.55, 95%CI 1.01 to 2.35) and withdrawals due to adverse events (OR 2.34, 95%CI 1.40 to 4.14) (*18*).

### *Early RA*

The network meta-analysis for early RA found no significant differences in serious adverse events or discontinuations attributable to adverse events between MTX monotherapy and any of the anti-TNF biologics (low strength of evidence). IFX + MTX also did not differ from csDMARD combination therapies (low strength of evidence). Anti-TNF therapy with a csDMARD did not differ significantly in serious adverse events or discontinuations attributable to adverse events compared to TNF biologic monotherapy (moderate strength of evidence) (*9*).

### *Advanced RA*

The systematic review for advanced RA found that there were no significant differences in serious adverse events or withdrawals attributable to adverse events between the anti-TNF biologics in combination with MTX and MTX monotherapy. ETN + MTX had lower odds of withdrawals attributable to adverse events compared to a csDMARD in combination with MTX (OR 0.33, 95%CrI 0.11 to 0.89). There was insufficient evidence to detect any differences in anti-TNF treatment comparisons for mortality, serious infections, tuberculosis, cancer, leukaemia, lymphoma, congestive heart failure, major adverse cardiac events and herpes zoster. A pairwise meta-analysis found no statistically significant difference in mortality for IFX + MTX and MTX monotherapy. Additional pairwise meta-analyses found that there were no differences in serious infections for patients treated with the ETN, IFX or GOL (plus MTX) versus MTX alone. There was insufficient evidence for this outcome for ADA + MTX.

A pooled estimate from two trials comparing ETN monotherapy and MTX combination therapy, found that were no significant differences in cancer, and a pairwise meta-analysis found no significant differences between IFX + MTX and MTX groups (*10*).

### *Ankylosing spondylitis*

Pooled results for all anti-TNF biologics demonstrated a moderate level of evidence that there is an increased risk of withdrawals due to adverse events compared to placebo (Peto OR 2.44, 95%CI 1.26 to 4.72), with an absolute increase of 1% (95%CI 0% to 2%). There was no difference in risk for serious adverse events (Peto OR 1.45, 95%CI 0.85 to 2.48). ETN (25 and 50 mg) was the only anti-TNF biologic that had an individual increase in withdrawals due to adverse events versus placebo (RR 3.65, 95%CI 1.27 to 11.79) with an absolute increased harm of 2% (95%CrI 0.2% to 8%). The effect of ETN compared to placebo for serious adverse events was uncertain. There was uncertainty reported for adverse effects or withdrawals due to adverse effects between either ADA, GOL or IFX and placebo. The strength of evidence was moderate for all safety outcomes (*4*).

### *Juvenile idiopathic arthritis*

The systematic review for JIA found that biologics were safe in short-term use among both polyarticular course and active systemic patients. For polyarticular course, one RCT found that no serious adverse effects or withdrawals due to adverse effects occurred for high or low doses of ETN. Another RCT found no withdrawals due to adverse events occurred for ADA with or without methotrexate and few withdrawals due to adverse events (*11*).

### *Crohn disease*

IFX + azathioprine (OR 0.27, 95%CrI 0.08 to 0.72) and ADA monotherapy (OR 0.43, 95%CrI 0.26 to 0.69) were associated with significantly lower odds of total withdrawals compared to placebo. Similarly, IFX + azathioprine was associated with significantly lower odds of total withdrawals compared to Azathioprine/6-mercaptopurine (OR 0.39, 95%CrI 0.14 to 0.98) and methotrexate (OR 0.29, 95%CrI 0.07 to 0.93) (*12*).

For withdrawals due to adverse events, IFX (OR 2.7, 95%CrI 1.6 to 4.7) and IFX + azathioprine (OR 3.2, 95%CrI 1.6–6.1) had significantly greater odds of withdrawals due to adverse events compared to placebo. Adalimumab had over a 99% probability of having less withdrawals due to adverse events than placebo (OR 0.48, 95%CrI 0.31 to 0.74). CZP (OR 0.23, 95%CrI 0.13 to 0.40) and ADA (OR 0.12, 95%CrI 0.06 to 0.24) had significantly less odds of withdrawals due to adverse events compared to azathioprine/6-mercaptopurine and methotrexate (CZP: OR 0.07, 95%CrI 0.01 to 0.28 and ADA: OR 0.04, 95%CrI 0.00 to 0.16).

Infliximab monotherapy had significantly lower odds of withdrawals due to adverse events compared to methotrexate (OR 0.21, 95%CrI 0.02 to 0.93) (*12*).

Anti-TNF comparisons indicated that ADA (OR 0.0, 95%CrI 0.24 to 0.96) and IFX + azathioprine (OR 0.32, 95%CrI 0.09 to 0.94) have significantly lower odds of total withdrawals than CZP. ADA had lower odds of withdrawals due to adverse events than CZP (OR 0.55, 95%CrI 0.32 to 0.93) and IFX (OR 0.18, 95%CrI 0.09 to 0.34). IFX + azathioprine (OR 3.6, 95%CrI 1.7 to 7.5) and IFX monotherapy (OR 3.1, 95%CrI 1.7 to 5.8) had significantly greater odds of withdrawals due to adverse events than CZP. IFX + azathioprine also had greater odds than ADA of withdrawals due to adverse events (OR 6.5, 95%CrI 3.0 to 14) (*12*).

**Additional evidence** (not in the application)

N/A

**WHO Guidelines**

None available

**Costs/cost-effectiveness**

The application presented details of available information on drug costs for the anti-TNF biologics from Australia, Canada, the United Kingdom and the United States. These medicines are associated with a significant budget impact to health systems due to both price and volume of use.

In addition, the application identified and summarized the findings numerous economic evaluations conducted primarily in Canada, the United Kingdom and the United States involving anti-TNF biologics for the indications proposed for EML listing (*19–35*).

**Availability**

These medicines have wide marketing approval globally. Biosimilars are available for ETN, IFX and ADA.

**Other considerations**

The Committee noted that most of the evidence presented in the application comes from countries with low levels of tuberculosis and/or hepatitis B infection. Reactivation of latent tuberculosis infection and hepatitis B in patients receiving anti-TNF biologics has been reported (36, 37), and this risk should be taken into consideration when anti-TNF biologics are considered in settings where there is a higher burden of TB and hepatitis B.

### Committee recommendations

The Committee recognized that these auto-immune disorders are highly debilitating and that there is a public health need for effective treatments for patients who do not respond adequately to first-line treatments (e.g. methotrexate). The Expert Committee recommended the addition of adalimumab with a square box to the complementary list of the EML and EMLc for the second-line treatment of severe chronic inflammatory autoimmune disorders (rheumatoid arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and Crohn disease) on the basis of the positive benefit to harm profile of these medicines.

For adult patients, therapeutically equivalent alternatives to adalimumab are limited to etanercept, infliximab, certolizumab pegol and golimumab. For children, therapeutically equivalent alternatives should be limited to etanercept and infliximab.

The Committee also recognized that these medicines are associated with a significant budget impact on health systems. However, the availability of several therapeutically equivalent alternatives and the increasing availability of biosimilar products could lead to more market competition. The Committee recognized a potential expansion of the role of the Medicines Patent Pool to biological medicines such as these as an opportunity to facilitate affordable access. Quality-assured available biosimilars of these medicines should also be considered as therapeutically equivalent for procurement purposes.

The Expert Committee recommended that WHO take action to facilitate access to these medicines through the WHO pre-qualification programme, and through collaboration with partners such as the Medicines Patent Pool.

## References

1. GBD Results Tool | GHDx. 2018 [website]. Seattle: Institute for Health Metrics and Evaluation, University of Washington; 2018. (http://ghdx.healthdata.org/gbd-results-tool, accessed 29 September 2019).
2. Stolwijk C, van Tubergen A, Castillo-Ortiz JD, Boonen A. Prevalence of extra-articular manifestations in patients with ankylosing spondylitis: a systematic review and meta-analysis. Ann Rheum Dis. 2015;74(1):65–73.
3. Stolwijk C, van Onna M, Boonen A, van Tubergen A. Global Prevalence of Spondyloarthritis: A Systematic Review and Meta-Regression Analysis. Arthritis Care Res (Hoboken). 2016;68(9): 1320–31.
4. Maxwell LJ, Zochling J, Boonen A, Singh JA, Veras MM, Tanjong Ghogomu E et al. TNF-alpha inhibitors for ankylosing spondylitis. Cochrane Database Syst Rev. 2015(4):CD005468.
5. Manners PJ, Bower C. Worldwide prevalence of juvenile arthritis why does it vary so much? J Rheumatol. 2002;29(7):1520–30.
6. Thierry S, Fautrel B, Lemelle I, Guillemin F. Prevalence and incidence of juvenile idiopathic arthritis: a systematic review. Joint Bone Spine. 2014;81(2):112–7.

7. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2018;390(10114):2769–78.

8. Benchimol EI, Bernstein CN, Bitton A, Carroll MW, Singh H, Otley AR et al. Trends in Epidemiology of Pediatric Inflammatory Bowel Disease in Canada: Distributed Network Analysis of Multiple Population-Based Provincial Health Administrative Databases. Am J Gastroenterol. 2017;112(7):1120–34.

9. Donahue KE, Gartlehner G, Schulman ER, Jonas B, Coker-Schwimmer E, Patel SV et al. AHRQ Comparative Effectiveness Reviews. Drug Therapy for Early Rheumatoid Arthritis: A Systematic Review Update. Rockville: Agency for Healthcare Research and Quality (US); 2018.

10. Wells GA, Smith C, Hossain A, Karsh J, Singh J, Hazlewood G et al. CADTH Health Technology Assessments. Drugs for the Management of Rheumatoid Arthritis: Clinical Evaluation. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2018.

11. Smith C. Efficacy and Safety of Pharmacological and Non-Pharmacological Interventions in Juvenile Idiopathic Arthritis: A Series of Systematic Reviews and Network Meta-Analyses (Doctoral dissertation). Ottawa: Université d'Ottawa/University of Ottawa; 2017. Available from https://ruor.uottawa.ca/bitstream/10393/35744/1/Smith_Christine_2017_thesis.pdf, accessed 29 September 2019.

12. Hazlewood GS, Rezaie A, Borman M, Panaccione R, Ghosh S, Seow CH et al. Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: a network meta-analysis. Gastroenterology. 2015;148(2):344-54.e5; quiz e14–5.

13. Bonovas S, Moja L, Danese S. In the Presence of Conceptual Heterogeneity, Results of Network Meta-analysis Comparing Therapies in Crohn's Disease Need to Be Interpreted With Caution. Gastroenterology. 2015;148(7):1483–4.

14. Singh S, Fumery M, Sandborn WJ. Systematic review and network meta-analysis: first- and second-line biologic therapies for moderate-severe Crohn's disease. 2018;48(4):394–409.

15. Singh S, Garg SK, Pardi DS, Wang Z, Murad MH, Loftus EV, Jr. Comparative efficacy of biologic therapy in biologic-naive patients with Crohn disease: a systematic review and network meta-analysis. Mayo Clin Proc. 2014;89(12):1621–35.

16. Stidham RW, Lee TC, Higgins PD, Deshpande AR, Sussman DA, Singal AG et al. Systematic review with network meta-analysis: the efficacy of anti-TNF agents for the treatment of Crohn's disease. Aliment Pharmacol Ther. 2014;39(12):1349–62.

17. Singh S, Garg SK, Pardi DS, Wang Z, Murad MH, Loftus EV, Jr. Comparative efficacy of pharmacologic interventions in preventing relapse of Crohn's disease after surgery: a systematic review and network meta-analysis. Gastroenterology. 2015;148(1):64–76 e2; quiz e14.

18. Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev. 2011(2):CD008794.

19. Curtis JR, Chastek B, Becker L, Quach C, Harrison DJ, Yun H et al. Cost and effectiveness of biologics for rheumatoid arthritis in a commercially insured population. J Manag Care Spec Pharm. 2015;21(4):318–29.

20. Joensuu JT, Huoponen S, Aaltonen KJ, Konttinen YT, Nordstrom D, Blom M. The cost-effectiveness of biologics for the treatment of rheumatoid arthritis: a systematic review. PLoS One. 2015;10(3):e0119683.

21. van der Velde G, Pham B, Machado M, Ieraci L, Witteman W, Bombardier C et al. Cost-effectiveness of biologic response modifiers compared to disease-modifying antirheumatic drugs for rheumatoid arthritis: a systematic review. Arthritis Care Res (Hoboken). 2011;63(1):65–78.
22. Malottki K, Barton P, Tsourapas A, Uthman AO, Liu Z, Routh K et al. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a tumour necrosis factor inhibitor: a systematic review and economic evaluation. Health Technol Assess. 2011;15(14):1–278.
23. Chen YF, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W et al. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. Health Technol Assess. 2006;10(42):iii-iv, xi-xiii, 1–229.
24. Wailoo AJ, Bansback N, Brennan A, Michaud K, Nixon RM, Wolfe F. Biologic drugs for rheumatoid arthritis in the Medicare program: a cost-effectiveness analysis. Arthritis Rheum. 2008;58(4):939–46.
25. Liu Y, Wu EQ, Bensimon AG, Fan CP, Bao Y, Ganguli A et al. Cost per responder associated with biologic therapies for Crohn's disease, psoriasis, and rheumatoid arthritis. Adv Ther. 2012;29(7):620–34.
26. Corbett M, Soares M, Jhuti G, Rice S, Spackman E, Sideris E et al. Tumour necrosis factor-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis: a systematic review and economic evaluation. Health Technol Assess. 2016;20(9):1-334, v–vi.
27. McLeod C, Bagust A, Boland A, Dagenais P, Dickson R, Dundar Y et al. Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation. Health Technol Assess. 2007;11(28):1-158, iii–iv.
28. Kirchhoff TD, Mittendorf T, Schmidt RE, Jablonka A, Merkesdal S. Cost-effectiveness of TNF-alpha inhibition in active ankylosing spondylitis: a systematic appraisal of the literature. Expert Rev Pharmacoecon Outcomes Res. 2012;12(3):307–17.
29. Ungar WJ, Costa V, Hancock-Howard R, Feldman BM, Laxer RM. Cost-effectiveness of biologics in polyarticular-course juvenile idiopathic arthritis patients unresponsive to disease-modifying antirheumatic drugs. Arthritis Care Res (Hoboken). 2011;63(1):111–9.
30. Shepherd J, Cooper K, Harris P, Picot J, Rose M. The clinical effectiveness and cost-effectiveness of abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis: a systematic review and economic evaluation. Health Technol Assess. 2016;20(34):1–222.
31. Huoponen S, Blom M. A Systematic Review of the Cost-Effectiveness of Biologics for the Treatment of Inflammatory Bowel Diseases. PLoS One. 2015;10(12):e0145087.
32. Dretzke J, Edlin R, Round J, Connock M, Hulme C, Czeczot J et al. A systematic review and economic evaluation of the use of tumour necrosis factor-alpha (TNF-alpha) inhibitors, adalimumab and infliximab, for Crohn's disease. Health Technol Assess. 2011;15(6):1–244.
33. Beilman CL, Kirwin E, Ma C, McCabe C, Fedorak RN, Halloran B. Early Initiation of Tumor Necrosis Factor Antagonist-Based Therapy for Patients With Crohn's Disease Reduces Costs Compared With Late Initiation. Clin Gastroenterol Hepatol. 2018.
34. Bodger K, Kikuchi T, Hughes D. Cost-effectiveness of biological therapy for Crohn's disease: Markov cohort analyses incorporating United Kingdom patient-level cost data. Aliment Pharmacol Ther. 2009;30(3):265–74.

35. Blackhouse G, Assasi N, Xie F, Marshall J, Irvine EJ, Gaebel K et al. Canadian cost-utility analysis of initiation and maintenance treatment with anti-TNF-alpha drugs for refractory Crohn's disease. J Crohn's Colitis. 2012;6(1):77–85.

36. Minozzi S, Bonovas S, Lytras T, Pecoraro V, Gonzalez-Lorenzo M, Bastiampillai AJ et al. Risk of infections using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a systematic review and meta-analysis. Expert Opin Drug Saf. 2016;15(sup1):11–34.

37. Watanabe T, Fukae J, Fukaya S, Sawamukai N, Isobe M, Matsuhashi M et al. Incidence and risk factors for reactivation from resolved hepatitis B virus in rheumatoid arthritis patients treated with biological disease-modifying antirheumatic drugs. Int J Rheum Dis. 2019;22(4):574–82.

## 8.2 Antineoplastics and supportive medicines

*Cancer medicines for children – addition/new indication – EMLc*

**Cancer medicines for children** **ATC Code: various**

**Proposal**

The application proposed an extension of adult cancer indications to paediatrics and corresponding inclusion on the EMLc. The proposal involves both the inclusion of new indications for some cancer medicines currently on the EMLc and the addition of selected new cancer and supportive care medicines to the EMLc. The proposed listing extensions are presented in the following table:

| **New medicines to be added to the EMLc – extending adult indications to children** | |
|---|---|
| Medicine | Paediatric indication(s) |
| All-trans retinoic acid (ATRA) | Acute promyelocytic leukaemia |
| Dasatinib | Imatinib-resistant chronic myeloid leukaemia |
| Enoxaparin | For use as anticoagulant |
| Hydroxycarbamide | Chronic myeloid leukaemia |
| Imatinib | Chronic myeloid leukaemia<br>Gastrointestinal stromal tumour |
| Irinotecan | Metastatic colorectal cancer |
| Nilotinib | Imatinib-resistant chronic myeloid leukaemia |
| Oxaliplatin | Early stage colon cancer<br>Metastatic colorectal cancer |
| Procarbazine | Hodgkin lymphoma |
| Rituximab | Diffuse large B-cell lymphoma |
| Zoledronic acid | Malignancy-related bone disease |
| **New indications for existing medicines on the EMLc** | |
| **Indication** | **Medicine(s)** |
| Kaposi sarcoma | Bleomycin<br>Doxorubicin<br>Vincristine |
| Nasopharyngeal cancer | Cisplatin<br>Fluorouracil |

Table *continued*

| New indications for existing medicines on the EMLc | |
|---|---|
| **Indication** | **Medicine(s)** |
| Diffuse large B-cell lymphoma | Cyclophosphamide<br>Doxorubicin<br>Prednisolone<br>Vincristine |
| Colorectal cancers | Cisplatin<br>Fluorouracil |
| Acute promyelocytic leukaemia | Cytarabine<br>Daunorubicin<br>Mercaptopurine<br>Methotrexate |
| Acute myeloid leukaemia | Cytarabine |

**Applicant**

Catherine Lam, Scott C. Howard

**WHO Technical Department**

Comments on the application were received from the WHO Department of Management of NCDs, Disability, Violence & Injury Prevention. The technical unit advised that it supports the proposal to extend the listing of specified cancer medicines and indications on the EML to the EMLc.

**EML/EMLc**

EMLc

**Section**

8.2 Antineoplastic and supportive medicines

**Dose form(s) & strengths(s)**

Various

**Core/Complementary**

Complementary

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

The proposed medicines and corresponding indications had not previously been considered for inclusion on the EMLc.

The application applied the following rationale in proposing the medicines and indications for inclusion on the EMLc:

- The medicine must already be listed on the EML or EMLc.
- The indications listed for adults are also diagnosed in children aged 12 years and under.
- The medicines have been reported for treatment in children aged 12 years and under for the same indication as listed on the EML for treatment in adults.
- Published literature supports the extension of the indication to children, including clinical studies, peer-reviewed consensus documents and/or clinical guidelines support the medicine's role as standard of care.

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**Public health relevance** (burden of disease)

Cancer is a leading cause of death for children globally with the most common cancer types occurring in children being leukaemias, lymphomas and central nervous system tumours (*1*). Childhood cancers generally cannot be prevented nor screened for, so improving outcomes for children with cancer relies on early and accurate diagnosis and access to effective treatments.

In 2018, WHO launched the Global Initiative for Childhood Cancer, to provide leadership and technical assistance to Member States to build and sustain high quality childhood cancer programmes. The goal of this initiative is to achieve at least 60% survival for all children with cancer globally by 2030 (*2*).

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**Summary of evidence: benefits** (from the application)

**Acute promyelocytic leukaemia (APML)**

New medicine: all-trans retinoic acid (ATRA)
New indication: cytarabine, daunorubicin, mercaptopurine, methotrexate

The median age of children with APML has been reported as 10 years (*3*). Standard regimens used for children with APML include ATRA (*3*, *4*), with prior randomized trial data demonstrating significant disease-free survival improvement for children randomized to receive ATRA vs not (48% at 5 years, vs 0%, $p<0.0001$), with overall survival rates sustained at 10 years (5). The use of ATRA is acknowledged in standard guidelines for the treatment of APML, and is considered to be a paradigm for a targeted approach to the treatment of leukaemia (*6*–*10*). The treatment of APML is typically provided in the context

of poly-chemotherapy, involving cytarabine, daunorubicin, mercaptopurine and methotrexate (*3*–*5*).

#### Acute myeloid leukaemia (AML)

New indication: cytarabine

The safety and effectiveness of cytarabine for the treatment of childhood AML have been evaluated in controlled clinical trials (*11*–*13*). It is considered the standard of care, used internationally for children with AML, as in adults (*14*, *15*).

#### Chronic myeloid leukaemia (CML)

New medicines: imatinib, dasatinib, nilotinib, hydroxycarbamide

CML is a very rare disease in children, estimated to be responsible for 2% of all leukaemias in children less than 15 years of age with an annual incidence of one case per million children in that age range (*16*). The tyrosine kinase inhibitors introduced a chance of cure for CML, with long lasting disease control and significantly improved outcomes (*17*).

Imatinib has shown clinical benefit in children with CML, with results comparable to those seen in adults (*18*). In particular, a clinical study of the use of imatinib in patients aged less than 18 years with CML in the chronic phase demonstrated the efficacy, safety and long-term benefit of imatinib in children (*19*).

Dasatinib and nilotinib have been used in children with CML including (but not limited to) imatinib-resistant cases. A Phase II trial of dasatinib in 113 paediatric patients with CML demonstrated a complete cytogenetic response was achieved in 76% of imatinib-resistant patients, with an acceptable safety profile that did not include pleural or pericardial effusion, commonly seen in dasatinib-treated adults (*20*). The effectiveness and safety of nilotinib in children with CML has also been reported (*21*). Nilotinib has been approved by the United States FDA for treatment of paediatric patients with newly diagnosed or resistant CML on the basis of the results from two open-label, single-arm trials involving 69 patients (*22*, *23*). For imatinib-resistant patients, the major molecular response rate was 40.9%. No new safety concerns were reported, noting transient and manageable laboratory abnormalities: hyperbilirubinaemia and moderate to severe transaminitis.

Hydroxycarbamide has a recognized debulking/cytoreductive role for myeloid malignancies and for palliative purpose in all settings. In addition, hydroxycarbamide can have an important role in settings where resource limitations affect access to imatinib or other tyrosine kinase inhibitors, to allow commencement of antineoplastic therapy (*24*). A general expert consensus recommendation for childhood CML includes hydroxycarbamide as standard initial therapy in all settings, while awaiting confirmatory diagnostic testing results as well as initial clinical response (*25*).

### Gastrointestinal stromal tumour (GIST)

New medicine: imatinib

Imatinib is the preferred treatment for molecularly-selected GIST in adults and children, where c-KIT sensitive mutations are demonstrated. Paediatric GISTs represent a distinct entity, and may be associated with genetic syndromes (such as Carney Triad, Carney-Stratakis syndrome or neurofibromatosis 1 (NF1)/ Von Recklinghausen disease). It is also less common for paediatric patients with GIST to have the activating mutations in KIT and platelet-derived growth factor receptor alpha (PDGFRA) seen in adults. Data on the effectiveness and activity of imatinib in paediatric GIST is scarce, as it is a very rare entity (1–2% of all the cases). Children less than 18 years of age typically have more indolent disease with more favourable prognosis than in adults (approximating 100% five-year overall survival), as reported in a long-term retrospective analysis of a large observational study, that included a sub-group of 28 patients in this age group (*26*).

### Diffuse large B-cell lymphoma (DLBCL)

New medicine: rituximab
New indication: cyclophosphamide, doxorubicin, prednisolone, vincristine

Different studies of DLBCL have established a role for rituximab in paediatric populations, with studies often spanning all age groups including adults and children starting at age 9 years (27), and confirming efficacy and safety in children (*28*). Rituximab is administrated in the context of a combination regimen with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) (*27*, *28*). CHOP alone may be administered in settings where rituximab is not available.

### Kaposi sarcoma

New indication: bleomycin, doxorubicin, vincristine

Kaposi sarcoma in children primarily occurs as either endemic (HIV-unrelated) or epidemic (HIV-related) disease. According to the data known from registries and literature, Kaposi's sarcoma primarily occurs in the elderly population of the Mediterranean region, while the occurrence in children is restricted to smaller series (*29*). Data from paediatric cohorts and clinical trials showed a median age of diagnosis at 8 years old. Chemotherapy indicated for Kaposi sarcoma includes bleomycin, vincristine and doxorubicin (*30–34*). One of the regimens combining doxorubicin, bleomycin and vincristine (ABV) has reported 80% remission for stage I HIV-positive patients treated in South Africa (*32*). Bleomycin, vincristine and doxorubicin have also been included as standard treatment agents in international expert consensus recommendations (*35*).

#### Nasopharyngeal cancer

New indication: cisplatin, fluorouracil

Nasopharyngeal carcinoma (NPC) is the most commonly diagnosed head and neck malignant neoplasm in China and South-East Asian countries, but is considered relatively rare among children. Treatment schemes are typically adapted for children from adult-based regimens. Cisplatin-based regimens are the standard of care for children with NPC. Together with cisplatin, fluorouracil (5-FU) is included in standard regimens for children with NPC, with standard administration of two courses 21 days apart (*36–39*). The use of cisplatin including as a radiosensitizer (with concomitant cisplatin and radiation therapy) following cisplatin/5-FU in the systemic treatment of NPC in children is recognized as standard across different institutions and countries, extrapolating from the adult treatment experience (*40–43*).

#### Colon and rectal cancers

New medicine: irinotecan, oxaliplatin
New indication: cisplatin, fluorouracil

While very rare, colorectal cancers can occur in children (reported in as young as nine months old) and typically utilize the same chemotherapy agents as in adults, including 5-FU for the neoadjuvant treatment of rectal cancer, 5-FU and oxaliplatin for the adjuvant treatment of colon and rectal tumours, and 5-FU, oxaliplatin and irinotecan for advanced or metastatic colorectal cancer (*44–47*).

#### Hodgkin lymphoma

New medicine: procarbazine

Procarbazine is commonly included as a drug of choice in children for the treatment of Hodgkin lymphoma. According to clinical guidelines and literature, procarbazine is a standard inclusion in multi-agent chemotherapy regimens for Hodgkin lymphoma in children (*48*, *49*). For the paediatric population, multiple regimens containing procarbazine are used, in particular BEACOPP that contains bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone. It is often used in more resource-limited settings. Local selection and use should consider known gonadotoxicity and effects on male fertility (*50*).

#### Malignancy-related bone disease

New medicine: zoledronic acid

Although certain malignancy-related bone diseases, such as osteonecrosis, occur more often in older children, patients as young as age 4 to 6 years have been affected and required treatment (*51–53*). The administration of zoledronic acid in paediatric oncology appears safe, and may result in improved bone strength

and pain control. In a retrospective chart review of inpatients and outpatients less than 21 years old who received zoledronic acid at the Children's Hospital of Philadelphia, safety of the bisphosphonate was assessed. The safety profile was consistent with the known experience in adults, including preventable alterations in calcium levels, with no major side-effects reported (*51*).

**Anti-coagulation**

New medicines: enoxaparin

The use of low molecular weight heparin (LMWH) as an anticoagulant is considered standard of care for prophylaxis and treatment in children, including but not limited to children with cancer. Malignancy as well as treatment-related factors such as immobilization and central venous access can increase risk for thrombosis (*54*). Enoxaparin as standard antithrombotic therapy is used as a first option in routine practice in many settings (*55–57*).

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**Summary of evidence: harms** (from the application)

Not reported separately in the application.

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**Additional evidence** (not in the application)

A randomized, multicentre, open-label Phase III trial (OS2006) compared standard chemotherapy with or without zoledronic acid in 318 patients aged between 5 years and 50 years (median 15.5 years) with newly diagnosed high-grade osteosarcoma (*58*). The trial results indicated that zoledronic acid did not improve event-free survival, percentage of good histological response or overall survival. No significant differences in toxicity or orthopaedic complications were observed between treatment groups. The trial was stopped after the second interim analysis for futility and the authors concluded that the use of zoledronic acid in osteosarcoma patients was not recommended.

A retrospective analysis of the use of zoledronic acid for treatment of chemotherapy related osteonecrosis in 20 children and adolescents with osteonecrosis found that zoledronic acid was well tolerated and improved joint pain in the majority of patients (*53*). However, among patients with osteonecrosis of the hip, the majority had progressive joint destruction requiring arthroplasty, despite treatment with zoledronic acid.

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**WHO Guidelines**

None available

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**Costs/cost-effectiveness**

Not reported in the application.

**Availability**

The proposed medicines are already included on the EML and/or EMLc.

**Other considerations**

The Expert Committee recognized the public health need for access to cancer therapies for children. The Committee acknowledged that there is limited clinical trial evidence available for the use of many cancer medicines in children, and that it is often necessary to rely on extrapolated data from trials in adults, clinical consensus and/or clinical practice guidelines, that lend support to a medicine's role as the standard of care in paediatric patients.

**Committee recommendations**

The Expert Committee recommended the addition to the complementary list of the EMLc of ATRA, dasatinib, fluorouracil, imatinib, irinotecan, nilotinib, oxaliplatin, procarbazine and rituximab for the paediatric cancer indications outlined in the table below.

The Committee also recommended the extension of the current listings on the EMLc of bleomycin, doxorubicin, vincristine, cisplatin, cyclophosphamide, prednisolone, cytarabine, daunorubicin, mercaptopurine, methotrexate, cytarabine and hydroxycarbamide to include the indications outlined in the table below.

The Committee also recommended the addition to the core list of the EMLc of enoxaparin with a square box for use as an anticoagulant in children.

The Expert Committee did not recommend the addition of zoledronic acid to the complementary list of the EMLc for the treatment of malignancy-related bone disease. The Committee noted that data for its use in children are scant and fragmented. The Committee was also concerned that the effects of zoledronic acid in some paediatric cancers (e.g. osteosarcoma) were largely negative, and that there are insufficient long-term safety data of bisphosphonate use in paediatric cancer patients to be reassured of an acceptable benefit–to–harm ratio.

Furthermore, the Committee noted that although use of bisphosphonates in paediatric patients has been reported to be well tolerated, the impact of use in the context of patients with actively growing skeleton is not yet fully known.

| New medicines for EMLc | |
|---|---|
| All-trans retinoic acid | Acute promyelocytic leukaemia |
| Dasatinib | Imatinib-resistant chronic myeloid leukaemia |
| Fluorouracil | Nasopharyngeal carcinoma<br>Early-stage colon cancer<br>Early-stage rectal cancer<br>Metastatic colorectal cancer |

Table *continued*

| | |
|---|---|
| **New medicines for EMLc** | |
| Imatinib | Chronic myeloid leukaemia<br>Gastrointestinal stromal tumour |
| Irinotecan | Metastatic colorectal cancer |
| Nilotinib | Imatinib-resistant chronic myeloid leukaemia |
| Oxaliplatin | Early stage colon cancer<br>Metastatic colorectal cancer |
| Procarbazine | Hodgkin lymphoma |
| Rituximab | Diffuse large B-cell lymphoma |
| ☐ Enoxaparin | Anticoagulant (core list) |
| **Extension of indications for currently listed medicines** | |
| Bleomycin | Kaposi sarcoma |
| Doxorubicin | Kaposi sarcoma |
| Vincristine | Kaposi sarcoma |
| Cisplatin | Nasopharyngeal carcinoma |
| Cyclophosphamide | Diffuse large B-cell lymphoma |
| Prednisolone | Diffuse large B-cell lymphoma |
| Cytarabine | Acute promyelocytic leukaemia |
| Daunorubicin | Acute promyelocytic leukaemia |
| Mercaptopurine | Acute promyelocytic leukaemia |
| Methotrexate | Acute promyelocytic leukaemia |
| Cytarabine | Acute myelogenous leukaemia |
| Hydroxycarbamide | Chronic myeloid leukaemia |

## References

1. Steliarova-Foucher E, Colombet M, Ries LAG, Moreno F, Dolya A, Bray F et al. International incidence of childhood cancer, 2001-10: a population-based registry study. Lancet Oncol. 2017;18(6):719–31.
2. Cancer in children. Fact Sheet [website]. Geneva: World Health Organization; 2018. (https://www.who.int/news-room/fact-sheets/detail/cancer-in-children, accessed 29 September 2019).

3. Testi AM, Pession A, Diverio D, Grimwade D, Gibson B, de Azevedo AC et al. Risk-adapted treatment of acute promyelocytic leukemia: results from the International Consortium for Childhood APL. Blood. 2018;132(4):405–12.
4. Zhang L, Zou Y, Chen Y, Guo Y, Yang W, Chen X et al. Role of cytarabine in paediatric acute promyelocytic leukemia treated with the combination of all-trans retinoic acid and arsenic trioxide: a randomized controlled trial. BMC Cancer. 2018;18(1):374.
5. Gregory J, Kim H, Alonzo T, Gerbing R, Woods W, Weinstein H et al. Treatment of children with acute promyelocytic leukemia: results of the first North American Intergroup trial INT0129. Pediatr Blood Cancer. 2009;53(6):1005–10.
6. Fenaux P, Chastang C, Chevret S, Sanz M, Dombret H, Archimbaud E et al. A randomized comparison of all transretinoic acid (ATRA) followed by chemotherapy and ATRA plus chemotherapy and the role of maintenance therapy in newly diagnosed acute promyelocytic leukemia. The European APL Group. Blood. 1999;94(4):1192–200.
7. Tallman MS, Andersen JW, Schiffer CA, Appelbaum FR, Feusner JH, Ogden A et al. All-trans-retinoic acid in acute promyelocytic leukemia. N Engl J Med. 1997;337(15):1021–8.
8. Imaizumi M, Tawa A, Hanada R, Tsuchida M, Tabuchi K, Kigasawa H et al. Prospective study of a therapeutic regimen with all-trans retinoic acid and anthracyclines in combination of cytarabine in children with acute promyelocytic leukaemia: the Japanese childhood acute myeloid leukaemia cooperative study. Br J Haematol. 2011;152(1):89–98.
9. Sanz MA, Grimwade D, Tallman MS, Lowenberg B, Fenaux P, Estey EH et al. Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. Blood. 2009;113(9):1875–91.
10. Lo-Coco F, Avvisati G, Vignetti M, Thiede C, Orlando SM, Iacobelli S, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med. 2013;369(2):111-21.
11. Creutzig U, Ritter J, Zimmermann M, Reinhardt D, Hermann J, Berthold F et al. Improved treatment results in high-risk pediatric acute myeloid leukemia patients after intensification with high-dose cytarabine and mitoxantrone: results of Study Acute Myeloid Leukemia-Berlin-Frankfurt-Munster 93. J Clin Oncol. 2001;19(10):2705–13.
12. Bishop JF, Matthews JP, Young GA, Szer J, Gillett A, Joshua D et al. A randomized study of high-dose cytarabine in induction in acute myeloid leukemia. Blood. 1996;87(5):1710–7.
13. Wells RJ, Woods WG, Lampkin BC, Nesbit ME, Lee JW, Buckley JD et al. Impact of high-dose cytarabine and asparaginase intensification on childhood acute myeloid leukemia: a report from the Childrens Cancer Group. J Clin Oncol. 1993;11(3):538–45.
14. De Moerloose B, Reedijk A, de Bock GH, Lammens T, de Haas V, Denys B et al. Response-guided chemotherapy for pediatric acute myeloid leukemia without hematopoietic stem cell transplantation in first complete remission: Results from protocol DB AML-01. Pediatr Blood Cancer. 2019;66(5):e27605.
15. Rasche M, Zimmermann M, Borschel L, Bourquin JP, Dworzak M, Klingebiel T et al. Successes and challenges in the treatment of pediatric acute myeloid leukemia: a retrospective analysis of the AML-BFM trials from 1987 to 2012. Leukemia. 2018;32(10):2167–77.
16. Ries LAG, Smith MA, Gurney JG, Linet M, Tamra T, Young JL et al. Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995 (NIH Pub. No. 99-4649). Bethesda: National Cancer Institute; 1999.
17. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med. 2001;344(14):1031–7.

18. Suttorp M, Schulze P, Glauche I, Gohring G, von Neuhoff N, Metzler M et al. Front-line imatinib treatment in children and adolescents with chronic myeloid leukemia: results from a phase III trial. Leukemia. 2018;32(7):1657–69.
19. Giona F, Santopietro M, Menna G, Putti MC, Micalizzi C, Santoro N et al. Real-Life Management of Children and Adolescents with Chronic Myeloid Leukemia: The Italian Experience. Acta Haematol. 2018;140(2):105–11.
20. Gore L, Kearns PR, de Martino ML, Lee, De Souza CA, Bertrand Y et al. Dasatinib in Pediatric Patients With Chronic Myeloid Leukemia in Chronic Phase: Results From a Phase II Trial. J Clin Oncol. 2018;36(13):1330–8.
21. Kurosawa H, Tanizawa A, Muramatsu H, Tono C, Watanabe A, Shima H et al. Sequential use of second-generation tyrosine kinase inhibitors following imatinib therapy in pediatric chronic myeloid leukemia: A report from the Japanese Pediatric Leukemia/Lymphoma Study Group. Pediatr Blood Cancer. 2018;65(12):e27368.
22. A Pharmacokinetic (PK) Study of Nilotinib in Pediatric Patients With Philadelphia Chromosome-positive (Ph+) Chronic Myelogenous Leukemia (CML) or Acute Lymphoblastic Leukemia (ALL) (ClinicalTrials.gov Identifier NCT01077544). Bethesda: U.S. National Library of Medicines; 2016. Available from https://clinicaltrials.gov/ct2/show/study/NCT01077544, accessed 29 September 2019.
23. Open Label, Phase II Study to Evaluate Efficacy and Safety of Oral Nilotinib in Philadelphia Positive (Ph+) Chronic Myelogenous Leukemia (CML) Pediatric Patients (Dialog) (ClinicalTrials.gov Identifier: NCT01844765). Bethesda: U.S. National Library of Medicine; 2018. Available from https://clinicaltrials.gov/ct2/show/NCT01844765, accessed 29 September 2019.
24. Kiarie GW, Othieno-Abinya NA, Riyat MS. The GLIVEC international patient assistance programme: the Nairobi experience. East Afr Med J. 2009;86(12 Suppl):S106–7.
25. Andolina JR, Neudorf SM, Corey SJ. How I treat childhood CML. Blood. 2012;119(8):1821–30.
26. Call J, Walentas CD, Eickhoff JC, Scherzer N. Survival of gastrointestinal stromal tumor patients in the imatinib era: life raft group observational registry. BMC Cancer. 2012;12:90.
27. Giulino-Roth L, O'Donohue T, Chen Z, Bartlett NL, LaCasce A, Martin-Doyle W et al. Outcomes of adults and children with primary mediastinal B-cell lymphoma treated with dose-adjusted EPOCH-R. Br J Haematol. 2017;179(5):739–47.
28. Egan G, Goldman S, Alexander S. Mature B-NHL in children, adolescents and young adults: current therapeutic approach and emerging treatment strategies. Br J Haematol. 2019;185(6):1071–85.
29. El-Mallawany NK, McAtee CL, Campbell LR, Kazembe PN. Pediatric Kaposi sarcoma in context of the HIV epidemic in sub-Saharan Africa: current perspectives. Pediatric Health Med Ther. 2018;9:35–46.
30. Chagaluka G, Stanley C, Banda K, Depani S, Nijram'madzi J, Katangwe T et al. Kaposi's sarcoma in children: an open randomised trial of vincristine, oral etoposide and a combination of vincristine and bleomycin. Eur J Cancer. 2014;50(8):1472–81.
31. Macken M, Dale H, Moyo D, Chakmata E, Depani S, Israels T et al. Triple therapy of vincristine, bleomycin and etoposide for children with Kaposi sarcoma: Results of a study in Malawian children. Pediatr Blood Cancer. 2018;65(2).
32. Hesseling PB, Katayi E, Wharin P, Bardin R, Kouya F, Palmer D et al. Kaposi's sarcoma: Good outcome with doxorubicin, bleomycin and vincristine sulphate (ABV) chemotherapy and highly active antiretroviral therapy. S Afr Med J. 2017;107(11):952–3.

33. Cox CM, El-Mallawany NK, Kabue M, Kovarik C, Schutze GE, Kazembe PN et al. Clinical characteristics and outcomes of HIV-infected children diagnosed with Kaposi sarcoma in Malawi and Botswana. Pediatr Blood Cancer. 2013;60(8):1274–80.
34. Stefan DC, Stones DK, Wainwright L, Newton R. Kaposi sarcoma in South African children. Pediatr Blood Cancer. 2011;56(3):392–6.
35. Molyneux E, Davidson A, Orem J, Hesseling P, Balagadde-Kambugu J, Githanga J et al. The management of children with Kaposi sarcoma in resource limited settings. Pediatr Blood Cancer. 2013;60(4):538–42.
36. Casanova M, Bisogno G, Gandola L, Cecchetto G, Di Cataldo A, Basso E et al. A prospective protocol for nasopharyngeal carcinoma in children and adolescents: the Italian Rare Tumors in Pediatric Age (TREP) project. Cancer. 2012;118(10):2718–25.
37. Casanova M, Ozyar E, Patte C, Orbach D, Ferrari A, Veyrat-Follet C et al. International randomized phase 2 study on the addition of docetaxel to the combination of cisplatin and 5-fluorouracil in the induction treatment for nasopharyngeal carcinoma in children and adolescents. Cancer Chemother Pharmacol. 2016;77(2):289–98.
38. Buehrlen M, Zwaan CM, Granzen B, Lassay L, Deutz P, Vorwerk P et al. Multimodal treatment, including interferon beta, of nasopharyngeal carcinoma in children and young adults: preliminary results from the prospective, multicenter study NPC-2003-GPOH/DCOG. Cancer. 2012;118(19):4892–900.
39. Mertens R, Granzen B, Lassay L, Bucsky P, Hundgen M, Stetter G et al. Treatment of nasopharyngeal carcinoma in children and adolescents: definitive results of a multicenter study (NPC-91-GPOH). Cancer. 2005;104(5):1083–9.
40. Radhakrishnan V, Kumar P, Totadri S, Ganesan P, Selvaluxmy G, Ganesan T et al. Pediatric nasopharyngeal carcinoma: Experience from a tertiary cancer center in India. Indian J Cancer. 2016;53(3):377–80.
41. Khalil EM, Anwar MM. Treatment results of pediatric nasopharyngeal carcinoma, NCI, Cairo University experience. J Egypt Natl Canc Inst. 2015;27(3):119–28.
42. Liu W, Tang Y, Gao L, Huang X, Luo J, Zhang S et al. Nasopharyngeal carcinoma in children and adolescents - a single institution experience of 158 patients. Radiat Oncol. 2014;9:274.
43. Gonzalez-Motta A, Gonzalez G, Bermudez Y, Maldonado MC, Castaneda JM, Lopez D et al. Pediatric Nasopharyngeal Cancer: Case Report and Review of the Literature. Cureus. 2016;8(2):e497.
44. Saab R, Furman WL. Epidemiology and management options for colorectal cancer in children. Paediatr Drugs. 2008;10(3):177–92.
45. Hill DA, Furman WL, Billups CA, Riedley SE, Cain AM, Rao BN et al. Colorectal carcinoma in childhood and adolescence: a clinicopathologic review. J Clin Oncol. 2007;25(36):5808–14.
46. Kim ST, Choi YJ, Park KH, Oh SC, Seo JH, Shin SW et al. Capecitabine monotherapy as salvage treatment after failure of chemotherapy containing oxaliplatin and irinotecan in patients with metastatic colorectal cancer. Asia Pac J Clin Oncol. 2011;7(1):82–7.
47. Goldberg J, Furman WL. Management of colorectal carcinoma in children and young adults. J Pediatr Hematol Oncol. 2012;34 Suppl 2:S76–9.
48. Geel JA, Chirwa TC, Rowe B, Eyal KC, Omar F, Stones DK et al. Treatment outcomes of children with Hodgkin lymphoma between 2000 and 2010: First report by the South African Children's Cancer Study Group. Pediatr Blood Cancer. 2017;64(10).
49. Radhakrishnan V, Dhanushkodi M, Ganesan TS, Ganesan P, Sundersingh S, Selvaluxmy G et al. Pediatric Hodgkin Lymphoma Treated at Cancer Institute, Chennai, India: Long-Term Outcome. J Glob Oncol. 2017;3(5):545–54.

50. Dorffel W, Riepenhausen M, Luders H, Bramswig J. Late Effects Following Treatment of Hodgkin Lymphoma During Childhood and Adolescence. Results of the Hodgkin Lymphoma Late Effects Research Project. Klin Padiatr. 2016;228(6-07):286–93.

51. Bowden SA, Mahan JD. Zoledronic acid in pediatric metabolic bone disorders. Transl Pediatr. 2017;6(4):256–68.

52. Padhye B, Dalla-Pozza L, Little D, Munns C. Incidence and outcome of osteonecrosis in children and adolescents after intensive therapy for acute lymphoblastic leukemia (ALL). Cancer Med. 2016;5(5):960–7.

53. Padhye B, Dalla-Pozza L, Little DG, Munns CF. Use of zoledronic acid for treatment of chemotherapy related osteonecrosis in children and adolescents: a retrospective analysis. Pediatr Blood Cancer. 2013;60(9):1539–45.

54. Monagle P, Chan AKC, Goldenberg NA, Ichord RN, Journeycake JM, Nowak-Gottl U et al. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e737S–e801S.

55. Malhotra P, Jain S, Kapoor G. Symptomatic Cerebral Sinovenous Thrombosis Associated With L-Asparaginase In Children With Acute Lymphoblastic Leukemia: A Single Institution Experience Over 17 Years. J Pediatr Hematol Oncol. 2018;40(7):e450–e3.

56. Fan JL, Roberts LE, Scheurer ME, Yee DL, Shah MD, Lee-Kim YJ. Association of outcomes and anti-Xa levels in the treatment of pediatric venous thromboembolism. Pediatr Blood Cancer. 2017;64(11).

57. Goldenberg NA, Takemoto CM, Yee DL, Kittelson JM, Massicotte MP. Improving evidence on anticoagulant therapies for venous thromboembolism in children: key challenges and opportunities. Blood. 2015;126(24):2541–7.

58. Piperno-Neumann S, Le Deley MC, Redini F, Pacquement H, Marec-Berard P, Petit P et al. Zoledronate in combination with chemotherapy and surgery to treat osteosarcoma (OS2006): a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol. 2016;17(8):1070–80.

*Cancer medicines for children – text clarifications*

## Medicines for children with cancer – text clarifications

**Proposal**

The application requested amendments to the text of the listings for a number of medicines and cancer indications on the EMLc:

1. Include alternate common names for some currently listed cancer medicines.
2. Include alternate common names for some listed indications.
3. Revised diagnosis terminology for germ cell tumours.
4. Alignment and addition of formulations.
5. Inclusion of variant formulations of listed medicines.
6. Addition of usage and supportive indications.

**Applicant**

Catherine Lam, Scott C. Howard.

**WHO Technical Department**

Comments on the application were received from the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it generally supported the text clarifications proposed in the application.

**EML/EMLc**

EML and EMLc

**Section**

8.2 Antineoplastic and supportive medicines

**Dose form(s) & strengths(s)**

Various

**Core/Complementary**

Complementary

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

N/A

**Public health relevance** (burden of disease)

N/A

**Summary of request** (from the application)

1. The application proposed inclusion of the following alternate, commonly used names for medicines currently listed on the EML and EMLc:

| Current medicine name | Proposed alternatives |
|---|---|
| Calcium folinate | Leucovorin; Folinic acid |
| Dactinomycin | Actinomycin; Actinomycin-D |
| Etoposide | VP-16 |
| Fluorouracil | 5-Fluorouracil (5-FU) |
| Hydroxycarbamide | Hydroxyurea |
| Mercaptopurine | 6-mercaptopurine (6-MP) |
| Tioguanine | 6-thioguanine (6-TG) |
| Lidocaine | Lignocaine |
| Ciclosporin | Cyclosporine; Cyclosporin |
| Aciclovir | Acyclovir |

2. The application proposed inclusion of the following alternate, commonly used names for diagnoses/indications currently included on the EML and EMLc:

| Current indication | Proposed alternative |
|---|---|
| Acute myelogenous leukaemia | Acute myeloid leukaemia |
| Wilms tumour | Nephroblastoma |

3. The application proposed replacing the indications of ovarian and testicular germ cell tumours with the broader term "malignant germ cell tumour" to include other common locations where children develop malignant germ cell tumours (e.g., sacrococcygeal, mediastinal), as they are treated with the same chemotherapy agents.

4. The application proposed the following formulation amendments and additions:

| Medicine | Proposed formulation(s) for EML and EMLc |
|---|---|
| Dexamethasone | Include the same formulations of dexamethasone for use in cancer therapy as are currently included in Section 2.3 for palliative care indications. |
| Calcium folinate | - Add an oral solution formulation that can be made extemporaneously from IV formulation (strength not specified).<br>- Add 5 mg and 25 mg tablets. |
| Cyclophosphamide | Add 50 mg tablet/capsule. |
| Etoposide | - Add 50 mg capsule.<br>- Add oral liquid 20 mg/mL. |
| Mercaptopurine | Add 20 mg/mL suspension. |
| Methotrexate | Add 20 mg/mL oral liquid. |

5. The application proposed the addition of variant formulations of the following medicines:

| Current medicine | Proposed variant |
|---|---|
| Prednisolone | Prednisone (multiple strength tablets). |
| Etoposide | Etoposide phosphate 100 mg/mL. |
| Lidocaine | Lidocaine 2.5% + prilocaine 2.5% topical formulation. |

6. The application proposed inclusion of usage and supportive-care indications for the following listed medicines:

| Medicine | Proposed indication(s) |
|---|---|
| Allopurinol | "for patients at risk of tumour lysis" |
| Calcium folinate | "in combination as supportive care agent, in regimens with higher dose methotrexate to decrease side-effects of methotrexate, or in some regimens with fluorouracil to increase anticancer effects" |
| Mesna | "in combination as supportive care agent, in regimens with higher doses of ifosfamide or cyclophosphamide to mitigate toxicity" |

Table *continued*

| Medicine | Proposed indication(s) |
|---|---|
| Methotrexate | "for high-dose and intrathecal administration, must ensure ONLY preservative-free methotrexate is used" |
| Vincristine | "must ensure NEVER delivered via intrathecal administration as fatal" |
| ☐ Morphine | "codeine should not be used as a substitute for pain management in children" |

**Summary of evidence: harms** (from the application)

N/A

**Additional evidence** (not in the application)

N/A

**WHO Guidelines**

None available

**Costs/cost-effectiveness**

N/A

**Availability**

N/A

**Other considerations**

N/A

**Committee recommendations**

Following consideration of the proposals in the application, the Expert Committee made the following recommendations:

1. The additional alternate common names for medicines should not be added to the Model Lists. The current listings refer to the international non-proprietary names (INN) of the medicines. INN is the preferred nomenclature for medicines on the Model Lists.
2. The indication terminology for acute myelogenous leukaemia and Wilms tumour should be amended as proposed, as this would be consistent with ICD-11 terminology for these indications.

3. The indication of "malignant germ cell tumour" should not replace the indications of ovarian and testicular germ cell tumour as the Committee has not reviewed evidence for use of the relevant medicines in the treatment of germ cell tumours other than ovarian and testicular. Extending the indication to all germ cell tumours would require a full application.
4. With regard to formulation amendments, the Committee recommended that formulations of dexamethasone should be consistently listed across different sections of the list(s). The Committee also recommended that proposed new strengths of existing dose forms of calcium folinate, cyclophosphamide, etoposide should be added. However, the Committee did not recommend listing of the new dose forms for these medicines, and for mercaptopurine and methotrexate.
5. The Committee did not recommend the separate listing of prednisone with prednisolone, noting that the square box listing of prednisolone should be interpreted as including prednisone as an alternative. The Committee did not recommend the listing of etoposide phosphate as a variant of etoposide, as it considered that a full application would be appropriate to consider the clinical place of this medicine as an alternative to etoposide. The Committee also did not recommend listing for topical lidocaine + prilocaine, again considering that a full application would be required for this new combination product.
6. The Committee recommended including the indication "tumour lysis syndrome" with the listing for allopurinol. The Committee did not recommend including the other proposed supportive care indications with the listings of calcium folinate and mesna. Nor did the Committee recommend the proposed cautionary text for methotrexate and vincristine. The Committee acknowledged the critical importance of these messages, but considered that this text was better suited for clinical practice guidelines, medication safety information and product packaging, than on the Model Lists. The Committee did not recommend the proposed cautionary text about codeine with the listing for morphine. The Committee noted that codeine is not listed on the EMLc, and that alternatives to morphine are specified in the current listing as being limited to hydromorphone and oxycodone.

*Arsenic therapies – addition – EML and EMLc*

| | |
|---|---|
| **Arsenic trioxide** | **ATC Code: L01XX27** |
| **Realgar-Indigo naturalis formula (RIF)** | **ATC Code: N/A** |

**Proposal**

The application proposed the inclusion of arsenic therapies on the EML for the treatment of acute promyelocytic leukaemia (APML).

**Applicant**

Scott C. Howard
Professor, University of Tennessee Health Science Center
Secretary General, International Pediatric Oncology Society (SIOP)

**WHO Technical Department**

Comments on the application were received from the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it supported the inclusion of arsenic therapies for acute promyelocytic leukaemia on the EML. The technical unit stated that arsenic, used in combination with ATRA and chemotherapy, is curative in its use and is generally accepted as the standard of care.

**EML/EMLc**

EML and EMLc

**Section**

8.2.1 Cytotoxic medicines

**Dose form(s) & strengths(s)**

Arsenic trioxide: Injection 1 mg/mL
Realgar-Indigo naturalis formula (RIF): tablet 270 mg

**Core/Complementary**

Complementary

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Arsenic trioxide was previously considered by the Expert Committee in 2015 for treatment of APL as part of a comprehensive review of cancer medicines (*1*).

The Committee noted that addition of arsenic trioxide as consolidation therapy for acute promyelocytic leukaemia (APML) did not produce a clinically relevant increase in overall survival in naive patients. The Committee also noted the extremely high price and low availability of arsenic trioxide and considered that this would be unaffordable in many low- and middle-income countries (LMICs). This new application focuses on clinical trial results that have been published in the past few years and examines the oral arsenic preparation realgar-Indigo naturalis formula (RIF), which has not been previously submitted. RIF represents a feasible and inexpensive alternative to intravenous arsenic trioxide that could benefit patients in LMICs.

Currently listed medicines for treatment of APML on the EML are all-trans retinoic acid (ATRA), cytarabine, daunorubicin, mercaptopurine and methotrexate. These medicines are not currently included on the EMLc for this indication.

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**Public health relevance** (burden of disease)

The GLOBOCAN initiative estimates the worldwide incidence of new leukaemia cases for 2018 to be 437 033, with an age-standardized rate (ASR) of 5.2 per 100 000 per year (*2*). Mortality was 309 006 worldwide, with an ASR of 3.5 per 100 000 per year. The ASR was higher (3.6 per 100 000) in countries with "high human development" than in countries of "low human development" (2.7 per 100 000). However, over time, differences are becoming less evident. Unfortunately, the International Agency for Research on Cancer (IARC) does not sub-classify leukaemias into acute and chronic, and myeloid or lymphoid, in its GLOBOCAN analysis.

APML accounts for 10% of AML cases and its incidence in Europe is estimated to be 1/1 000 000 people (*3*).

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**Summary of evidence: benefits** (from the application)

A 2009 systematic review of the effectiveness of arsenic in APML patients included five RCTs with 328 cases (*4*). All the RCTs focused on the comparison of ATRA plus arsenic regimen with ATRA monotherapy. Meta-analysis showed that the effect sizes for time to complete remission, two-year disease-free survival rate and relapse rate were −1.20 (95%CI −1.68 to −0.72), 8.64 (95%CI 1.66 to 45.00), and 0.21 (95%CI 0.09 to 0.47), respectively. The authors concluded that arsenic added to ATRA-based regimens improved remission rates and event-free survival.

A 2019 review conducted for the UK National Institute for Health and Care Excellence (NICE) led the NICE Appraisal Committee to recommend approval of arsenic trioxide for newly diagnosed and relapsed APL (*5*). The review presented three RCTs, in newly diagnosed APML patients and in patients with relapsed APML. In newly diagnosed cases, results showed that more patients

having ATRA plus arsenic regimen were alive at 50 months compared with people having ATRA in combination with idarubicin (99% vs 93%; p=0.007). The number of cumulative relapses at 50 months were also lower in the arsenic regimen when compared to the alternative regimen (2% vs 14%; p=0.001). At four years, results from a second trial showed a significant difference in event-free survival (91% vs 70%; p=0.002) favouring ATRA plus arsenic regimen. However, results for overall survival were less certain (93% vs 89%; p=0.250). The only included trial presented for relapsed/refractory patients compared ATRA plus arsenic regimen with arsenic regimen, a comparison that is not relevant to assess the potential benefits associated with arsenic regimens.

In patients with newly diagnosed APML, several studies included and not included in the previously cited systematic reviews have confirmed the superiority of the ATRA plus arsenic regimen over ATRA/chemotherapy in children, adults and elderly patients (*6*–*11*). Many international cooperative group and single centre studies have documented the superiority of ATRA plus arsenic therapy over ATRA plus chemotherapy (usually anthracyclines), with higher remission rates, and absolute improvements in disease-free and overall survival ranging from 5% to 20% (*11*–*21*). Low-risk patients can be cured up to 98% of the time with protocols comprising ATRA plus arsenic (*21*, *22*). The relevant advantage in the two-year event-free survival with the ATRA plus arsenic regimen is likely to be driven by the lower mortality from causes other than relapse (e.g. reduced severe haematologic toxicity as compared to chemotherapy) together with similar antileukaemic efficacy of arsenic trioxide. High-risk patients have cure rates above 85% using protocols that include ATRA, arsenic, and chemotherapy (*21*, *23*). A 2016 meta-analysis showed that in patients treated with an ATRA plus arsenic regimen the risk of death was more than halved as compared to patients receiving ATRA plus chemotherapy (HR 0.44, 95%CI 0.24 to 0.82) (*24*).

Arsenic-based regimens are also effective for relapsed patients with APML, many of whom (about 80%) can have their lives significantly prolonged (*25*–*28*). Although protocols with arsenic alone have proven curative for some patients on both first-line and relapsed settings, the highest cure rates have been documented with combinations of ATRA and arsenic therapy used in newly diagnosed patients.

Arsenic-containing medications are now available from several suppliers in both intravenous and oral formulations, which has decreased cost and increased feasibility of arsenic-containing therapy for APML (*29*).

Realgar-indigo naturalis formula (RIF) has proven effective in adults and children with first-line and relapsed APL in large randomized controlled trials, with event-free survival of 95%–100% for newly diagnosed patients, comparable to outcomes in the control arms that received intravenous arsenic trioxide, and five-year overall survival rates close to 90% (*7*, *30*–*34*).

**Summary of evidence: harms** (from the application)

Arsenic-based regimens for APML are less toxic than chemotherapy-based regimens. Grade 3 or 4 neutropenia and thrombocytopenia, including episodes lasting more than 15 days, were significantly more frequent both during induction therapy and after each consolidation course in the ATRA and chemotherapy group than in the ATRA and arsenic trioxide group (*11*, *22*, *35*). However, it is associated with QTc prolongation, which can lead to cardiac dysrhythmias in patients who receive other drugs that prolong the QTc interval (*36*). Cardiac toxicity is rare in APML patients who receive arsenic therapy and can largely be prevented by avoiding drug–drug interactions and careful monitoring. Arsenic-based regimens have lower rates of second cancers than anthracycline-based regimens (though not statistically significant in the small studies conducted to date) (*37*). Finally, oral arsenic (RIF) has similar safety profile when compared to arsenic trioxide in patients with APML (*38*).

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**Additional evidence** (not in the application)

N/A

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**WHO Guidelines**

None available

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**Costs/cost-effectiveness**

Arsenic trioxide was found to be highly cost-effective for relapsed APML in Canada using prices that were current prior to the availability of generic formulations (*39*). Cost-effectiveness in the first-line setting would be expected to be even higher, with very high remission rates and long-term survival, and decreased need for hospitalization, blood products and supportive care. Use of an oral arsenic available at a low price point would improve cost-effectiveness even more by removing the need for daily infusions with cardiac monitoring.

Costs associated with oral arsenic are about half of those associated with intravenous arsenic. In an RCT the median total medical costs were US$ 13 183.49 in the RIF group compared with US$ 24 136.98 in the arsenic trioxide group (*40*). The large difference in costs was mostly caused by the varying costs of maintenance treatment. During induction therapy the length of hospitalization for the RIF group was significantly shorter than that for the arsenic trioxide group (24 vs 31 days). During maintenance treatment, in the RIF group the estimated medical costs to treat a patient at home were US$ 2047.14 compared with US$ 11 273.81 to treat a patient in the arsenic trioxide group in an outpatient setting.

### Availability

The United States Food and Drug Administration (FDA) approved arsenic trioxide in 2002 for relapsed APML and in 2017 for newly diagnosed patients.

The European Medicines Agency (EMA) has granted marketing authorization for arsenic trioxide for newly diagnosed in relapsed APL in 2002 (provisional approval) and 2010 (full approval). Main patents have expired (2019) but secondary patents might remain active in some jurisdictions. Several generics are available (in India).

Realgar-Indigo naturalis formula (RIF) is available as 270 mg tablets and it is produced by the Yifan Pharmaceutical Co (Tianchang, China). RIF contains Realgar (tetra-arsenic tetrasulfide $As_4S_4$, 30 mg per tablet), Indigo naturalis (125 mg per tablet), Radix salvia miltiorrhizae (50 mg per tablet), Radix pseudostellariae (45 mg per tablet), and garment film (a cover to contain the drug components; 20 mg per tablet) (*29*, *38*). The dose for first-line and relapsed acute promyelocytic leukaemia is 60 mg/kg/day divided into three daily doses (20 mg/kg/dose). It is the only oral arsenic formulation commercially available and, as such, warrants special consideration, especially for use in LMICs, where the high cost of intravenous arsenic trioxide and the need for daily intravenous arsenic trioxide infusions over many months may pose important access and safety concerns.

### Other considerations

Arsenic trioxide-based regimens require daily intravenous infusions during the arsenic-containing component of therapy. This means that patients must stay near the treatment centre to receive daily infusions for six weeks during remission-induction therapy followed by four four-week blocks. Infusions are given over 1–2 hours and ideally administration should occur in an infusion centre or hospital setting with availability of cardiac monitoring and resuscitation capabilities. Oral arsenic makes delivery of therapy more feasible in countries, and is of particular relevance in LMICs, where logistical and financial barriers are numerous.

Diagnosis of acute promyelocytic leukaemia depends on clinical findings (haemorrhage and coagulopathy), laboratory findings (leucocytosis, anaemia, thrombocytopenia), morphology (presence of myeloid blasts containing Auer rods), and documentation of the t(15;17) chromosome translocation in the leukaemia blasts by cytogenetics, fluorescence *in situ* hybridization (FISH), or polymerase chain reaction (PCR). Risk stratification of patients allows each to receive the appropriate intensity of therapy to achieve cure, and includes a low-risk group, defined as patients whose presenting white blood cell count is less than 10 000 and a high-risk group (all other patients).

### Committee recommendations

The Committee endorsed the recommendations of the Cancer Medicine Working Group with regard to the proposed threshold of four to six months of overall survival benefit as a guiding principle for prioritizing cancer medicines for inclusion on the EML, and applied this principle to the consideration arsenic-containing regimens for APML.

The Expert Committee recommended the addition of arsenic therapies (intravenous arsenic trioxide and oral realgar-Indigo naturalis formulation) to the complementary list of the EML and EMLc for use in combination with ATRA for treatment of patients with APML, both newly diagnosed and relapsed. In consideration of a separate application of cancer medicines for children, the Committee also recommended the addition of ATRA to the EMLc, and extending the listings on the EMLc of cytarabine, daunorubicin, mercaptopurine and methotrexate to include APML.

The Committee noted that treatment with ATRA plus arsenic was associated with high response rates and significant improvements in event-free and overall survival compared to ATRA plus chemotherapy, and has a more favourable toxicity profile.

## References


1. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 4. Effects of various classes of antihypertensive drugs--overview and meta-analyses. J Hypertens. 2015;33(2):195–211.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
3. Acute promyelocytic leukemia [website]. Paris: Orphanet; 2019. (https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=520, accessed 29 September 2019).
4. Xu SN, Chen JP, Liu JP, Xia Y. Efficacy of arsenic trioxide for acute promyelocytic leukemia: a systematic review and meta-analysis. Zhong Xi Yi Jie He Xue Bao. 2009;7(9):801–8.
5. Ramaekers BLT, Riemsma R, Grimm S, Fayter D, Deshpande S, Armstrong N et al. Arsenic Trioxide for Treating Acute Promyelocytic Leukaemia: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. Pharmacoeconomics. 2019; (7):887–894.
6. Zhang L, Zou Y, Chen Y, Guo Y, Yang W, Chen X et al. Role of cytarabine in paediatric acute promyelocytic leukemia treated with the combination of all-trans retinoic acid and arsenic trioxide: a randomized controlled trial. BMC Cancer. 2018;18(1):374.
7. Yang MH, Wan WQ, Luo JS, Zheng MC, Huang K, Yang LH et al. Multicenter randomized trial of arsenic trioxide and Realgar-Indigo naturalis formula in pediatric patients with acute promyelocytic leukemia: Interim results of the SCCLG-APL clinical study. Am J Hematol. 2018;93(12):1467–73.
8. Xu W, Li X, Quan L, Yao J, Mu G, Guo J et al. Arsenic trioxide decreases the amount and inhibits the function of regulatory T cells, which may contribute to its efficacy in the treatment of acute promyelocytic leukemia. Leuk Lymphoma. 2018;59(3):650–9.

9. Testi AM, Pession A, Diverio D, Grimwade D, Gibson B, de Azevedo AC et al. Risk-adapted treatment of acute promyelocytic leukemia: results from the International Consortium for Childhood APL. Blood. 2018;132(4):405–12.
10. Tao S, Wang C, Chen Y, Deng Y, Song L, Shi Y et al. Long-term effect of all-trans retinoic acid and arsenic trioxide sequential maintenance in patients with acute promyelocytic leukemia. Leuk Lymphoma. 2018:1–9.
11. Platzbecker U, Avvisati G, Cicconi L, Thiede C, Paoloni F, Vignetti M et al. Improved Outcomes With Retinoic Acid and Arsenic Trioxide Compared With Retinoic Acid and Chemotherapy in Non-High-Risk Acute Promyelocytic Leukemia: Final Results of the Randomized Italian-German APL0406 Trial. J Clin Oncol. 2017;35(6):605–12.
12. Estey E, Garcia-Manero G, Ferrajoli A, Faderl S, Verstovsek S, Jones D et al. Use of all-trans retinoic acid plus arsenic trioxide as an alternative to chemotherapy in untreated acute promyelocytic leukemia. Blood. 2006;107(9):3469–73.
13. Huang BT, Zeng QC, Gurung A, Zhao WH, Xiao Z, Li BS. The early addition of arsenic trioxide versus high-dose arabinoside is more effective and safe as consolidation chemotherapy for risk-tailored patients with acute promyelocytic leukemia: multicenter experience. Med Oncol. 2012;29(3):2088–94.
14. Huang H, Qin Y, Xu R, You X, Teng R, Yang L et al. Combination therapy with arsenic trioxide, all-trans retinoic acid, and chemotherapy in acute promyelocytic leukemia patients with various relapse risks. Leuk Res. 2012;36(7):841–5.
15. Cheng Y, Zhang L, Wu J, Lu A, Wang B, Liu G. Long-term prognosis of childhood acute promyelocytic leukaemia with arsenic trioxide administration in induction and consolidation chemotherapy phases: a single-centre experience. Eur J Haematol. 2013;91(6):483–9.
16. Efficace F, Mandelli F, Avvisati G, Cottone F, Ferrara F, Di Bona E et al. Randomized phase III trial of retinoic acid and arsenic trioxide versus retinoic acid and chemotherapy in patients with acute promyelocytic leukemia: health-related quality-of-life outcomes. J Clin Oncol. 2014;32(30):3406–12.
17. Lou Y, Qian W, Meng H, Mai W, Tong H, Tong Y et al. Long-term efficacy of low-dose all-trans retinoic acid plus minimal chemotherapy induction followed by the addition of intravenous arsenic trioxide post-remission therapy in newly diagnosed acute promyelocytic leukaemia. Hematol Oncol. 2014;32(1):40–6.
18. Leech M, Morris L, Stewart M, Smith BD, Bashey A, Holland K et al. Real-life experience of a brief arsenic trioxide-based consolidation chemotherapy in the management of acute promyelocytic leukemia: favorable outcomes with limited anthracycline exposure and shorter consolidation therapy. Clin Lymphoma Myeloma Leuk. 2015;15(5):292–7.
19. Liu CC, Wang H, Wang WD, Zhu MY, Geng QR, Lu Y. Consolidation therapy of arsenic trioxide alternated with chemotherapy achieves remarkable efficacy in newly diagnosed acute promyelocytic leukemia. Onco Targets Ther. 2015;8:3297–303.
20. Rahme R, Ades L, Thomas X, Guerci-Bresler A, Pigneux A, Vey N et al. Reducing mortality in newly diagnosed standard-risk acute promyelocytic leukemia in elderly patients treated with arsenic trioxide requires major reduction of chemotherapy: a report by the French Belgian Swiss APL group (APL 2006 trial). Haematologica. 2018;103(11):e519–e21.
21. Lou Y, Qian W, Meng H, Mai W, Tong H, Tong Y et al. High efficacy of arsenic trioxide plus all-trans retinoic acid based induction and maintenance therapy in newly diagnosed acute promyelocytic leukemia. Leuk Res. 2013;37(1):37–42.

22. Lo-Coco F, Avvisati G, Vignetti M, Thiede C, Orlando SM, Iacobelli S et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med. 2013;369(2):111–21.
23. Zhu HH, Liu YR, Jia JS, Qin YZ, Zhao XS, Lai YY. Oral arsenic and all-trans retinoic acid for high-risk acute promyelocytic leukemia. Blood. 2018;131(26):2987–9.
24. Ma Y, Liu L, Jin J, Lou Y. All-Trans Retinoic Acid plus Arsenic Trioxide versus All-Trans Retinoic Acid plus Chemotherapy for Newly Diagnosed Acute Promyelocytic Leukemia: A Meta-Analysis. PLoS One. 2016;11(7):e0158760.
25. Au WY, Lie AK, Chim CS, Liang R, Ma SK, Chan CH et al. Arsenic trioxide in comparison with chemotherapy and bone marrow transplantation for the treatment of relapsed acute promyelocytic leukaemia. Ann Oncol. 2003;14(5):752–7.
26. Thomas X, Pigneux A, Raffoux E, Huguet F, Caillot D, Fenaux P. Superiority of an arsenic trioxide-based regimen over a historic control combining all-trans retinoic acid plus intensive chemotherapy in the treatment of relapsed acute promyelocytic leukemia. Haematologica. 2006;91(7):996–7.
27. Lou Y, Suo S, Tong Y, Tong H, Qian W, Meng H et al. Outcomes and prognostic factors of first relapsed acute promyelocytic leukemia patients undergoing salvage therapy with intravenous arsenic trioxide and chemotherapy. Ann Hematol. 2014;93(6):941–8.
28. Cicconi L, Breccia M, Franceschini L, Latagliata R, Molica M, Divona M et al. Prolonged treatment with arsenic trioxide (ATO) and all-trans-retinoic acid (ATRA) for relapsed acute promyelocytic leukemia previously treated with ATRA and chemotherapy. Ann Hematol. 2018;97(10):1797–802.
29. Wang L, Zhou GB, Liu P, Song JH, Liang Y, Yan XJ et al. Dissection of mechanisms of Chinese medicinal formula Realgar-Indigo naturalis as an effective treatment for promyelocytic leukemia. Proc Natl Acad Sci USA. 2008;105(12):4826–31.
30. Xiang-Xin L, Lu-Qun W, Hao L, Xiao-Peng H, Fang-Lin L, Ling-Ling W et al. Clinical study on prospective efficacy of all-trans Acid, realgar-indigo naturalis formula combined with chemotherapy as maintenance treatment of acute promyelocytic leukemia. Evid Based Complement Alternat Med. 2014;2014:987560.
31. Au WY, Kumana CR, Lee HK, Lin SY, Liu H, Yeung DY et al. Oral arsenic trioxide-based maintenance regimens for first complete remission of acute promyelocytic leukemia: a 10-year follow-up study. Blood. 2011;118(25):6535–43.
32. Zhu HH, Wu DP, Jin J, Li JY, Ma J, Wang JX et al. Oral tetra-arsenic tetra-sulfide formula versus intravenous arsenic trioxide as first-line treatment of acute promyelocytic leukemia: a multicenter randomized controlled trial. J Clin Oncol. 2013;31(33):4215–21.
33. Zhu HH, Huang XJ. Oral arsenic and retinoic acid for non-high-risk acute promyelocytic leukemia. N Engl J Med. 2014;371(23):2239–41.
34. Gill H, Yim R, Lee HKK, Mak V, Lin SY, Kho B et al. Long-term outcome of relapsed acute promyelocytic leukemia treated with oral arsenic trioxide-based reinduction and maintenance regimens: A 15-year prospective study. Cancer. 2018;124(11):2316–26.
35. Lo-Coco F, Di Donato L, Gimema, Schlenk RF, German-Austrian Acute Myeloid Leukemia Study G, Study Alliance L. Targeted Therapy Alone for Acute Promyelocytic Leukemia. N Engl J Med. 2016;374(12):1197–8.
36. Sanz MA, Grimwade D, Tallman MS, Lowenberg B, Fenaux P, Estey EH et al. Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. Blood. 2009;113(9):1875–91.

37. Eghtedar A, Rodriguez I, Kantarjian H, O'Brien S, Daver N, Garcia-Manero G et al. Incidence of secondary neoplasms in patients with acute promyelocytic leukemia treated with all-trans retinoic acid plus chemotherapy or with all-trans retinoic acid plus arsenic trioxide. Leuk Lymphoma. 2015;56(5):1342–5.

38. Zhu HH, Wu DP, Du X, Zhang X, Liu L, Ma J et al. Oral arsenic plus retinoic acid versus intravenous arsenic plus retinoic acid for non-high-risk acute promyelocytic leukaemia: a non-inferiority, randomised phase 3 trial. Lancet Oncol. 2018;19(7):871–9.

39. Lachaine J, Mathurin K, Barakat S, Couban S. Economic evaluation of arsenic trioxide compared to all-trans retinoic acid + conventional chemotherapy for treatment of relapsed acute promyelocytic leukemia in Canada. Eur J Haematol. 2015;95(3):218–29.

40. Jiang H, Liang GW, Huang XJ, Jiang Q, Han S, Shi LW et al. Reduced medical costs and hospital days when using oral arsenic plus ATRA as the first-line treatment of acute promyelocytic leukemia. Leuk Res. 2015;39(12):1319–24.

*Medicines for cervical cancer – new indication – EML*

| | |
|---|---|
| **Cisplatin** | **ATC Code: L01XA01** |
| **Carboplatin** | **ATC Code: L01XA02** |
| **Paclitaxel** | **ATC Code: L01CD01** |
| **Fluorouracil** | **ATC Code: L01BC02** |

**Proposal**

The application requested listing for cisplatin, carboplatin, paclitaxel and fluorouracil for the additional indication of treatment of invasive cervical cancer.

**Applicant**

WHO Department for Management of Noncommunicable Diseases

**WHO Technical Department**

Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention

**EML/EMLc**

EML

**Section**

8.2.1 Cytotoxic medicines

**Dose form(s) & strengths(s)**

As currently listed

**Core/Complementary**

Complementary

**Individual/Square box listing**

Core

**Background** (if relevant, eg. resubmission, previous EC consideration)

As part of the comprehensive review of cancer medicines on the EML undertaken in 2015, the Expert Committee recommended the addition of single-agent cisplatin to the complementary list of the EML for the treatment of early-stage cervical cancer for use concurrently with radiotherapy in women at high risk of recurrence following surgery (*1*).

All of the medicines proposed in this application for cervical cancer are included on the EML. However, carboplatin, paclitaxel and fluorouracil lack

a specific endorsement for the indication of cervical cancer, and the listing for cisplatin is specific for use as a radiosensitizer.

**Public health relevance** (burden of disease)

Cervical cancer is the fourth most common cancer among women globally, with an estimated 570 000 new cases and 311 000 deaths annually in 2018 (*2*). The burden of cervical cancer is estimated to increase by almost 50%, reaching 460 000 related deaths by 2040, of which the large majority will occur in low- and middle-income countries (LMICs). Currently, the majority of cases in LMICs are diagnosed at late stage, as a result of delayed clinical presentation and untimely referral of symptomatic patients to the appropriate pathway of care for diagnosis and treatment (*3*).

In response to a rising public health problem, the United Nations Joint Global Programme on Cervical Cancer Prevention and Control was established in 2016, as an inter-Agency programme to engage partners and key stakeholders, providing technical expertise to orient an evidence-based policy for cervical cancer planning and provide pragmatic solutions (*4*).

The elimination of cervical cancer is a priority in the Sustainable Development Goals (SDG) agenda, contributing to the reduction of premature mortality due to noncommunicable diseases by one-third by 2030 and the realization of universal health coverage, in terms of access to essential health care interventions and financial risk protection (*5*, *6*). The final aim is to reduce drastically the incident cases of cervical cancer per year, through prevention (human papilloma virus vaccination) and early detection (cervical cancer early detection and screening, and treatment of pre-invasive cancer) along with treatment of more advanced forms through diagnosis, cancer surgery and radiotherapy, systemic therapy and palliative care services (*7*).

**Summary of evidence: benefits** (from the application)

**Cisplatin**

Cisplatin is a critical cytotoxic agent for the treatment of cervical cancer for radiotherapy is appropriate (*8*–*12*). It is also a key agent (alone or in combination with other agents) for the management of advanced disease, that is not amenable to locoregional control alone (i.e. surgery, radiotherapy, chemoradiotherapy (*13*–*15*).

Clinical trials of cisplatin 50 mg/m² every three weeks as monotherapy for cervical cancer provided disappointing results for disease control (objective response rate (ORR, 20%; progression-free survival (PFS), approximately three months) and poor survival (overall survival (OS), approximately eight months) (*16*, *17*).

When combined with other cytotoxic agents, improved outcomes have been reported. A Phase III clinical trial tested the combination of cisplatin and paclitaxel against cisplatin monotherapy, for FIGO IV B (metastatic), recurrent (after locoregional treatments) or persistent (not responding to locoregional treatments) cervical cancer (n=280) (*18*). The addition of paclitaxel increased the ORR (19% to 36%) and the median PFS (2.8 to 4.8 months), with no relevant difference in overall survival. However, 92% of patients had prior exposure to cisplatin, the majority pre-treated with a cisplatin-paclitaxel combination regimen. Different cisplatin combinations have been compared with cisplatin monotherapy in another trial enrolling patients with stage IV B recurrent or persistent cervix uteri carcinoma (*19*). Patients in the experimental arm received either cisplatin 50 mg/m² plus topotecan (Cto) 0.75 mg/m² every three weeks or MVAC (cisplatin, vinblastine, doxorubicin and cisplatin); the standard arm consisted of single-agent cisplatin 50 mg/m² every three weeks (n=364). The escalated polychemotherapy (Cto or MVAC) showed a longer PFS (median PFS 2.9 vs 4.6 months; RR 0.76, 95%CI 0.58 to 0.94) and OS (median OS 6.5 vs 9.4 months, RR 0.76, 95%CI 0.60 to 0.99) when compared to monotherapy. The greatest effect size on survival was observed in cisplatin-naive patients, where the gain of OS was 6.6 months vs 1.9 months in pre-exposed patients.

The open-label, randomized, Phase III JCOG0505 trial compared cisplatin or carboplatin in combination with paclitaxel, in a non-inferiority (NI) design, with a NI-margin of 1.29 for hazard ratio (HR) of OS. The schedules used were: paclitaxel 135 mg/m² plus cisplatin 50 mg/m² every three weeks and paclitaxel 135 mg/m² plus carboplatin 5 mg/mL/min (area-under-the-curve) each three weeks (n=253) (*20*). 98% of patients had a good performance status (WHO-ECOG scale 0-1), 83% presenting with squamous histology, 79% previously irradiated and 48% pre-exposed to cisplatin. The trial met the primary endpoint and confirmed carboplatin-based to be non-inferior to cisplatin-based chemotherapy, reporting HR 0.99, (90%CI, 0.79 to 1.25), and median OS of 18.3 and 17.5 months, respectively. Median PFS was 6.9 and 6.2 months. An exploratory sub-group analysis showed cisplatin to provide a greater effect size in platinum-naive patients, with a median OS of 23 months and 13 months for cisplatin and carboplatin, respectively. The sub-group analysis also favoured carboplatin and paclitaxel over cisplatin combination for platinum-resistant and platinum-intermediate sensitive disease (platinum-free interval inferior to 6 months or between 6–12 months), suggesting that carboplatin can still provide a benefit after cisplatin failure and, otherwise, that cisplatin provides the greatest effect in the naive and eligible patients (HR for platinum-resistant in cisplatin pre-treated patients: 0.57; HR for platinum-intermediate: 0.71). However, all platinum pre-treated patients were exposed to cisplatin and none to carboplatin, suggesting that the re-challenge with the same platinum compound would be less effective and an inter-class switch preferred, where possible.

The 2009 GOG-204 Phase III clinical trial compared four different cisplatin-containing doublet combinations for stage IVB, recurrent or persistent cervical carcinoma patients (*21*). Patients were enrolled to receive vinorelbine, gemcitabine, topotecan or paclitaxel in combination as doublets with cisplatin 50 mg/m² each three weeks (n=513). Patients presented predominantly with squamous cell (80–88%) persistent (74–80%) cervical cancer, mostly pre-treated with cisplatin and radiotherapy (70–81%). The trial was interrupted after 513 patients enrolled, as the futility analysis proved the different combinations to be non-superior to cisplatin plus paclitaxel. ORR ranged between 22% and 29%; median PFS between 4–5.8 months and OS 10–12.9 months. Nevertheless, paclitaxel–cisplatin showed the highest response rate (29%), median PFS (5.8 months) and median OS (12.8 months).

The use of cisplatin requires the fulfilment of specific criteria for treatment initiation, particularly a conserved glomerular kidney function. Patients are considered to be cisplatin- unfit if presenting one of more of the following characteristics: Eastern Clinical Oncology Group (ECOG) performance status (PS) of 2 or more; creatinine clearance of less than 60 mL/minute; treatment-related hearing loss of Grade 2 or more according to the Common Terminology Criteria for Adverse Events (CTCAE) system and treatment-related neuropathy of Grade 2 or more (*22*).

**Carboplatin**

Guidelines include carboplatin in the treatment of advanced disease for cisplatin-unfit patients, as a category 1 treatment (according to National Comprehensive Cancer Network (NCCN) guidelines) (*15*). The role of carboplatin is highlighted in the present submission as an alternative in cisplatin-unfit patients, both as radiosensitizer and systemic agent for combination treatment in the locally advanced, refractory, relapsed and metastatic settings. The acknowledgment of carboplatin as an agent for cervical cancer is relevant for the specific anatomic topography and local invasiveness of the disease. Different series have described hydronephrosis in 20–35% of cervical cancer patients, with possible retrograde kidney parenchyma impairment, due to the close anatomical proximity of the ureter with genitourinary organs. A Nigerian analysis of the renal status of patients with cervical cancer prior to commencement of treatment, reported one-third of patients having a clinically significant urethral involvement or obstruction and nearly 10% having a kidney dysfunction for related parenchyma disease (*23*).

Carboplatin has been shown in a sub-group analysis of the JCOG0505 trial to provide a greater benefit in cisplatin pre-treated patients compared to cisplatin (*20*). These findings were confirmed in a retrospective analysis of a cohort of Asian patients treated with paclitaxel combined either with cisplatin or carboplatin (n=116) (*24*). In the curative setting, the role of carboplatin

must be restricted to the patients unfit for cisplatin but still eligible to receive a curative treatment, in the context of a concomitant chemoradiotherapy, as a radiosensitizer.

Data on the efficacy of concurrent weekly carboplatin with radiotherapy in the treatment of cervical cancer have been evaluated in a recent meta-analysis, exploring whether differences between cisplatin and carboplatin exist when used as radiosensitizers (*25*). Twelve studies (1698 patients) were eligible for meta-analysis. Complete response (CR), PFS and OS were assessed. The use of carboplatin provided a lower rate of CR (OR 0.53, 95%CI 0.34 to 0.82); lower PFS and OS were assessed at 3 years, with HR of 0.71 and 0.70, indicative of a potential difference. However, the authors concluded that carboplatin should still be a priority for cisplatin-ineligible patients, as it is the preferable alternative choice of treatment.

### Paclitaxel

As previously described, paclitaxel represents the optimal partner of chemotherapy platinum- based doublets for the treatment of advanced disease. The doublet cisplatin plus paclitaxel (or carboplatin plus paclitaxel, in cisplatin-ineligible patients) is the recommended regimen for advanced cervical cancer, as reported by the principal guidelines (*13–15*). In a large randomized Phase III clinical trial (GOG-204), paclitaxel showed a greater effect size and a manageable safety profile, when compared with the combinations with topotecan, gemcitabine and vinorelbine (*21*).

### Fluorouracil

Fluorouracil (5-FU) has a role as a radiosensitizer and is extensively used across different cancer indications. For cervical cancer, women with high-risk disease are eligible to receive concomitant adjuvant chemoradiotherapy. The features of high risk are defined as: positive pelvic lymph nodes, positive surgical margins, and positive parametrium. The use of adjuvant chemotherapy in combination with radiotherapy has been tested in a clinical trial, enrolling 268 patients with clinical stage FIGO IA2 and IIA carcinoma of the cervix, treated with radical hysterectomy and pelvic lymph node dissection, and found to have lymph node involvement, invaded parametrium and positive margins (*11*). Patients received cisplatin as a bolus of 70 mg/m² followed by 5-FU as continuous IV infusion over 96 hours at 1000 mg/m² every three weeks, for four cycles concomitantly with radiotherapy for the first and second cycle. The pelvic radiotherapy consisted of 1.7 Gy per day on days 1 to 5 of each week, for a total of 29 fractions (49.3 Gy). Around one-third of patients presented with involvement of parametria, and 85% presented with metastatic pelvic lymph nodes after surgery. The addition of chemotherapy to radiotherapy showed a gain in overall survival, with 10%

more patients alive at four years (OS 81% vs 71% at four years; HR 1.96, CI not reported, p=0.007). The projected progression-free survival at four years was 80% vs 63% (HR 2.01, p=0.003), favouring the chemotherapy + radiotherapy arm.

The role of 5-FU as a radiosensitizer agent has been investigated in three clinical trials for stage IB2 to IVA cervical cancer patients (*8*, *26*, *27*). The three trials reported similar results, supporting the use of cisplatin-based chemotherapy, including the combination of cisplatin and 5-FU, as radiosensitizer in as an adjunct to radiotherapy for locally advanced cervical cancer: HRs for OS ranged between 0.52 (stage IB2- IVA) and 0.72 (stage IIB-IVA).

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**Summary of evidence: harms** (from the application)

### Cisplatin and carboplatin

In the JCOG0505 trial, cisplatin or carboplatin in combination with paclitaxel were associated with similar proportions of patients who terminated treatment because of intolerable adverse events, 9.5% in the carboplatin group and 11.8% in the cisplatin group (*20*). Most patients experience haematological toxicity from the medication combination including neutropenia, thrombocytopenia and anaemia, all of which are typically rapidly reversible upon discontinuation of agents (*28*, *29*).

Cisplatin is highly emetogenic, prophylactic antiemetics are necessary to reduce nausea and vomiting in all patients (*30*). Mild peripheral neuropathy is common. Patients should be followed carefully, and dose reduction or discontinuation may be required for moderate or severe symptoms. Ototoxicity is observed with cisplatin and is more common with increasing dose and number of cycles. Audiometry should be considered to monitor patients with toxicity; vestibular defects are less common. Serious renal toxicity caused by cisplatin can be significant and may result in electrolyte abnormalities. Hypomagnesaemia, hypocalcaemia and hypokalaemia should be followed and deficits addressed. Intravenous hydration both before and after administering cisplatin is necessary to reduce the incidence of renal toxicity (*31*).

### Paclitaxel

Paclitaxel is associated with infusion reactions in about 30% of patients; most reactions are mild and easily managed (*32*, *33*). Paclitaxel frequently causes alopecia and peripheral neuropathy, which is often mild and reversible (*32*, *34*).

### Fluorouracil

The use of adjuvant chemotherapy (cisplatin followed by 5-FU), in combination with radiotherapy, is associated with an increase in Grade 4 adverse events, mostly haematological toxicity (Grade 4 adverse events: 17% vs 4%; Grade 3 and 4 granulocytopenia: 29% vs 2%) compared to radiotherapy alone (*11*).

**Additional evidence** (not in the application)

N/A

**WHO Guidelines**

None available

**Costs/cost-effectiveness**

An economic analysis of cisplatin alone versus cisplatin doublets in women with advanced or recurrent cervical cancer evaluated the impact of: (i) extending the use of cytotoxic agents to the advanced disease, with a highlight on systemic therapy; and (ii) the use of 5-FU and carboplatin as alternative radiosensitizers (*35*). The cost analysis showed that chemotherapy medicine costs for six cycles of cisplatin was US$ 89 while for cisplatin plus paclitaxel it was US$ 489. The highest chemotherapy cost was for gemcitabine plus cisplatin at US$ 18 306. According to the major effect size and manageable safety profile, the combination of cisplatin and paclitaxel was the most cost-effective option for the treatment of advanced cervical cancer, and, to a large extent, more cost-effective than cisplatin monotherapy. Sensitivity analyses confirmed that cisplatin plus paclitaxel would be the regimen of choice. For the same setting, another model showed that the incremental cost-effectiveness ratio for combination cisplatin plus paclitaxel compared to cisplatin alone was US $13 654 per quality-adjusted life-year (QALY) gained (*36*).

**Availability**

Originator and generic brands of the proposed medicines are available.

**Other considerations**

N/A

**Committee recommendations**

The Expert Committee recommended extending the indications for cisplatin, carboplatin and paclitaxel on the complementary list of the EML to include treatment of invasive cervical cancer. The Committee considered that the evidence presented demonstrated these medicines to be associated with relevant survival benefits for patients. The Committee noted that regimens including these medicines are considered standard care in the curative and non-curative settings for cervical cancer.

Cisplatin is currently listed for use in the curative setting as a radiosensitizer and its listing is recommended to be extended to include the non-curative setting. Carboplatin is recommended for listing both in the curative

and non-curative settings, and paclitaxel is recommended for listing in the non-curative setting.

The Expert Committee did not recommend extending the indications for fluorouracil to include treatment of cervical cancer in the curative setting. The Committee noted that when combined with radiotherapy, fluorouracil alone or in combination with cisplatin, was not associated with additional benefit compared to radiotherapy alone or cisplatin plus radiotherapy.

## References


1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of Essential Medicines and the 5rd WHO Model List of Essential Medicines for Children) (WHO Technical Report Series, No. 994). Geneva: World Health Organization; 2015. Available from https://apps.who.int/iris/bitstream/handle/10665/189763/9789241209946_eng.pdf, accessed 30 October 2019.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
3. Ginsburg O, Bray F, Coleman MP, Vanderpuye V, Eniu A, Kotha SR et al. The global burden of women's cancers: a grand challenge in global health. Lancet. 2017;389(10071):847–60.
4. UN Joint Global Programme on Cervical Cancer Prevention and Control. Geneva: United Nations Inter-Agency Task Force on the Prevention and Control of Noncommunicable Diseases (UNIATF); 2016. Available from https://www.who.int/ncds/un-task-force/un-joint-action-cervical-cancer-leaflet.pdf, accessed 29 September 2019.
5. SDG health and health-related targets. In: World Health Statistics 2016: Monitoring health for the SDGs. Geneva: World Health Organization; 2016. Available from https://www.who.int/gho/publications/world_health_statistics/2016/en/, accessed 30 October 2019.
6. Service delivery and safety: Quality in universal health coverage [Internet]. Geneva: World Health Organization; 2019. Available from https://www.who.int/servicedeliverysafety/areas/qhc/en/, accessed 29 September 2019.
7. How WHO will report in 2017 to the United Nations General Assembly on the progress achieved in the implementation of commitments included in the 2011 UN Political Declaration and 2014 UN Outcome Document on NCDs [Technical note]. Geneva: World Health Organization; 2017. Available from https://www.who.int/nmh/events/2015/Updated-WHO-Technical-Note-NCD-Progress-Monitor-September-2017.pdf, accessed 29 September 2019.
8. Whitney CW, Sause W, Bundy BN, Malfetano JH, Hannigan EV, Fowler WC, Jr. et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. J CLin Oncol. 1999;17(5):1339–48.
9. Eifel PJ, Winter K, Morris M, Levenback C, Grigsby PW, Cooper J et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90-01. J Clin Oncol. 2004;22(5):872–80.
10. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med. 1999;340(15):1144–53.

11. Peters WA, 3rd, Liu PY, Barrett RJ, 2nd, Stock RJ, Monk BJ, Berek JS et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol. 2000;18(8):1606–13.
12. Keys HM, Bundy BN, Stehman FB, Muderspach LI, Chafe WE, Suggs CL et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med. 1999;340(15):1154–61.
13. Marth C, Landoni F, Mahner S, McCormack M, Gonzalez-Martin A, Colombo N et al. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl_4):iv72–iv83.
14. Linee guida. Neoplasie dell'utero: endometrio e cervice. Edizione 2018. Milan: Associazione Italiana di Oncologia Medica (AIOM); 2018. Available from https://www.aiom.it/wp-content/uploads/2018/11/2018_LG_AIOM_Utero.pdf, accessed 30 October 2019.
15. Koh WJ, Abu-Rustum NR, Bean S, Bradley K, Campos SM, Cho KR et al. Cervical Cancer, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019;17(1):64–84.
16. Bonomi P, Blessing JA, Stehman FB, DiSaia PJ, Walton L, Major FJ. Randomized trial of three cisplatin dose schedules in squamous-cell carcinoma of the cervix: a Gynecologic Oncology Group study. J Clin Oncol. 1985;3(8):1079–85.
17. Thigpen T, Shingleton H, Homesley H, Lagasse L, Blessing J. Cis-platinum in treatment of advanced or recurrent squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Cancer. 1981;48(4):899–903.
18. Moore DH, Blessing JA, McQuellon RP, Thaler HT, Cella D, Benda J et al. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a gynecologic oncology group study. J Clin Oncol. 2004;22(15):3113–9.
19. Long HJ, 3rd, Bundy BN, Grendys EC, Jr., Benda JA, McMeekin DS, Sorosky J et al. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group Study. J Clin Oncol. 2005;23(21):4626–33.
20. Kitagawa R, Katsumata N, Shibata T, Kamura T, Kasamatsu T, Nakanishi T et al. Paclitaxel Plus Carboplatin Versus Paclitaxel Plus Cisplatin in Metastatic or Recurrent Cervical Cancer: The Open-Label Randomized Phase III Trial JCOG0505. J Clin Oncol. 2015;33(19):2129–35.
21. Monk BJ, Sill MW, McMeekin DS, Cohn DE, Ramondetta LM, Boardman CH et al. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. J Clin Oncol. 2009;27(28):4649–55.
22. Galsky MD, Hahn NM, Rosenberg J, Sonpavde G, Hutson T, Oh WK et al. Treatment of patients with metastatic urothelial cancer "unfit" for Cisplatin-based chemotherapy. J Clin Oncol. 2011;29(17):2432–8.
23. Abdus-salam AA ADB, Abdus-salam RA,. Renal Status of Patients with Cervical Cancer Prior to Treatment Commencement. Tropical Journal of Nephrology. 2009;4(1):17–20.
24. Friedlander M, Grogan M, Force USPST. Guidelines for the treatment of recurrent and metastatic cervical cancer. Oncologist. 2002;7(4):342–7.
25. Xue R, Cai X, Xu H, Wu S, Huang H. The efficacy of concurrent weekly carboplatin with radiotherapy in the treatment of cervical cancer: A meta-analysis. Gynecol Oncol. 2018;150(3):412–9.
26. Morris M, Eifel PJ, Lu J, Grigsby PW, Levenback C, Stevens RE et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med. 1999;340(15):1137–43.

27. Rose PG, Ali S, Watkins E, Thigpen JT, Deppe G, Clarke-Pearson DL et al. Long-term follow-up of a randomized trial comparing concurrent single agent cisplatin, cisplatin-based combination chemotherapy, or hydroxyurea during pelvic irradiation for locally advanced cervical cancer: a Gynecologic Oncology Group Study. J Clin Oncol. 2007;25(19):2804–10.

28. Parmar MK, Ledermann JA, Colombo N, du Bois A, Delaloye JF, Kristensen GB et al. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. Lancet. 2003;361(9375):2099–106.

29. Bookman MA, Brady MF, McGuire WP, Harper PG, Alberts DS, Friedlander M et al. Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: a Phase III Trial of the Gynecologic Cancer Intergroup. J Clin Oncol. 2009;27(9):1419–25.

30. Hesketh PJ. Prevention and treatment of chemotherapy-induced nausea and vomiting [website]. Waltham: UpToDate; 2019. (https://www.uptodate.com/contents/prevention-and-treatment-of-chemotherapy-induced-nausea-and-vomiting-in-adults, accessed 29 September 2019).

31. Portilla D, Safar AM, Shannon ML, Penson RT. Cisplatin nephrotoxicity [website]. Waltham: UpToDate; 2019. (https://www.uptodate.com/contents/cisplatin-nephrotoxicity, accessed 29 September 2019).

32. Castells M, Matulonis U, Horton T. Infusion reactions to systemic chemotherapy [website]. Waltham: UpToDate; 2019. (https://www.uptodate.com/contents/infusion-reactions-to-systemic-chemotherapy, accessed 29 September 2019).

33. LaCasce A, Castells M, Burnstein H, Meyerhardt J. Infusion reactions to therapeutic monoclonal antiboties used for cancer therapy [website]. Waltham: UpToDate; 2019. (https://www.uptodate.com/contents/infusion-related-reactions-to-therapeutic-monoclonal-antibodies-used-for-cancer-therapy, accessed 29 September 2019).

34. Floyd J, Morgan JP. Cardiotoxicity of non-anthracycline cancer chemotherapy agents [website]. Waltham: UpToDate; 2019. (https://www.uptodate.com/contents/cardiotoxicity-of-non-anthracycline-cancer-chemotherapy-agents, accessed 29 September 2019).

35. McKim A, Walter AC, Sheely KM, Manahan KJ, Geisler JP. An economic analysis of cisplatin alone versus cisplatin doublets in the treatment of women with advanced or recurrent cervical cancer. Eur J Gynaecol Oncol. 2016;37(3):353–6.

36. Geisler JP, Swathirajan J, Wood KL, Manahan KJ. Treatment of advanced or recurrent cervical cancer with Cisplatin or Cisplatin containing regimens: a cost effective analysis. J Cancer. 2012;3:454–8.

*Pegaspargase – addition – EML and EMLc*

**Pegaspargase** **ATC Code: L01XX24**

**Proposal**

The application requested the addition of pegaspargase (PEGylated *Escherichia coli* asparaginase) to the EML and EMLc for use in the treatment of acute lymphoblastic leukaemia (ALL).

**Applicant**

Scott C. Howard
Professor, University of Tennessee Health Science Center
Secretary General, International Paediatric Oncology Society (SIOP)

**WHO Technical Department**

Comments on the application were received from the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it supported the inclusion of pegaspargase and related approved biotherapeutics to the EML and EMLc, considering that the application requested inclusion of a related formation to an existing listed medicine within the same class (asparaginase).

**EML/EMLc**

EML and EMLc

**Section**

8.2.1 Cytotoxic medicines

**Dose form(s) & strengths(s)**

Solution for injection 3,750 units/5 mL in vial

**Core/Complementary**

Complementary

**Individual/Square box listing**

Individual listing, including approved, quality-assured biosimilars.

**Background (if relevant, eg. resubmission, previous EC consideration)**

Pegaspargase had not previously been considered by the Expert Committee for addition to the EML. Native *E. coli* asparaginase is currently included on the EML and EMLc for treatment of ALL.

Asparaginases represent a therapeutic group including native *E. coli* asparaginase, PEGylated *E. coli* asparaginase, Erwinia asparaginase, and biosimilars. When asparaginases are used at the recommended dose and schedule, and when use is not limited by hypersensitivity or neutralizing antibodies, any of these three asparaginases effectively treat ALL.

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**Public health relevance** (burden of disease)

Acute lymphoblastic leukaemia (ALL) is a rare haematological malignancy. Globally, from 2003 to 2007, the age-standardized incidence rate of ALL ranged from 1.08 to 2.12 per 100 000 person-years. ALL accounts for approximately 25% of all cancers (80% of leukaemias) in children. The disease is far less common in adults (<1% of all cancers) where is associated with much lower cure rate that that achievable for children (*1*).

Allergic reactions to native *E. coli* asparaginase occur in 20% to 42% of patients with ALL, and silent (asymptomatic) neutralizing antibody formation in another 30 to 40%, such that around two thirds of patients do not complete all their required asparaginase unless they have access to a second asparaginase product, usually Erwinia asparaginase (*2–10*).

Hypersensitivity or silent antibody formation necessitate a change to another form of asparaginase. The supply of Erwinia asparaginase has been limited to high-income countries, and supply is often insufficient to meet the needs of patients who react to first-line native *E. coli* asparaginase.

When no second product is available (or an allergy occurs to the alternate asparaginase), the inability to complete asparaginase treatment increases the risk of relapse, which is associated with poor prognosis, with survival after relapse ranging from 20% to 50% (*11*). Furthermore, relapse therapy entails intense salvage chemotherapy followed by allogeneic stem cell transplantation, which greatly increases treatment costs (*9*). Minimization of allergic reactions to the initial form of asparaginase improves outcomes and reduces costs.

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**Summary of evidence: benefits** (from the application)

PEGylation of *E. coli* asparaginase to create pegaspargase increases the half-life of asparaginase and decreases immunogenicity and allergic reactions/antibody formation from 20–42% to 2–11% (*12*).

The UKALL 2003 trial used pegaspargase in a schedule that included several days of glucocorticoids prior to each dose of pegaspargase in low- and intermediate-risk patients. Glucocorticoid pre-treated patients had a 1% rate of allergic reaction and five-year event-free survival of around 95% (*13*).

Patients in the high-risk arm received several doses of pegaspargase without preceding glucocorticoids and had a reaction rate of 6%, such that in the whole study the reaction rate was 2% (*13*, *14*). These findings led to a change in clinical practice, and modification of existing ALL treatment protocols to include

glucocorticoid pre-treatment before each pegaspargase dose, to reduce the incidence of allergic reactions, thus allowing patients to complete asparaginase therapy and reducing the need for a second-line asparaginase (e.g. Erwinia).

Asparaginase products have different molecular structures, different half-lives, and different clinical activities per unit. Pegaspargase is six to nine times more potent than native *E. coli* asparaginase and each dose lasts 2–3 weeks instead of 2–3 days. Modern ALL protocols require lower doses and fewer doses of pegaspargase to provide the asparaginase needed for patients.

Treatment strategies using pegaspargase as initial therapy are more effective because they reduce the rates of hypersensitivity and neutralizing antibodies from a total of 50–65% (including both) to 10–15% (including both) and thus allow more patients to continue first-line asparaginase and complete all doses of the treatment protocol. Completion of all doses of first-line asparaginase reduces the risk of relapse and thus reduces costs associated with salvage therapy (*15*). It also reduces the need for second-line Erwinia asparaginase, which is not available in many countries (especially LMICs) and which has suffered from recurrent shortages and stock-outs even in high-income countries (HICs).

**Summary of evidence: harms** (from the application)

No data were presented in the application in relation to the comparative safety of pegaspargase.

**Additional evidence** (not in the application)

A randomized, open-label Phase III trial compared the relative toxicity and efficacy of intravenous (IV) pegaspargase and intramuscular (IM) native *E coli* asparaginase in 463 children with newly diagnosed ALL who had achieved complete remission following induction therapy (*16*). Five-year disease-free survival was similar between treatment groups: 90% vs 89% for IV pegaspargase and IM native *E coli* asparaginase treated patients, respectively (p=0.58). There was no significant difference in the frequency of asparaginase-related toxicities (allergy, pancreatitis or thrombotic or bleeding adverse events) between the treatment groups: 28% vs 26% in the pegaspargase and native *E. coli* asparaginase groups, respectively (p=0.60). Pegaspargase was associated with less anxiety than native *E. coli* asparaginase. The most common adverse events of Grade 3 or higher were infections (bacterial or fungal) and occurred at a similar rate in both treatment groups.

A retrospective study compared the efficacy and safety of pegaspargase and native *E. coli* asparaginase in 122 adolescents and adults with newly diagnosed ALL (*17*). Both treatments demonstrated comparable complete remission rates (95.65 vs 90.79%), median overall survival (14.07 vs 16.29 months) and median relapse-free survival (10.00 vs 8.57 months). Pegaspargase-treated patients aged

less than 35 years had a higher median relapse-free survival time compared with *E. coli* asparaginase-treated patients (10.93 vs 8.97 months; p=0.037). Both treatments were found to be acceptably tolerable and demonstrated similar incidences of allergy, hepatic toxicity, pancreatic lesions, and bleeding and coagulation effects.

In patients with relapsed ALL, and with hypersensitivity to native *E. coli* asparaginase, pegaspargase treatment was associated with similar tolerability as in newly diagnosed patients (*18*).

**WHO Guidelines**

None available.

**Costs/cost-effectiveness**

The application estimated that, on average, the ratio of the number of vials of *E. coli* asparaginase needed versus vials of pegaspargase was 10.3 (assuming no obesity and no vial sharing between patients) meaning that a per-vial price of pegaspargase that is 10.3 times greater than that of a vial of native *E. coli* asparaginase would be cost-neutral, without considering differences in efficacy.

Costs for native *E. coli* asparaginase were reported as between US$ 150–177 per vial, compared to US$ 1300–1400 per vial for pegaspargase in Europe and Latin America.

**Availability**

Pegaspargase is marketed by Servier Pharmaceuticals. Biosimilars of pegaspargase are in development in some jurisdictions.

**Other considerations**

The risk of allergic hypersensitivity reactions to asparaginase therapy increases with the number of doses and up to one third of patients experience a reaction by the fourth dose. This is one of the highest reported sensitivity reactions reported from chemotherapy drugs. Approximately 10% of reactions are life-threatening.

Reactions involving the formation of silent neutralizing antibodies result in inactivation of asparaginase and reduced serum asparaginase activity levels. This results in a low therapeutic threshold of the drug. For these patients, therapeutic drug monitoring is essential, but not generally available in LMICs.

**Committee recommendations**

The Expert Committee recommended the addition of pegaspargase to the complementary list of the EML and EMLc for use in the treatment of acute lymphoblastic leukaemia. The listing should indicate that quality-assured biosimilars of pegaspargase should also be considered as essential.

The Committee noted pegaspargase was associated with less immunogenicity and development of neutralizing antibodies than native asparaginase, which may offer advantages in terms of improved patient adherence enabling completion of treatment, thereby reducing the risk of relapse.

## References


1. Katz AJ, Chia VM, Schoonen WM, Kelsh MA. Acute lymphoblastic leukemia: an assessment of international incidence, survival, and disease burden. Cancer Causes Control. 2015;26(11):1627–42.
2. Schore RJ, Devidas M, Bleyer A, Reaman GH, Winick N, Loh ML et al. Plasma asparaginase activity and asparagine depletion in acute lymphoblastic leukemia patients treated with pegaspargase on Children's Oncology Group AALL07P4(). Leuk Lymphoma. 2019:1–9.
3. Russell HV. Asparaginase products in upfront acute lymphoblastic leukemia therapy: Value, location, and style. Pediatr Blood Cancer. 2019;66(1):e27497.
4. Salzer W, Bostrom B, Messinger Y, Perissinotti AJ, Marini B. Asparaginase activity levels and monitoring in patients with acute lymphoblastic leukemia. Leuk Lymphoma. 2018;59(8):1797–806.
5. Fernandez CA, Smith C, Yang W, Mullighan CG, Qu C, Larsen E et al. Genome-wide analysis links NFATC2 with asparaginase hypersensitivity. Blood. 2015;126(1):69–75.
6. Fernandez CA, Smith C, Yang W, Date M, Bashford D, Larsen E et al. HLA-DRB1*07:01 is associated with a higher risk of asparaginase allergies. Blood. 2014;124(8):1266–76.
7. Vrooman LM, Stevenson KE, Supko JG, O'Brien J, Dahlberg SE, Asselin BL et al. Postinduction dexamethasone and individualized dosing of Escherichia Coli L-asparaginase each improve outcome of children and adolescents with newly diagnosed acute lymphoblastic leukemia: results from a randomized study--Dana-Farber Cancer Institute ALL Consortium Protocol 00-01. J Clin Oncol. 2013;31(9):1202–10.
8. Liu C, Kawedia JD, Cheng C, Pei D, Fernandez CA, Cai X et al. Clinical utility and implications of asparaginase antibodies in acute lymphoblastic leukemia. Leukemia. 2012;26(11):2303–9.
9. Kawedia JD, Liu C, Pei D, Cheng C, Fernandez CA, Howard SC et al. Dexamethasone exposure and asparaginase antibodies affect relapse risk in acute lymphoblastic leukemia. Blood. 2012;119(7):1658–64.
10. Pui CH, Campana D, Pei D, Bowman WP, Sandlund JT, Kaste SC et al. Treating childhood acute lymphoblastic leukemia without cranial irradiation. N Engl J Med. 2009;360(26):2730–41.
11. Nguyen K, Devidas M, Cheng SC, La M, Raetz EA, Carroll WL et al. Factors influencing survival after relapse from acute lymphoblastic leukemia: a Children's Oncology Group study. Leukemia. 2008;22(12):2142–50.
12. Pieters R, Hunger SP, Boos J, Rizzari C, Silverman L, Baruchel A et al. L-asparaginase treatment in acute lymphoblastic leukemia: a focus on Erwinia asparaginase. Cancer. 2011;117(2):238–49.
13. Vora A, Goulden N, Wade R, Mitchell C, Hancock J, Hough R et al. Treatment reduction for children and young adults with low-risk acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): a randomised controlled trial. Lancet Oncol. 2013;14(3):199–209.
14. Pui CH. Reducing delayed intensification therapy in childhood ALL. Lancet Oncol. 2013;14(3): 178–9.

15. Kloos RQH, van Litsenburg RRL, Wolf S, Wismans L, Kaspers GJL, Uyl-de Groot CA et al. A cost-effectiveness analysis of Erwinia asparaginase therapy in children with acute lymphoblastic leukemia. Pediatr Blood Cancer. 2019;66(1):e27458.
16. Place AE, Stevenson KE, Vrooman LM, Harris MH, Hunt SK, O'Brien JE et al. Intravenous pegylated asparaginase versus intramuscular native Escherichia coli L-asparaginase in newly diagnosed childhood acute lymphoblastic leukaemia (DFCI 05-001): a randomised, open-label phase 3 trial. Lancet Oncol. 2015;16(16):1677–90.
17. Liang J, Shi P, Guo X, Li J, He L, Wang Y et al. A retrospective comparison of Escherichia coli and polyethylene glycol-conjugated asparaginase for the treatment of adolescents and adults with newly diagnosed acute lymphoblastic leukemia. Oncol Lett. 2018;15(1):75–82.
18. Heo YA, Syed YY, Keam SJ. Pegaspargase: A Review in Acute Lymphoblastic Leukaemia. Drugs. 2019;79(7):767–77.

*Pertuzumab – addition – EML*

## Pertuzumab — ATC Code: L01XC13

**Proposal**

The application requested the addition of pertuzumab to the complementary list of the EML for the treatment of early stage and metastatic human epidermal growth factor receptor 2 (HER2) positive breast cancer.

**Applicant**

F. Hoffmann-La Roche Ltd.

**WHO Technical Department**

Comments on the application were received from the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it did not support inclusion of pertuzumab on the EML at this time, though noting with interest ongoing studies of pertuzumab in the neoadjuvant and metastatic settings.

**EML/EMLc**

EML

**Section**

8.2.2 Targeted therapies

**Dose form(s) & strengths(s)**

Concentrated solution for IV infusion 420 mg/14 mL in 14 mL vial

**Core/Complementary**

Complementary

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Pertuzumab, in combination with trastuzumab and docetaxel, is indicated for treatment of patients with HER2-positive metastatic or locally recurrent, unresectable breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

Pertuzumab, in combination with trastuzumab and chemotherapy, is indicated for:

- neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer;
- adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence.

Pertuzumab has not previously been considered for EML inclusion. Trastuzumab, another anti-HER2 treatment, is currently included on the EML for treatment of early stage and metastatic HER2 positive breast cancer. Multiple cytotoxic medicines, including docetaxel, are included on the EML for early stage and metastatic breast cancer.

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**Public health relevance** (burden of disease)

Breast cancer is the leading cause of cancer death among women globally, responsible for 15% of all cancer deaths. In 2018, the global cancer burden increased to 18.1 million cases, causing 9.6 million deaths (*1*). Changes in lifestyle, life expectancy and reproductive factors are responsible in many low- and middle-income countries (LMICs) for a sharp increase in the incidence of breast cancer, and the number of deaths as a percentage of incident cases is greater than that seen in high-income countries (HICs). For example, in 2008, this figure was 24% in HICs, 38% in high-middle-income countries, 40% in low-middle-income and 48% in low-income (*2*).

The HER2 receptor has emerged as one of the most important targets for the treatment of breast cancer. HER2 is involved in regulating cell growth, survival, and differentiation (*3*). Amplification and/or overexpression of HER2 occurs in approximately 18%–22% of breast cancers (*4*, *5*). HER2 amplification/overexpression (HER2-positivity) is associated with increased tumour aggressiveness, higher rates of recurrence, and increased mortality (*5–10*). The median age of patients presenting with HER2-positive breast cancer is in the mid-50s, approximately five years younger than the general breast cancer population (*11*).

In the early breast cancer setting, surgery is the main modality of local treatment. Surgery and/or radiotherapy can control loco-regional disease in the majority of patients. Neoadjuvant therapy is given prior to surgery and has become commonly used in patients with newly diagnosed breast cancer. Neoadjuvant therapy is the primary modality of therapy for patients with inflammatory breast cancer, regardless of tumour size (*12*). If standard neoadjuvant chemotherapy has been completed, usually there is no need for additional postoperative chemotherapy.

Data from four Phase III trials has shown that the use of trastuzumab, for the adjuvant treatment of HER2-positive breast cancer reduces the relative risk of relapse by about 50% and the risk of death by about 30% (*13–15*). In these studies, trastuzumab was administered either sequentially or concurrently with

standard chemotherapy regimens consisting of anthracyclines and/or taxanes. However, despite the marked improvements conferred by adjuvant trastuzumab in these studies, a significant percentage of HER2-positive breast cancer patients still relapsed and ultimately died from metastatic disease (*16*).

**Summary of evidence: benefits** (from the application)

**Metastatic or locally recurrent, unresectable breast cancer**

The Phase III CLEOPATRA study was a randomized, multicentre, double-blind, placebo-controlled clinical trial that evaluated the efficacy of pertuzumab in 808 patients with HER2-positive, metastatic or locally recurrent, unresectable breast cancer who had not received previous anti-HER2 therapy or chemotherapy for metastatic disease (*17–19*). The primary efficacy endpoint was progression-free survival (PFS) assessed by an independent review facility (IRF). Key secondary efficacy endpoints included overall survival (OS) and quality of life (QoL) assessed through the Functional Assessment of Cancer Therapy–Breast (FCT–B) quality-of-life questionnaire. Patients were randomized to receive pertuzumab plus trastuzumab plus docetaxel (Ptz + T + D) or placebo plus trastuzumab plus docetaxel (Pla + T + D).

The CLEOPATRA study found a statistically significant and clinically relevant improvement in IRF-assessed PFS in the pertuzumab arm compared with the placebo arm (HR 0.62, 95%CI 0.51 to 0.75; $p<0.001$), with an increase of 6.1 months in median PFS (12.4 months in the placebo arm vs 18.5 months in the pertuzumab arm). The advantage in PFS appeared soon after the treatment is started (9 weeks), and was maintained from this point onwards. Benefit was observed in all pre-specified sub-groups tested.

At the data cut-off date for final OS analysis (February 2014) the results demonstrated a statistically significant improvement in survival with Ptz + T + D compared with Pla + T + D. Median OS was prolonged in the Ptz + T + D arm compared with the Pla + T + D arm (56.5 months vs 40.8 months; HR 0.68, 95%CI 0.56 to 0.84, $p<0.001$) (*19*). Sensitivity analyses defined to explore the impact of crossover on the OS result confirmed the robustness of the results in the intention-to-treat (ITT) population. Sub-group analyses of final OS were consistent with the analysis in the whole ITT population and confirmed results from previous analyses.

At the time of data cut-off, according to the investigator-assessed ITT-analysis of PFS, events had occurred in 78.8% of patients in the Pla + T + D arm and 70.6% of patients in the Ptz + T + D arm (*19*). The treatment benefit of Ptz + T + D compared with Pla + T + D was maintained in the updated analysis of investigator-assessed PFS (HR 0.68, 95%CI 0.58 to 0.80). The median PFS durations of 12.4 months in the placebo arm and 18.7 months in the pertuzumab arm were consistent with results from the previous analyses. Exploratory sub-

group analyses of investigator-assessed PFS indicated a treatment benefit with Ptz + T + D over Pla + T + D in all sub-groups analysed, and were consistent with the result in the whole ITT population, and with results from previous analyses.

In patients treated with pertuzumab–trastuzumab-based combinations, 239 of 402 (59.5%) patients in the pertuzumab arm and 229 of 404 (56.7%) patients in the placebo arm experienced a decrease from baseline of ≥5 points in a subset of the FACT-B questionnaire. Kaplan–Meier analysis showed a similar time decline of health-related QoL (HRQoL) between the two treatment arms (HR 0.97; 95%CI 0.81 to 1.16), showing that the combination of pertuzumab and trastuzumab with docetaxel had no major adverse impact on HRQoL (*20*).

#### Neoadjuvant treatment of locally advanced, inflammatory, or early stage breast cancer

The Phase II NeoSphere study was a multicentre, randomized, open-label study that evaluated the efficacy of pertuzumab as neoadjuvant treatment in 417 patients with HER2-positive locally advanced, inflammatory, or early stage breast cancer (*21*, *22*). Patients were randomized to receive trastuzumab plus docetaxel (T + D), pertuzumab plus trastuzumab plus docetaxel (Ptz + T + D), pertuzumab plus trastuzumab (Ptz + T), or pertuzumab plus docetaxel (Ptz + D).

The primary efficacy endpoint was rate of breast pathologic complete response (bpCR), defined as the proportion of patients with an absence of invasive neoplastic cells in the breast following primary systemic therapy (*in situ* disease might remain; nodal status not considered), also known as ypT0/is. Secondary efficacy endpoints included clinical PFS.

Efficacy results for the primary endpoint (9 March 2012 clinical cut-off date) showed a statistically significant and clinically meaningful improvement in bpCR rate in patients receiving Ptz + T + D compared with patients receiving T + D as neoadjuvant therapy (45.8% vs 29.0%). A consistent pattern of results was observed regardless of pathological complete response (pCR) definition, with a higher pCR (ypT0/is N0) rate also reported in patients receiving Ptz + T + D compared with T + D (39.3% vs 21.5%). bpCR rates were lower in the sub-group of patients with hormone receptor-positive disease (ranging from 5.9% to 26.0% among the four arms) than in the sub-group with hormone receptor-negative disease (ranging from 27.3% to 63.2%), but the difference in pCR still favoured Ptz + T + D compared with T + D (*21*).

Point estimates of PFS (defined as the time from the date of randomization to the first documentation of progressive disease or death) and DFS from the five-year analysis were consistent with the benefit shown from the addition of pertuzumab to trastuzumab plus docetaxel in the primary analysis of pCR (regardless of the definition of pCR used) but confidence intervals were wide and included the null value. Hazard ratios for PFS and DFS were 0.69 (95%CI 0.34 to 1.40) and 0.60 (95%CI 0.28 to 1.27), respectively, indicating a lower risk of PFS and DFS events in the Ptz + T + D arm compared with the T + D arm (*22*).

The efficacy of pertuzumab as neoadjuvant treatment was also assessed in the TRYPHAENA study, a multicentre, randomized, open-label Phase II study conducted in 225 patients with HER2-positive locally advanced, inflammatory, or early stage breast cancer (*23*, *24*).

The primary endpoint was cardiac safety during the neoadjuvant treatment period. The key efficacy endpoint was pCR rate (ypT0/is). Additional efficacy endpoints included DFS, PFS and OS. Patients were randomized to receive one of three neoadjuvant regimens:

- Three cycles of pertuzumab plus trastuzumab plus 5-fluorouracil, epirubicin and cyclophosphamide (FEC) followed by three cycles of pertuzumab plus trastuzumab plus docetaxel (Ptz + T + FEC/Ptz + T + D).
- Three cycles of FEC followed by three cycles of pertuzumab plus trastuzumab plus docetaxel (FEC/Ptz + T + D).
- Six cycles of carboplatin plus pertuzumab plus trastuzumab plus docetaxel (C + Ptz + T + D). Randomization was stratified by breast cancer type (operable, locally advanced, or inflammatory) and hormone receptor status.

High pCR rates were observed in all three treatment arms. A consistent pattern of results was observed regardless of pCR definition. pCR rates were lower in the sub-group of patients with hormone receptor-positive disease (ranging from 46.2% to 50.0% in the three arms) than in patients with hormone receptor-negative disease (ranging from 65.0% to 83.8%).

Long-term analyses of DFS and OS were conducted when median follow up exceeded 60 months in all trial arms. DFS at 3 years was 87% (95%CI 79 to 95) in patients treated with Ptz + T + FEC/Ptz + T + D, 88% (95%CI 80 to 96) in patients treated with FEC/Ptz + T + D, and 90% (95%CI 82 to 97) in patients treated with C + Ptz + T + D (3-year DFS was 89% (95%CI 81 to 96) in the first group, 89% (95%CI 81 to 96) in the second group and 87% (95%CI 80 to 95) in the third group). Three-year OS followed a similar pattern: 94% (95%CI 89 to100) in the first group, 94% (95%CI 89 to 100) in the second group and 93% (95%CI 87 to 99) in the third group.

#### Adjuvant Treatment of early breast cancer with a high risk of recurrence

The Phase III APHINITY study was a randomized multicentre, double-blind, placebo-controlled trial that evaluated the safety and efficacy of pertuzumab plus trastuzumab plus chemotherapy compared with placebo plus trastuzumab plus chemotherapy in 4805 patients with operable, HER2-positive primary breast cancer (*25*).

The primary efficacy endpoint was invasive disease-free survival (IDFS), defined as time from randomization to ipsilateral invasive breast cancer

recurrence, contralateral invasive breast cancer, distant recurrence, or death due to any cause. Other efficacy endpoints were DFS and OS.

At the clinical cut-off date, IDFS events had occurred in 171 patients (7.1%) in the pertuzumab-containing arm compared with 210 patients (8.7%) in the comparator arm. Treatment with pertuzumab-containing therapy resulted in a borderline significant improvement in IDFS, corresponding to a 19% relative reduction in the risk of relapse or death (HR 0.81, 95%CI 0.66 to 1.00). Estimates of IDFS event-free rates were 94.1% vs 93.2% at three years and 92.3% vs 90.6% at four years in the pertuzumab and comparator arms, respectively. The addition of pertuzumab to trastuzumab and chemotherapy reduced the rate of distant recurrences as first site of recurrence (4.7% vs 5.8%) and at any time in the study 5.0% vs 6.0%).

Interim OS results numerically favoured patients in the pertuzumab arm, but with only 26% of the events required for the final planned OS analysis, the data were immature at the primary data cut-off. There was no significant treatment effect with regard to mortality between treatment arms at this first interim overall survival analysis (HR 0.89, 95%CI 0.66 to 1.21).

Sub-group analysis across multiple, pre-specified, clinically relevant sub-groups showed that the IDFS improvements were seen for patients in the pertuzumab arm in the sub-group with node-positive disease. Improved IDFS was observed irrespective of the hormone receptor status, but the benefit of adding pertuzumab to trastuzumab and chemotherapy was more marked in patients with hormone receptor-negative disease (HR 0.76, 95%CI 0.56 to 1.04) than for patients with hormone receptor-positive disease (HR 0.86, 95%CI 0.66 to 1.13), indicating a 24% and 14% reduction in the risk of recurrence or death, respectively.

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**Summary of evidence: harms** (from the application)

Overall, data indicate that pertuzumab is well tolerated as monotherapy and that it can be given in combination with trastuzumab and a range of other therapeutic agents with manageable additional toxicity. No unexpected toxicities were encountered other than those that are known for agents that target the HER family of receptors. Serious or severe infusion-related symptoms have been rarely observed in patients receiving pertuzumab. A low level of cardiac toxicities, predominantly asymptomatic declines in left ventricular ejection fraction (LVEF), has been reported. In the pivotal Phase III CLEOPATRA trial, the rates of symptomatic and asymptomatic left ventricular systolic dysfunction were not higher in patients receiving Ptz + T + D than in those receiving Pla + T + D (*17*). However, patients who have received prior anthracyclines or radiotherapy to the chest area may be at higher risk of decreased LVEF.

There is a limited amount of data from the use of pertuzumab in pregnant women. Studies in animals have shown reproductive toxicity and pertuzumab is

not recommended during pregnancy and in women of childbearing potential not using contraception (*26*).

#### Metastatic breast cancer

In the Phase III CLEOPATRA trial in patients with HER2-positive metastatic breast cancer (N = 808), the safety profile of Ptz + T + D at the time of the latest clinical cut-off (11 February 2014) was generally similar to that of Pla + T + D (*17*, *19*). The most common adverse event (AE) in both arms combined was alopecia (an AE associated with docetaxel), followed by diarrhoea, neutropenia, nausea, fatigue and rash. The safety profile of pertuzumab plus trastuzumab and docetaxel in patients who crossed over (after initially being treated with placebo plus trastuzumab and docetaxel) was consistent with the safety profile observed in patients treated with pertuzumab plus trastuzumab and docetaxel from the beginning of the study. The majority of AEs following crossover from placebo to pertuzumab were Grade 1–2.

The ongoing Phase II PERTAIN study investigated the efficacy and safety of first-line trastuzumab plus an aromatase inhibitor (AI), with or without pertuzumab in patients with HER2 positive and hormone receptor positive metastatic or locally advanced breast cancer (*27*). All-grade AEs occurred in 96.1% of patients taking pertuzumab + trastuzumab + AI and in 98.4% of patients taking trastuzumab + AI. The incidence of Grade ≥3 AEs was higher in the pertuzumab treatment arm (50.4% vs 38.7%). The most common Grade ≥3 events reported (occurring in ≥5% of patients in either treatment arm) were hypertension, diarrhoea and neutropenia.

The Phase III PHEREXA study assessed the efficacy and safety of trastuzumab plus capecitabine, with or without pertuzumab in patients with HER2 positive metastatic breast cancer with disease progression despite trastuzumab-based therapy and prior taxane (*28*). The safety profile of the pertuzumab-containing regimen was consistent with previous pertuzumab studies and no new safety signals were observed. Almost all patients experienced an AE. The most common AEs were diarrhoea, palmar-plantar erythrodysesthesia (PPE) syndrome and nausea. The incidence of diarrhoea was higher in those patients who received pertuzumab. The incidence of Grade ≥3 AEs was lower in those patients who received pertuzumab. The incidence of serious adverse events (SAEs) was similar in the two treatment arms. The incidence of cardiac disorders, particularly LVD, was higher in patients who received pertuzumab (3.2% vs 7.5%). There was a total of 213 deaths, the majority of which were due to disease progression. Of these 213 deaths, 98 occurred in the pertuzumab arm.

#### Early breast cancer

In the Phase II NeoSphere study (*21*), the most frequently occurring AEs during neoadjuvant treatment were alopecia, neutropenia, diarrhoea, nausea, fatigue,

rash and mucosal inflammation. The overall safety profile of Ptz + T + D (Arm B) was comparable to that of T + D (Arm A). The tolerability of pertuzumab plus docetaxel (Arm D) was also broadly comparable to that of Arm B. Patients receiving trastuzumab and pertuzumab only (Arm C) reported fewer AEs across most body systems compared to patients who also received chemotherapy. At the final clinical cut-off date, the safety profile observed was consistent with what has been previously reported for the neoadjuvant, adjuvant and post-treatment follow-up periods, indicating that the combination of trastuzumab, pertuzumab and docetaxel was generally well tolerated. In addition, no late safety concerns (including delayed cardiac toxicity) have emerged.

In the Phase II TRYPHAENA study (*23*), the most common AEs were diarrhoea, alopecia, nausea, neutropenia, vomiting, fatigue, anaemia, dyspepsia and thrombocytopenia. The safety profile observed was consistent with what has been previously reported for the neoadjuvant, adjuvant and post-treatment follow-up periods, indicating that these combinations, whether given sequentially after or concomitantly with anthracycline-based or concomitantly with carboplatin-based treatment were generally well tolerated. In addition, there were no unexpected findings regarding cardiac safety.

In the ongoing Phase III APHINITY study (*25*), the most common AEs (≥30% in either treatment arm) were diarrhoea, nausea, alopecia, fatigue, vomiting, arthralgia, and constipation. The incidence of most of the common AEs was similar between treatment arms except for diarrhoea, nausea and fatigue, which were higher in the Ptz + T + chemotherapy arm, and arthralgia, which was higher in the Pla + T + chemotherapy arm. The incidence of Grade ≥3 AEs during the overall study treatment period was higher in the Ptz + T + chemotherapy arm than in the Pla + T + chemotherapy arm (64.2% patients in the Ptz + T + chemotherapy arm and 57.3% patients in the Pla + T + chemotherapy arm). The proportion of patients who experienced at least one AE that led to the withdrawal of pertuzumab or placebo was similar in the two treatment arms. The cardiac event rates were low in both treatment arms.

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**Additional evidence** (not in the application)

The Phase III MARIANNE randomized controlled trial studied untreated HER2 positive metastatic breast cancer patients receiving T-DM1 plus pertuzumab, T-DM1 plus placebo, or a combination of trastuzumab with a taxane (paclitaxel or docetaxel) (*29*, *30*). Approximately 30% of trial participants had been treated with trastuzumab in the adjuvant/neoadjuvant setting. The final MARIANNE results showed similar overall survival in the three treatment arms, with all regimens resulting in median OS greater than 50 months. Notably, in MARIANNE, the median OS of patients treated with trastuzumab and a taxane (50.9 months) was longer than that reported in the CLEOPATRA trial for trastuzumab plus docetaxel (40.8 months) and closer to the median OS of 56.5

months reported in CLEOPATRA for trastuzumab, docetaxel, and pertuzumab. Results from MARIANNE demonstrate the central role of trastuzumab, an anti-HER 2 medicine included into the WHO Model List, in the management of HER2-positive metastatic breast cancer, where median survival times longer than four years can be achieved.

Technology appraisal guidance documents released by National Institute for Health and Care Excellence on pertuzumab in early and metastatic breast cancer noted considerable uncertainty on incremental cost-effectiveness ratio (ICER) for pertuzumab as compared to control, given uncertainty on long treatment benefit associated with the medicine (*31*, *32*). In the United Kingdom, pertuzumab is priced at £ 2395 per 420 mg vial (excluding value-added tax; price referring to 2018). The company has a commercial arrangement that makes pertuzumab available to the National Health Service with a discount. The size of the discount is commercial in confidence.

**WHO Guidelines**

None available.

**Costs/cost-effectiveness**

**Metastatic breast cancer**

The application did not provide data in the context of metastatic breast cancer.

**Early breast cancer**

The application reported on a budget impact model developed by F. Hoffmann-La Roche assessing the cost impact of pertuzumab on further lines of treatment based on the reduction of metastatic events compared to trastuzumab + docetaxel. Long-term cost savings associated with event-free survival were estimated on a five-year time horizon. Cost and epidemiological data were derived from the Italian context but were not provided in the application. 1300 HER2-positive early breast cancer patients were considered eligible for neoadjuvant treatment with pertuzumab in the first year after launch. Average cost savings per year per patient for subsequent lines of treatment in Italy could go up to € 2800 three years after launch. In the third year after launch, the costs savings in later lines of treatment are estimated to be € 3.6 million resulting in accumulated costs of € 6.2 million within the first three years (*33*).

Cost-effectiveness analyses based on the Canadian setting, and the NeoSphere and TRYPHAENA trials, suggested that the addition of pertuzumab resulted in increased life-years and quality-adjusted life-years (QALYs). The incremental cost per QALY ranged from US$ 25 388 (CAD; NeoSphere analysis) to US$ 46 196 (TRYPHAENA analysis). Sensitivity analyses resulted in cost-effectiveness ratios ranging from US$ 9230 to US$ 64 421 (*34*).

The application reported on the results of an additional cost-effectiveness analysis based on costs derived from the Italian context. Few details were provided. The study concluded that the addition of pertuzumab in adjuvant therapy induces a cost increase ranging between € 23 000 and € 28 000 per patient for a gain of 0.45 to 1.00 QALY (*35*).

**Availability**

As of 7 June 2018, pertuzumab has been approved in more than 100 countries worldwide.

**Other considerations**

Based on results of the CLEOPATRA study (*17*, *19*, *20*), pertuzumab received a score of 4 on the ESMO-MCBS v1.1 for use in the first-line metastatic treatment setting (*36*).

Based on results of the NeoSphere study (*21*, *22*), pertuzumab received a score of C on the ESMO-MCBS v1.1 for use in the neoadjuvant setting in early breast cancer (*36*).

Based on results of the APHINITY study (*25*), pertuzumab received a score of 4 on the ESMO-MCBS v1.1 for use in the adjuvant setting in early breast cancer (*36*).

**Committee recommendations**

The Committee endorsed the recommendations of the EML Cancer Medicine Working Group with regard to the proposed threshold of four to six months of overall survival benefit as a guiding principle for prioritizing cancer medicines for inclusion on the EML, and applied this principle to the consideration of pertuzumab.

The Committee acknowledged that pertuzumab was associated with a relevant survival benefit, well beyond the established threshold, as first-line treatment of metastatic breast cancer, based on the results reported in the CLEOPATRA trial. However, the Committee expressed reservations about the generalizability of CLEOPATRA results in metastatic breast cancer and consistency of the clinical effectiveness of pertuzumab among studies both in early and metastatic breast cancer. These reservations are expanded below.

The Committee noted that only approximately 10% of patients in CLEOPATRA had received trastuzumab in the adjuvant or neoadjuvant setting. The Committee was concerned that the observed survival gains may not therefore be generalizable to patients with metastatic disease who have received prior adjuvant or neoadjuvant trastuzumab, making the magnitude of benefit in this population sub-group uncertain. The Committee also noted the results reported in the MARIANNE trial, where pertuzumab in combination with

T-DM1 was not shown to have greater clinical benefit compared to trastuzumab plus chemotherapy or T-DM1 alone. The Committee was unable to reconcile the differences in the outcomes reported in the MARIANNE and CLEOPATRA trials.

The Committee also noted that the relevant survival gains observed in CLEOPATRA for metastatic breast cancer were not replicated in trials of pertuzumab in early stage breast cancer. The Committee accepted that trial results suggest pertuzumab offers a small incremental overall and disease-free survival benefit compared to placebo, based on an analysis at around three years median follow-up. The Committee considered that continued follow up was important to assess long-term overall survival, but thought it unlikely that the magnitude of benefit would be greater with longer follow-up, given that anti-HER2 treatments are typically associated with a reduction in early recurrences, followed by a plateau effect.

The Committee therefore did not recommend the addition of pertuzumab to the complementary list of the Model List for the treatment of early stage and metastatic HER2 positive breast cancer. The Committee considered that the available evidence did not demonstrate a clinically meaningful survival benefit in early stage disease, and that there was important uncertainty surrounding the estimated magnitude of survival benefit in metastatic disease, with results seen in CLEOPATRA not replicated in other trials.

It was Committee's view that questions associated with differences in results from the CLEOPATRA and MARIANNE trials should be resolved by integration of the raw, individual patient trial data and independent re-analysis following a set of pre-planned hypotheses. The Committee recommended that WHO considers requesting access to the raw clinical trial data from CLEOPATRA and MARIANNE from the applicant, for an independent re-analysis arranged by WHO, and present the report of any such independent re-analysis to the 2021 Expert Committee for consideration.

## References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
2. Shulman LN, Willett W, Sievers A, Knaul FM. Breast cancer in developing countries: opportunities for improved survival. J Oncol. 2010;2010:595167.
3. Sundaresan S, Penuel E, Sliwkowski MX. The biology of human epidermal growth factor receptor 2. Curr Oncol Rep. 1999;1(1):16–22.
4. Wolff AC, Hammond ME, Schwartz JN, Hagerty KL, Allred DC, Cote RJ et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol. 2007;25(1):118–45.

5. Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM, Hortobagyi GN. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. Oncologist. 2009;14(4):320–68.
6. Borg A, Tandon AK, Sigurdsson H, Clark GM, Ferno M, Fuqua SA et al. HER-2/neu amplification predicts poor survival in node-positive breast cancer. Cancer Res. 1990;50(14):4332–7.
7. Ross JS, Fletcher JA. The HER-2/neu oncogene in breast cancer: prognostic factor, predictive factor, and target for therapy. Stem Cells. 1998;16(6):413–28.
8. Menard S, Fortis S, Castiglioni F, Agresti R, Balsari A. HER2 as a prognostic factor in breast cancer. Oncology. 2001;61 Suppl 2:67–72.
9. Brown M, Tsodikov A, Bauer KR, Parise CA, Caggiano V. The role of human epidermal growth factor receptor 2 in the survival of women with estrogen and progesterone receptor-negative, invasive breast cancer: the California Cancer Registry, 1999-2004. Cancer. 2008;112(4):737–47.
10. Curigliano G, Viale G, Bagnardi V, Fumagalli L, Locatelli M, Rotmensz N et al. Clinical relevance of HER2 overexpression/amplification in patients with small tumor size and node-negative breast cancer. J Clin Oncol. 2009;27(34):5693–9.
11. Neven P, Van Calster B, Van den Bempt I, Van Huffel S, Van Belle V, Hendrickx W et al. Age interacts with the expression of steroid and HER-2 receptors in operable invasive breast cancer. Breast Cancer Res Treat. 2008;110(1):153–9.
12. Dawood S, Merajver SD, Viens P, Vermeulen PB, Swain SM, Buchholz TA et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol. 2011;22(3):515–23.
13. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005;353(16):1659–72.
14. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE, Jr., Davidson NE et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005;353(16): 1673–84.
15. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011;365(14):1273–83.
16. Arteaga CL, Sliwkowski MX, Osborne CK, Perez EA, Puglisi F, Gianni L. Treatment of HER2-positive breast cancer: current status and future perspectives. Nat Rev Clin Oncol. 2011;9(1):16–32.
17. Baselga J, Cortes J, Kim SB, Im SA, Hegg R, Im YH, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2012;366(2):109-19.
18. Swain SM, Kim SB, Cortes J, Ro J, Semiglazov V, Campone M et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol. 2013;14(6):461–71.
19. Swain SM, Baselga J, Kim SB, Ro J, Semiglazov V, Campone M et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med. 2015;372(8):724–34.
20. Cortes J, Baselga J, Im YH, Im SA, Pivot X, Ross G et al. Health-related quality-of-life assessment in CLEOPATRA, a phase III study combining pertuzumab with trastuzumab and docetaxel in metastatic breast cancer. Ann Oncol. 2013;24(10):2630–5.
21. Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012;13(1):25–32.

22. Gianni L, Pienkowski T, Im YH, Tseng LM, Liu MC, Lluch A et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. Lancet Oncol. 2016;17(6):791–800.

23. Schneeweiss A, Chia S, Hickish T, Harvey V, Eniu A, Hegg R et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol. 2013;24(9):2278–84.

24. Schneeweiss A, Chia S, Hickish T, Harvey V, Eniu A, Waldron-Lynch M et al. Long-term efficacy analysis of the randomised, phase II TRYPHAENA cardiac safety study: Evaluating pertuzumab and trastuzumab plus standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer. Eur J Cancer. 2018;89:27–35.

25. von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med. 2017;377(2): 122–31.

26. Pejeta: EPAR - Product Information. Annex 1 Summary of product characteristics (Perjeta - EMEA/H/C/002547 - PSUSA/00010125/201806). Amsterdam: European Medicines Agency; 2019.

27. Rimawi M, Ferrero JM, de la Haba-Rodriguez J, Poole C, De Placido S, Osborne CK et al. First-Line Trastuzumab Plus an Aromatase Inhibitor, With or Without Pertuzumab, in Human Epidermal Growth Factor Receptor 2-Positive and Hormone Receptor-Positive Metastatic or Locally Advanced Breast Cancer (PERTAIN): A Randomized, Open-Label Phase II Trial. J Clin Oncol. 2018;36(28):2826–35.

28. Urruticoechea A, Rizwanullah M, Im SA, Ruiz ACS, Lang I, Tomasello G et al. Randomized Phase III Trial of Trastuzumab Plus Capecitabine With or Without Pertuzumab in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer Who Experienced Disease Progression During or After Trastuzumab-Based Therapy. J Clin Oncol. 2017;35(26):3030–8.

29. Ellis PA, Barrios CH, Eiermann W, Toi M, Im YH, Conte PF et al. Phase III, randomized study of trastuzumab emtansine (T-DM1) ± pertuzumab (P) vs trastuzumab + taxane (HT) for first-line treatment of HER2-positive MBC: Primary results from the MARIANNE study. 2015 ASCO Annual Meeting - Abstract 507 J Clin Oncol (Meeting Abstracts). 2015;33(Suppl).

30. Perez EA, Barrios C, Eiermann W, Toi M, Im YH, Conte P et al. Trastuzumab Emtansine With or Without Pertuzumab Versus Trastuzumab Plus Taxane for Human Epidermal Growth Factor Receptor 2-Positive, Advanced Breast Cancer: Primary Results From the Phase III MARIANNE Study. J Clin Oncol. 2017;35(2):141–8.

31. Pertuzumab for adjuvant treatment of HER2-positive early stage breast cancer (TA569). London: National Institute for Health and Care Excellence (NICE); 2019. Available from https://www.nice.org.uk/guidance/ta569, accessed 30 October 2019.

32. Pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer (TA509). London: National Institute for Health and Care Excellence (NICE); 2018. Available from https://www.nice.org.uk/guidance/ta509, accessed 30 October 2019.

33. Schleich W, Tournier C, Campagnoli E, Era S. 1225 Potential long-term cost savings due to significant clinical benefit of pertuzumab in combination with trastuzumab for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory or early stage breast cancer. Eur J Cancer. 2015;51:S180–S1.

34. Attard CL, Pepper AN, Brown ST, Thompson MF, Thuresson PO, Yunger S et al. Cost-effectiveness analysis of neoadjuvant pertuzumab and trastuzumab therapy for locally advanced, inflammatory, or early HER2-positive breast cancer in Canada. J Med Econ. 2015;18(3):173–88.

35. Pradelli L, Zaniolo O, Caputo A, Roussel M, Tournier C. PCN181 - Cost-utility analysis of adjuvant pertuzumab-based regimen in women with HER2-positive breast cancer in Italy. Value Health. 2018;21:S45.

36. ESMO-Magnitude of Clinical Benefit Scale. The ESMO-MCBS Score Card [website]. Lugano: European Society for Medical Oncology. (https://www.esmo.org/score/cards, accessed 29 September 2019).

*Rituximab – new formulation – EML*

**Rituximab** **ATC Code: L01XC02**

**Proposal**

The application requested the addition of new subcutaneous (SC) injection formulations of rituximab to the complementary list of the EML for use in the treatment of diffuse large B-cell lymphoma, chronic lymphocytic leukaemia and follicular lymphoma.

**Applicant**

F. Hoffmann-La Roche Ltd

**WHO Technical Department**

Comments on the application were received from the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it did not support the inclusion of SC rituximab at this time, suggesting that the addition of this formulation could be considered as evidence emerges regarding real-world evidence of SC formulations providing reduced costs of care for the health workforce and/or facilities.

**EML/EMLc**

EML

**Section**

8.2.2 Targeted therapies

**Dose form(s) & strengths(s)**

Injection (subcutaneous) 1400 mg/11.7 mL in 15 mL vial

- *Diffuse large B-cell lymphoma*
- *Follicular lymphoma*

Injection (sub-cutaneous) 1600 mg/13.4 mL in 20 mL vial (CLL)

- *Chronic lymphocytic leukaemia*

**Core/Complementary**

Complementary

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Rituximab intravenous (IV) injection was added to the complementary list of the EML in 2015 for treatment of diffuse large B-cell lymphoma, follicular lymphoma and chronic lymphocytic leukaemia (*1*).

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**Public health relevance** (burden of disease)

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL), accounting for more than 30% of lymphoma incidence (*2*). The crude incidence of DLBCL in Europe has been reported as 3.8/100 000/year, increasing with age (*2*).

Follicular lymphoma is the second most frequent sub-type, accounting for approximately 20% of the overall NHL incidence (*3*, *4*). Follicular lymphoma (FL) occurs most commonly in middle-aged patients and the elderly, with a median age at diagnosis of approximately 60 years (*5*, *6*).

Chronic lymphocytic leukaemia (CLL) is the most common form of adult leukaemia in Western Europe, accounting for 25%–40% of all leukaemias (*7*–*9*) with approximately 2–6 new cases in every 100 000 individuals per year (*8*, *10*). CLL is more prevalent in the elderly, with an estimated median age at first diagnosis of approximately 70 years (*11*) and with a male to female ratio of approximately 2:1 (*9*).

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**Summary of evidence: benefits** (from the application)

Evidence for the clinical effectiveness of rituximab was evaluated at the time of listing in 2015.

The SABRINA trial investigated non-inferiority of the pharmacokinetic profile, efficacy and safety of SC rituximab (in combination with chemotherapy) with IV rituximab (in combination with chemotherapy) in patients with previously untreated FL (*12*). Results showed that rituximab SC 1400 mg provides non-inferior pharmacokinetics (PK) ($C_{trough}$/AUC), as well as comparable efficacy and safety to rituximab IV. The point estimate for complete response (CR or unconfirmed complete response (CRu)) was numerically higher in the IV arm compared with the SC 1400 mg arm (34.8%, 95%CI 26.9 to 43.2 vs 28.2%, 95%CI 20.9 to 36.3). A higher proportion of patients in the IV arm (85.1%, 95%CI 78.1 to 90.5) achieved an overall response (CR, CRu and partial response (PR)) compared with patients in the SC 1400 mg arm (80.3%, 95%CI 72.8 to 86.5), whereas the rate of partial response was similar between the two arms (50.4%, 95%CI 41.8 to 58.9 vs 52.1%, 95%CI 43.6 to 60.6) (*13*, *14*).

The SAWYER trial investigated non-inferiority of the PK profile, efficacy and safety of 1600 mg SC rituximab (in combination with chemotherapy) with IV rituximab (in combination with chemotherapy) in patients with previously untreated chronic lymphocytic leukaemia (*15*). Response rates were similar for the IV and SC arms, with an overall response rate of 80.7% (95%CI 70.9 to 88.3)

and 85.2% (95%CI 76.1 to 91.9) in the IV and SC arms, respectively. Complete response rate point estimates were 33.0% (95%CI 23.3 to 43.8) and 26.1% (95%CI 17.3 to 36.6) in the IV and SC arms, respectively. Overall the results confirmed that rituximab SC 1600 mg has a comparable benefit/risk profile to that of rituximab IV 500 mg/m².

**Summary of evidence: harms** (from the application)

Evidence for the safety of rituximab was evaluated at the time of listing in 2015.

The safety profile of rituximab SC formulation was reported to be comparable to that of the intravenous formulation, with the exception of local injection site reactions. Administration-related reactions were very common in patients receiving the SC rituximab formulation in the SparkTera (*16*) and SABRINA (*12*) trials, reported in up to 50% of patients at some time during treatment. Symptoms included pain, swelling, induration, haemorrhage, erythema, pruritis and rash. The majority of the reactions following SC administration were reported as mild or moderate.

**Additional evidence (not in the application)**

N/A

**WHO Guidelines**

None available.

**Costs/cost-effectiveness**

No information was provided in the application regarding comparative drug costs of the SC and IV rituximab formulations, including biosimilars.

The application stated that IV administration takes approximately three to four hours, which can incur high costs on patients, health care professionals and the health care system. The SC formulation can be administered via hand-held syringe in less than ten minutes plus follow-up time and thus has the potential to realize considerable cost savings. A time and motion study of SC versus IV rituximab found time savings for patients and health care professionals associated with SC administration of rituximab compared to IV administration (*17*).

The Committee considered that whether time savings would be realized to the full extent found in the study was uncertain, given that rituximab is administered with other intravenous chemotherapy.

**Availability**

Rituximab SC 1400 mg has regulatory approval and market availability in more than 60 countries globally. The 1600 mg strength is approved and available in around 20 countries.

### Other considerations

The Committee noted the correspondence from the European Society for Medical Oncology (ESMO) requesting recognition of biosimilars of rituximab and trastuzumab on the EML. The Committee agreed that quality-assured biosimilars of these monoclonal antibodies represent an opportunity for expanding affordable access to cancer medicines for health systems.

### Committee recommendations

The Committee did not recommend the addition of new subcutaneous injection formulations of rituximab to the complementary list of the EML for use in the treatment of diffuse large B-cell lymphoma, chronic lymphocytic leukaemia and follicular lymphoma.

The Committee acknowledged the potential benefits of the subcutaneous formulation over the listed intravenous formulation. However, with the availability of biosimilar versions of intravenous rituximab, the Committee was concerned that listing of the subcutaneous formulation, for which biosimilars are not yet available, could limit competition and therefore limit access for patients.

To help improve access, the Committee recommended the current listing for intravenous rituximab on the EML should indicate that quality-assured biosimilars of rituximab should also be considered as essential medicines. In addition, the Expert Committee recommended that WHO continue to facilitate access to biosimilars through the Prequalification programme and WHO Collaborative Registration Procedure.

## References

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of Essential Medicines and the 5rd WHO Model List of Essential Medicines for Children) (WHO Technical Report Series, No. 994). Geneva: World Health Organization; 2015. Available from https://apps.who.int/iris/bitstream/handle/10665/189763/9789241209946_eng.pdf, accessed 30 October 2019.
2. Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 Suppl 5:v116–25.
3. Zinzani PL. Lymphoma: diagnosis, staging, natural history, and treatment strategies. Semin Oncol. 2005;32(1 Suppl 1):S4–10.
4. Winter JN, Gascoyne RD, Van Besien K. Low-grade lymphoma. Hematology Am Soc Hematol Educ Program. 2004:203–20.
5. Rohatiner AZ, Lister TA. The clinical course of follicular lymphoma. Best Pract Res Clin Haematol. 2005;18(1):1–10.
6. Vitolo U, Ferreri AJ, Montoto S. Follicular lymphomas. Crit Rev Oncol Hematol. 2008;66(3):248–61.
7. Watson L, Wyld P, Catovsky D. Disease burden of chronic lymphocytic leukaemia within the European Union. Eur J Haematol. 2008;81(4):253–8.

8. Ghia P, Ferreri AM, Caligaris-Cappio F. Chronic lymphocytic leukemia. Crit Rev Oncol Hematol. 2007;64(3):234–46.
9. Ikram N, Hassan K, Tufail S. Chronic Lymphocytic Leukaemia (CLL) - An Overview. Int J Pathol. 2003;1:48–59.
10. Eichhorst B, Dreyling M, Robak T, Montserrat E, Hallek M. Chronic lymphocytic leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2011;22 Suppl 6:vi50–4.
11. Mulligan SP, Tam CS. Chronic lymphocytic leukemia: diagnosis and clinical staging. In: Keating MJ, Tam CS, editors. Advances in the treatment of B-cell chronic lymphocytic leukemia. London: Future Medicine; 2012. p. 6–15.
12. Davies A, Merli F, Mihaljevic B, Mercadal S, Siritanaratkul N, Solal-Celigny P et al. Efficacy and safety of subcutaneous rituximab versus intravenous rituximab for first-line treatment of follicular lymphoma (SABRINA): a randomised, open-label, phase 3 trial. Lancet Haematol. 2017;4(6):e272–e82.
13. Davies A, Merli F, Mihaljevic B, Siritanaratkul N, Solal-Celigny P, Barrett M et al. Pharmacokinetics and safety of subcutaneous rituximab in follicular lymphoma (SABRINA): stage 1 analysis of a randomised phase 3 study. Lancet Oncol. 2014;15(3):343–52.
14. Davies A, Barrett M, Berge C. Primary Clinical Study Report – Protocol BO22334 – A two-stage phase III, international, multi-center, randomized, controlled, open-label study to investigate the pharmacokinetics, efficacy and safety of rituximab SC in combination with CHOP or CVP versus rituximab IV in combination with CHOP or CVP in patients with previously untreated follicular lymphoma followed by maintenance treatment with either rituximab SC or rituximab IV – Report No. 1058994. 2014.
15. Assouline S, Buccheri V, Delmer A, Gaidano G, Trneny M, Berthillon N et al. Pharmacokinetics, safety, and efficacy of subcutaneous versus intravenous rituximab plus chemotherapy as treatment for chronic lymphocytic leukaemia (SAWYER): a phase 1b, open-label, randomised controlled non-inferiority trial. Lancet Haematol. 2016;3(3):e128–38.
16. Salar A, Avivi I, Bittner B, Bouabdallah R, Brewster M, Catalani O et al. Comparison of subcutaneous versus intravenous administration of rituximab as maintenance treatment for follicular lymphoma: results from a two-stage, phase IB study. J Clin Oncol. 2014;32(17):1782–91.
17. De Cock E, Kritikou P, Sandoval M, Tao S, Wiesner C, Carella AM et al. Time Savings with Rituximab Subcutaneous Injection versus Rituximab Intravenous Infusion: A Time and Motion Study in Eight Countries. PLoS One. 2016;11(6):e0157957.

*Trastuzumab – new formulation – EML*

**Trastuzumab** **ATC Code: L01XC03**

**Proposal**

The application requested the addition of a subcutaneous injection formulation of trastuzumab to the complementary list of the EML for use in the treatment of early stage and metastatic HER2 positive breast cancer.

**Applicant**

F. Hoffmann-La Roche Ltd

**WHO Technical Department**

Comments on the application were received from the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it did not support the inclusion of SC trastuzumab at this time, suggesting that the addition of this formulation could be considered as evidence emerges regarding real-world use of SC formulations providing reduced costs of care for the health workforce and/or facilities.

**EML/EMLc**

EML

**Section**

8.2.2 Targeted therapies

**Dose form(s) & strengths(s)**

Injection (subcutaneous) 600 mg/5 mL in 5 mL vial

**Core/Complementary**

Complementary

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Trastuzumab powder for intravenous injection was added to the complementary list of the EML in 2015 for treatment of early stage and metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer (*1*).

**Public health relevance** (burden of disease)

Breast cancer is the most common form of malignancy in women (*2*). In 2018, the number of new breast cancer cases was over 2 million, with over 626 000 deaths (*3*).

The HER2 receptor is an important target for the treatment of breast cancer. Amplification and/or overexpression of HER2 occurs in approximately 18% to 22% of breast cancers (*4*, *5*). HER2 amplification/overexpression (HER2-positivity) is associated with increased tumour aggressiveness, higher rates of recurrence, and increased mortality (*5–10*). Approximately 15% to 20% of deaths from breast cancer are likely to be due to HER-positive disease.

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**Summary of evidence: benefits** (from the application)

Evidence for the clinical effectiveness of trastuzumab was evaluated at the time of listing in 2015.

The current application presented the results of the Phase III study BO22227, which was designed to demonstrate non-inferiority of treatment with SC trastuzumab (600 mg every three weeks) and IV trastuzumab (8 mg/kg loading dose, 6 mg/kg maintenance every three weeks) based on co-primary pharmacokinetic and efficacy endpoints, (trastuzumab $C_{trough}$ at pre-dose cycle 8, and pathological complete response (pCR) rate at definitive surgery, respectively) (*11*).

The pharmacokinetic results for the co-primary endpoint, $C_{trough}$ pre-dose cycle 8, showed non-inferiority of trastuzumab SC to trastuzumab IV, with dose adjusted by body weight.

Efficacy results for the co-primary end point of pCR also showed non-inferiority of trastuzumab SC to trastuzumab IV. 595 patients with HER2-positive, operable or locally-advanced breast cancer including inflammatory breast cancer received eight cycles of either trastuzumab IV or trastuzumab SC concurrently with chemotherapy, followed by surgery, and continued therapy with trastuzumab IV or SC as originally randomized for 10 additional cycles, for a total of one year of treatment. pCR rates were 40.7 % (95%CI 34.7 to 46.9) in the trastuzumab IV arm and 45.4 % (95%CI 39.2% to 51.7%) in the trastuzumab SC arm, a difference of 4.7 percentage points in favour of the trastuzumab SC arm. The lower boundary of the one-sided 97.5% confidence interval for the difference in pCR rates was −4.0.

Analyses with longer-term follow-up of a median duration exceeding 40 months and 70 months supported the non-inferior efficacy of the SC formulation with comparable results of both event-free survival (EFS) and overall survival (OS).

**Summary of evidence: harms** (from the application)

Evidence for the safety of trastuzumab was evaluated at the time of listing in 2015.

The current application stated that no new safety signals were reported in in Study MO28048, which investigated the safety and tolerability of trastuzumab SC as adjuvant therapy in HER2 positive early breast cancer (EBC) patients who were enrolled in either a trastuzumab SC vial cohort or a trastuzumab SC administration system cohort (*12*). Treatment of lower body weight patients with trastuzumab SC fixed dose in adjuvant EBC was not associated with increased safety risk, adverse events or serious adverse events, compared to the higher body weight patients (*13*).

The final results of study BO22227 at a median follow up exceeding 70 months were also consistent with the known safety profile for trastuzumab IV and trastuzumab SC, and no new safety signals were observed (*11*).

**Additional evidence** (not in the application)

N/A

**WHO Guidelines**

None available.

**Costs/cost-effectiveness**

No information was provided in the application regarding comparative drug costs of the SC and IV trastuzumab formulations, including biosimilars.

The application stated that IV administrations take approximately one hour, which can incur high costs on patients, health care professionals and the health care system. The SC formulation can be administered over five minutes via a hand-held syringe or a single-use injection device (SID) and thus has the potential to realize considerable cost savings. A time and motion study of SC versus IV trastuzumab found time savings for patients and health care professionals associated with SC administration of trastuzumab compared to IV administration (*14*).

The Committee considered that whether time savings would be realized to the full extent found in the study was uncertain, given that trastuzumab is administered with other intravenous chemotherapy.

**Availability**

The SC formulation of trastuzumab has regulatory approval and market availability in around 100 countries globally.

### Other considerations

The Committee noted the correspondence from the European Society for Medical Oncology (ESMO) requesting recognition of biosimilars of rituximab and trastuzumab on the EML. The Committee agreed that quality-assured biosimilars of these monoclonal antibodies represent an opportunity for expanding affordable access to cancer medicines for health systems.

### Committee recommendations

The Committee did not recommend the addition of new subcutaneous injection formulations of trastuzumab to the complementary list of the EML for use in the treatment of early stage and metastatic HER2 positive breast cancer.

The Committee acknowledged the potential benefits of the sub-cutaneous formulation over the listed intravenous formulation. However, with the availability of biosimilar versions of intravenous trastuzumab, the Committee was concerned that listing of the sub-cutaneous formulation, for which biosimilars are not yet available, could limit competition and therefore limit access for patients.

To help improve access, the Committee recommended the current listing for intravenous trastuzumab on the EML should indicate that quality-assured biosimilars of trastuzumab can also be considered as essential medicines. In addition, the Committee recommended that WHO continue to facilitate access to biosimilars through the Prequalification programme and WHO Collaborative Registration Procedure.

## References

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of Essential Medicines and the 5rd WHO Model List of Essential Medicines for Children) (WHO Technical Report Series, No. 994). Geneva: World Health Organization; 2015. Available from https://apps.who.int/iris/bitstream/handle/10665/189763/9789241209946_eng.pdf, accessed 30 October 2019.
2. Global Cancer Observatory: Cancer Today [website]. Lyon: International Agency for Research on Cancer; 2018. (https://gco.iarc.fr/today, accessed 29 September 2019).
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
4. Wolff AC, Hammond ME, Schwartz JN, Hagerty KL, Allred DC, Cote RJ et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol. 2007;25(1):118–45.
5. Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM, Hortobagyi GN. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. Oncologist. 2009;14(4):320–68.

6. Borg A, Tandon AK, Sigurdsson H, Clark GM, Ferno M, Fuqua SA et al. HER-2/neu amplification predicts poor survival in node-positive breast cancer. Cancer Res. 1990;50(14):4332–7.
7. Ross JS, Fletcher JA. The HER-2/neu oncogene in breast cancer: prognostic factor, predictive factor, and target for therapy. Stem Cells. 1998;16(6):413–28.
8. Menard S, Fortis S, Castiglioni F, Agresti R, Balsari A. HER2 as a prognostic factor in breast cancer. Oncology. 2001;61 Suppl 2:67–72.
9. Brown M, Tsodikov A, Bauer KR, Parise CA, Caggiano V. The role of human epidermal growth factor receptor 2 in the survival of women with estrogen and progesterone receptor-negative, invasive breast cancer: the California Cancer Registry, 1999-2004. Cancer. 2008;112(4):737–47.
10. Curigliano G, Viale G, Bagnardi V, Fumagalli L, Locatelli M, Rotmensz N et al. Clinical relevance of HER2 overexpression/amplification in patients with small tumor size and node-negative breast cancer. J Clin Oncol. 2009;27(34):5693–9.
11. Ismael G, Hegg R, Muehlbauer S, Heinzmann D, Lum B, Kim SB et al. Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I-III breast cancer (HannaH study): a phase 3, open-label, multicentre, randomised trial. Lancet Oncol. 2012;13(9):869–78.
12. Gligorov J, Ataseven B, Verrill M, De Laurentiis M, Jung KH, Azim HA et al. Safety and tolerability of subcutaneous trastuzumab for the adjuvant treatment of human epidermal growth factor receptor 2-positive early breast cancer: SafeHer phase III study's primary analysis of 2573 patients. Eur J Cancer. 2017;82:237–46.
13. Jung KH, Ataseven B, Verrill M, Pivot X, De Laurentiis M, Al-Sakaff N et al. Adjuvant Subcutaneous Trastuzumab for HER2-Positive Early Breast Cancer: Subgroup Analyses of Safety and Active Medical Conditions by Body Weight in the SafeHer Phase III Study. Oncologist. 2018;23(10): 1137–43.
14. De Cock E, Pivot X, Hauser N, Verma S, Kritikou P, Millar D et al. A time and motion study of subcutaneous versus intravenous trastuzumab in patients with HER2-positive early breast cancer. Cancer Med. 2016;5(3):389–97.

*Trastuzumab emtansine – addition – EML*

## Trastuzumab emtansine (T-DM1) ATC Code: L01XC14

**Proposal**

The application requested the addition of trastuzumab emtansine (T-DM1) to the complementary list of the EML for the treatment of unresectable, locally advanced and metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer.

**Applicant**

F. Hoffmann-La Roche Ltd

**WHO Technical Department**

Comments on the application were received from the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it did not support inclusion of trastuzumab emtansine on the EML at this time, though noting recent studies demonstrating its utility as second-line therapy in metastatic and non-metastatic settings. At the current time, given the narrow gain in overall survival and small benefit on disease-control, the technical unit considered that trastuzumab did not currently meet criteria as a priority medicine for breast cancer.

**EML/EMLc**

EML

**Section**

8.2.2 Targeted therapies

**Dose form(s) & strengths(s)**

Powder for injection 100 mg in vial
Powder for injection 160 mg in vial

**Core/Complementary**

Complementary

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Trastuzumab emtansine (T-DM1), as a single agent, is indicated for the treatment of adult patients with human epidermal growth factor receptor 2 (HER2)-positive, unresectable locally advanced or metastatic breast cancer (MBC) who had previously received trastuzumab and a taxane, separately or in combination. Both trastuzumab and taxanes are already included in the WHO Model List.

T-DM1 was considered for inclusion on the EML by the Expert Committee in 2017 and was not recommended. At that time the Committee acknowledged the significant public health burden of breast cancer and noted the availability of other medicines for this condition (e.g. pertuzumab, lapatinib), which have never been proposed for evaluation for inclusion on the EML. The Committee considered that it would have been preferable to consider T-DM1 as part of a comprehensive review encompassing additional medicines, compared with the standard of care, better understanding the additional value and implications of adding them to national EMLs.

Trastuzumab is currently included on the EML for treatment of metastatic HER2-positive breast cancer. EML-listed cytotoxic medicines for metastatic breast cancer include capecitabine, cyclophosphamide, docetaxel, doxorubicin, paclitaxel and vinorelbine. EML-listed hormonal therapies for MBC include anastrozole and tamoxifen.

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**Public health relevance** (burden of disease)

Breast cancer is the leading cause of cancer death among women globally, responsible for 15% of all cancer deaths. In 2018, the global cancer burden increased to 18.1 million cases, causing 9.6 million deaths (*1*). Changes in lifestyle, life expectancy and reproductive factors are responsible in many low- and middle-income countries (LMICs) for a sharp increase in the incidence of breast cancer, and the number of deaths as a percentage of incident cases is greater than that seen in high-income countries. For example, in 2008, this figure was 24% in high-income countries, 38% in high-middle-income countries, 40% in low-middle-income and 48% in low-income (*2*).

The HER2 receptor has emerged as one of the most important targets for the treatment of breast cancer. HER2 is involved in regulating cell growth, survival, and differentiation (*3*). Amplification and/or overexpression of HER2 occurs in approximately 18%–22% of breast cancers (*4*, *5*). HER2 amplification/overexpression (HER2-positivity) is associated with increased tumour aggressiveness, higher rates of recurrence, and increased mortality (*5*–*10*). The median age of patients presenting with HER2-positive breast cancer is in the mid-50s, approximately five years younger than the general breast cancer population (*11*).

At the early stage, breast cancer is usually operable and can be treated with curative intent. However, approximately 20%–35% of patients experience

relapse (*12*) and those with metastatic or unresectable disease are generally incurable. Such tumours often continue to express high levels of HER2 (13). Patients with metastatic disease have a 5-year life expectancy of approximately 18% in Europe (*14*).

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**Summary of evidence: benefits** (from the application)

**Locally advanced and metastatic breast cancer**

The efficacy of single-agent T-DM1 at a dose of 3.6 mg/kg every three weeks has been investigated in Phase II and III trials in HER2-positive advanced breast cancer.

The pivotal Phase III EMILIA trial was a randomized, multicentre, international, two-arm, open-label clinical trial that evaluated the efficacy and safety of treatment with T-DM1 was compared with the efficacy and safety of treatment with lapatinib plus capecitabine in 991 patients with HER2-positive, unresectable, locally advanced or metastatic breast cancer who had been previously treated with trastuzumab and a taxane (*15*, *16*). The primary efficacy endpoints were overall survival (OS) and independent review committee-assessed progression-free survival (PFS). The study demonstrated a statistically significant improvement in both PFS (9.6 months vs 6.4 months, HR 0.65, 95%CI 0.59 to 0.77) and OS (30.9 months vs 25.1 months, HR 0.68, 95%CI 0.55 to 0.85) for T-DM1 compared with lapatinib plus capecitabine. The final OS analysis was scheduled to be conducted after the occurrence of 632 deaths. At the data cut-off date for this analysis (December 2014), median OS was prolonged in patients treated with T-DM1 (29.9 months) when compared with patients treated with capecitabine plus lapatinib (25.9 months; HR 0.75, 95%CI 0.64 to 0.88) (*16*).

The comparator regimen of lapatinib plus capecitabine used in the EMILIA trial has not been considered for inclusion on the Model List.

The Phase III TH3RESA trial was a randomized, open-label, multicentre trial that compared T-DM1 with treatment of physician's choice in 602 patients with progressive HER2-positive advanced breast cancer, previously treated with at least two HER2-directed regimens (*17*, *18*). The study demonstrated a statistically significant improvement in both PFS (6.2 months vs 3.3 months, HR 0.53, 95%CI 0.42 to 0.66) and OS (median not reached at that time vs 14.9, HR 0.55, 95%CI 0.37 to 0.83) for T-DM1 compared with treatment of physician's choice (17). At the data cut-off date for final OS analysis (February 2015), median OS was prolonged in patients treated with T-DM1 compared with treatment of physician's choice (22.7 months vs 15.8 months; HR 0.68, 95%CI 0.54 to 0.85) (*18*).

**Early breast cancer**

The Phase III KRISTINE study evaluated neoadjuvant T-DM1 plus pertuzumab compared with docetaxel, carboplatin and trastuzumab plus pertuzumab in

444 patients with HER2-positive early breast cancer (*19*). The study found that total pathological complete response rates (a surrogate outcome for survival) were higher in patients receiving trastuzumab emtansine plus pertuzumab or docetaxel, carboplatin, than trastuzumab plus pertuzumab. However, OS was not significantly different between treatment groups (HR 1.21, 95%CI 0.37 to 3.96). Event-free survival significantly favoured trastuzumab-containing regimens, without T-DM1 (HR 2.61, 95%CI 1.36 to 4.98) (*20*).

In the KATHERINE study, adjuvant T-DM1 significantly improved Invasive disease–free survival rates compared to trastuzumab group in 1486 patients with residual disease following neoadjuvant chemotherapy plus trastuzumab-based anti-HER2 treatment (HR for invasive disease or death 0.50, 95%CI 0.39 to 0.64) (21). OS did not significantly differ (HR 0.70, 95%CI 0.47 to 1.05). These results are based on an early interim analysis based on few events.

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**Summary of evidence: harms** (from the application)

The safety profile of T-DM1 in MBC is based on pooled data from 1871 patients receiving single-agent T-DM1 treatment at 3.6 mg/kg every three weeks (Studies TDM3569g, TDM4258g, TDM4374g, TDM4688g, TDM4450g/BO21976, TDM4370g/BO21977, TDM4788g/BO22589, TDM4997g/BO25734 and TDM4529g/BO25430). The most common adverse events (AEs) for single-agent T-DM1 (AEs in ≥25% of patients) were nausea, fatigue and headache (*22*).

The Phase III EMILIA study compared T-DM1 with lapatinib plus capecitabine treatment, in patients with HER2-positive locally-advanced or metastatic breast cancer (*15*). In accordance with the differing mechanisms of action, the safety profile of T-DM1 was different from that of lapatinib plus capecitabine, as shown by differences in incidence of common AEs. In the T-DM1 arm, the most common events (occurring in at least 25% of patients) were nausea, fatigue, thrombocytopenia, headache, constipation, diarrhoea and increased aspartate aminotransferase, whereas the most common events associated with lapatinib plus capecitabine treatment were diarrhoea, palmar-plantar erythrodysesthesia syndrome, nausea, vomiting, fatigue and rash (Roche, data on file). Fewer patients were reported with AEs of Grade 3 or higher, and serious adverse events (SAEs) in the T-DM1 arm than in the lapatinib plus capecitabine arm.

In the Phase III TH3RESA study, fewer patients receiving T-DM1 than those receiving treatment of physician's choice had AEs of Grade 3 or higher. Grade 3 or higher thrombocytopenia was reported more frequently in patients receiving T-DM1 (≥2% more patients than in the TPC arm), whereas patients receiving TPC reported more Grade ≥3 neutropenia, leukopenia, febrile neutropenia and diarrhoea (*17*).

Cardiac safety of T-DM1 in patients with early breast cancer was evaluated in the Phase II study TDM4874g/BO22857 (*23*). There were no events of

symptomatic heart failure. One patient discontinued T-DM1 treatment as a result of an asymptomatic left ventricular ejection fraction (LVEF) decline. The most common AEs while receiving T-DM1 (in at least 20% of patients) were nausea, headache, epistaxis, asthenia, pyrexia, fatigue, arthralgia, thrombocytopenia and myalgia. The most common Grade 3 or higher AEs (>2%) reported while receiving T-DM1 were thrombocytopenia, alanine transaminase (ALT) increase, aspartate aminotransferase (AST) increase, neutropenia, and hypertension; all of which occurred in less than 10% of patients.

In the neoadjuvant KRISTINE (BO28408) study, safety was better in the T-DM1 + pertuzumab arm compared with trastuzumab, pertuzumab plus chemotherapy, with a lower incidence of, Grade 3 or higher: 13.0% in the T-DM1 + pertuzumab arm vs 64.4% in the trastuzumab, pertuzumab plus chemotherapy arm; serious AEs: 4.9% in T-DM1 + pertuzumab arm vs 28.8% in trastuzumab, pertuzumab plus chemotherapy arm; and AEs leading to treatment discontinuation: 3.1% in the T-DM1 + pertuzumab arm vs 8.7% in the trastuzumab, pertuzumab plus chemotherapy arm. The most common Grade 3–4 adverse events in the docetaxel, carboplatin, and trastuzumab plus pertuzumab group were neutropenia (55 [25%] of 219 vs one [<1%] of 223 with T-DM1 plus pertuzumab), diarrhoea (33 [15%] vs 2 [<1%]), and febrile neutropenia (33 [15%] vs 0). No deaths were reported during neoadjuvant treatment (*19*).

The overall safety profile of the T-DM1 arm in the adjuvant KATHERINE (BO27938) study was consistent with the known safety profile of T-DM1 (*21*). Any-grade AEs were more common in the T-DM1 arm (98.8% vs 93.3%). Adverse events leading to randomized treatment discontinuation occurred in 133 (18.0%) T-DM1–treated patients and 15 (2.1%) trastuzumab-treated patients. The most common adverse events leading to discontinuation in the T-DM1 arm were laboratory abnormalities (platelet count decreased (4.2%), blood bilirubin increased (2.6%), aspartate aminotransferase increased (1.6%), alanine aminotransferase increased (1.5%)), peripheral sensory neuropathy (1.5%), and ejection fraction decreased (1.2%). The most common Grade 3 or higher adverse events were decreased platelet count (5.7%) and hypertension (2.0%) in the T-DM1 group. Serious adverse events occurred in 94 patients (12.7%) receiving T-DM1. One fatal adverse event of intracranial haemorrhage after subject fall occurred in the T-DM1 arm. Adjudicated cardiac events occurred in four patients (0.6%) in the trastuzumab arm and in one patient in the T-DM1 arm (0.1%).

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**Additional evidence** (not in the application)

The following is a summary of additional evidence presented as part of the 2017 Expert Committee consideration of T-DM1 in 2017 (*24*).

A 2016 meta-analysis of nine studies evaluated the safety and efficacy of T-DM1 in advanced HER2-positive breast cancer. The overall hazard ratios for PFS and OS were calculated by meta-analysing, respectively, three (EMILIA (*15*),

TH3RESA (*17*), BO21976 (*25*)) and two (EMILIA, TH3RESA,) controlled trials. Median PFS significantly favoured T-DM1; difference ranged from 2.9 months to 5 months (total HR 0.60; 95%CI 0.53 to 0.69). Cumulative OS was associated with an improved survival for T-DM1 compared with treatment physician's choice (odds ratio (OR) 0.60; 95%CI 0.48 to 0.75). Heterogeneity was low in both analyses.

The National Institute for Health and Care Excellence (NICE) published its technology appraisal for T-DM1, assessing efficacy and cost–effectiveness (*26*–*28*). As part of the process, NICE reviewed evidence submitted by Roche, clinical experts and other stakeholders; clinical evidence came primarily from EMILIA and TH3RESA clinical trials. Because head-to-head treatment comparisons were available only for lapatinib in combination with capecitabine (LC), the company conducted a Bayesian network meta-analysis using a fixed-effect model involving five clinical trials (EMILIA, CEREBEL, EGF100151, NCT00777101 and GBG26). NICE's Evidence Review Group (ERG), reviewing Roche's submission, repeated the network meta-analysis using a random-effects model. From the ERG's model, compared with LC, T-DM1 was associated with a 32% decrease in hazard of death (HR 0.68, 95% credible Interval (CrI) 0.37 to 1.25) and a 35% reduction in the hazard of tumour progression or death (HR 0.65, 95%CrI 0.35 to 1.20). However, the authors report that CrI values "do not rule out the possibility that T-DM1 is less efficacious than comparators" (*28*).

After analysing the technology appraisal, NICE concluded that T-DM1 was clinically effective for treatment for HER2-positive, unresectable, locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane, but ultimately did not find it to be cost effective at the price that Roche was offering at the time (*27*).

#### Comparison with trastuzumab

Trastuzumab is associated with relevant benefits in HER2-positive breast cancer patients. In a systematic review of eight studies, total 11 991 patients, the combined HRs for OS and disease-free survival (DFS) significantly favoured trastuzumab-containing regimens (HR 0.66, 95%CI 0.57 to 0.77; $p<0.00001$; and HR 0.60, 95%CI 0.50 to 0.71; $p<0.00001$, respectively) (*29*). Currently, a combination of trastuzumab with a taxane is considered to be the standard of care (i.e. first-line) in metastatic breast cancer. Medicines in this regimen are included on the WHO EML.

The Phase III MARIANNE randomized controlled trial studied untreated HER2-positive metastatic breast cancer patients receiving T-DM1 plus pertuzumab, T-DM1 plus placebo, or a combination of trastuzumab with a taxane (paclitaxel or docetaxel) (*30*, *31*). At the cut-off date of May 2016, therapies containing T-DM1 were non-inferior to trastuzumab and taxane treatments for PFS. However, OS curves essentially overlapped (trastuzumab

+ taxane vs trastuzumab emtansine + placebo, HR 0.93, 95%CI 0.73 to 1.20; trastuzumab + taxane vs trastuzumab emtansine + pertuzumab HR 0.86, 95%CI 0.67 to 1.11) with survival medians approaching one another (trastuzumab + taxane 50.86 months, trastuzumab emtansine + placebo 53.68, trastuzumab emtansine + pertuzumab 51.78) (*32*). T-DM1 was better tolerated, contributing to better quality of life secondary endpoints and less treatment discontinuation related to adverse events (*31*).

**WHO Guidelines**

None available.

**Costs/cost-effectiveness**

A Canadian study demonstrated that the use of T-DM1 for the management of HER2-positive metastatic breast cancer results in substantial savings to the public health care system when the costs of treatment related AEs are taken into account, due to less toxicity compared with lapatinib plus capecitabine (*33*). The findings were confirmed in sensitivity analyses in which the number and costs of AEs were changed, however, the magnitude of cost savings varied. Whether the same findings would be realized in other countries and health care systems is not known.

T-DM1 has been accepted as a cost-effective treatment option in eligible patients with HER2-positive metastatic breast cancer in the United Kingdom (*34*), Canada (*35*), Australia (*36*), Scotland (*37*), Ireland (*38*), France (*39*), and Sweden (*40*).

**Availability**

T-DM1 was first granted marketing approval in United States on February 2013, followed by the European Union (EU) and Japan in the same year. As of 15 November 2018, T-DM1 has been approved in more than 100 countries worldwide.

**Other considerations**

Based on results of the EMILIA study (*15*, *41*), T-DM1 received a score of 4 on the ESMO-MCBS v1.1 for use in the metastatic breast cancer setting as second-line therapy after trastuzumab failure (*42*).

The U.S. National Comprehensive Cancer Network (NCCN) v3, 25 October 2018 clinical guidelines and compendium recommend use of T-DM1 as a first-line treatment option for patients with HER2-positive MBC in patients not eligible for pertuzumab-trastuzumab plus a taxane. Based on the trial data from Study BO22589/TDM4788g that demonstrated T-DM1 is noninferior with better quality of life compared with trastuzumab plus taxane, and possibly

better tolerated for some patients, the NCCN panel included T-DM1 as one of the first-line options for the treatment of patients with HER2-positive MBC. Pertuzumab, trastuzumab, and a taxane, however, remain the preferred first-line regimen for HER2-positive metastatic disease based on data demonstrating improved overall survival compared with trastuzumab and a taxane. T-DM1 as first-line therapy should be considered only in patients not suitable for the preferred treatment (*43*).

The American Society of Clinical Oncology (ASCO) clinical practice guideline recommends the use of T-DM1 for the treatment of HER2-positive advanced breast cancer that has progressed during or after first-line HER2-targeted therapy (Evidence quality: High; Strength of recommendation: Strong) (*44*). The same guideline also recommends the use of T-DM1 in patients whose HER2-positive breast cancer has progressed during or after second-line or greater HER2-targeted therapy if they have not previously been treated with T-DM1 (*44*).

Updated European Society for Medical Oncology (ESMO) guidelines recommend T-DM1 in patients who have progressed through at least one line of trastuzumab-based therapy based on its OS benefit (Category IA) (*45*).

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**Committee recommendations**

The Committee endorsed the recommendations of the EML Cancer Medicine Working Group with regard to the proposed threshold of four to six months of overall survival benefit as a guiding principle for prioritizing cancer medicines for inclusion on the EML, and applied this principle to the consideration of trastuzumab emtansine. The Committee acknowledged that for second-line treatment of metastatic breast cancer, trastuzumab emtansine was associated with a relevant survival benefit, within the range of the established threshold. However, the Committee noted that survival benefits did not meet the four to six month threshold when trastuzumab emtansine was used as first-line treatment in the metastatic setting, or in early stage breast cancer.

Existing EML-listed options are available for metastatic disease and may be suitable alternatives (e.g., trastuzumab, taxanes, etc.). However, the Committee noted the current challenges in achieving full access to trastuzumab in many settings. Taking this into account, trastuzumab emtansine for second-line treatment of metastatic disease (i.e. late in the care pathway) was considered to be a lower priority for EML inclusion at this time.

Compared to the 2017 application, the Committee noted that few new clinical data were included in the current application and that the request was not based on a comprehensive review encompassing additional breast cancer medicines, compared with the standard of care, which would allow countries to understand the additional value of adding each option to national EMLs.

The Expert Committee therefore did not recommend the addition of trastuzumab emtansine to the complementary list of the EML for the treatment of unresectable, locally advanced and metastatic HER2-positive breast cancer.

## References


1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
2. Shulman LN, Willett W, Sievers A, Knaul FM. Breast cancer in developing countries: opportunities for improved survival. J Oncol. 2010;2010:595167.
3. Sundaresan S, Penuel E, Sliwkowski MX. The biology of human epidermal growth factor receptor 2. Curr Oncol Rep. 1999;1(1):16–22.
4. Wolff AC, Hammond ME, Schwartz JN, Hagerty KL, Allred DC, Cote RJ et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol. 2007;25(1):118–45.
5. Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM, Hortobagyi GN. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. Oncologist. 2009;14(4):320–68.
6. Borg A, Tandon AK, Sigurdsson H, Clark GM, Ferno M, Fuqua SA et al. HER-2/neu amplification predicts poor survival in node-positive breast cancer. Cancer Res. 1990;50(14):4332–7.
7. Ross JS, Fletcher JA. The HER-2/neu oncogene in breast cancer: prognostic factor, predictive factor, and target for therapy. Stem Cells. 1998;16(6):413–28.
8. Menard S, Fortis S, Castiglioni F, Agresti R, Balsari A. HER2 as a prognostic factor in breast cancer. Oncology. 2001;61 Suppl 2:67–72.
9. Brown M, Tsodikov A, Bauer KR, Parise CA, Caggiano V. The role of human epidermal growth factor receptor 2 in the survival of women with estrogen and progesterone receptor-negative, invasive breast cancer: the California Cancer Registry, 1999-2004. Cancer. 2008;112(4):737–47.
10. Curigliano G, Viale G, Bagnardi V, Fumagalli L, Locatelli M, Rotmensz N et al. Clinical relevance of HER2 overexpression/amplification in patients with small tumor size and node-negative breast cancer. J Clin Oncol. 2009;27(34):5693–9.
11. Neven P, Van Calster B, Van den Bempt I, Van Huffel S, Van Belle V, Hendrickx W et al. Age interacts with the expression of steroid and HER-2 receptors in operable invasive breast cancer. Breast Cancer Res Treat. 2008;110(1):153–9.
12. Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet. 2011; 378(9804):1707–16.
13. Spector NL, Xia W, Burris H, 3rd, Hurwitz H, Dees EC, Dowlati A et al. Study of the biologic effects of lapatinib, a reversible inhibitor of ErbB1 and ErbB2 tyrosine kinases, on tumor growth and survival pathways in patients with advanced malignancies. J Clin Oncol. 2005;23(11):2502–12.
14. Sant M, Allemani C, Capocaccia R, Hakulinen T, Aareleid T, Coebergh JW et al. Stage at diagnosis is a key explanation of differences in breast cancer survival across Europe. Int J Cancer. 2003;106(3):416–22.

15. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367(19):1783–91.

16. Dieras V, Miles D, Verma S, Pegram M, Welslau M, Baselga J et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. Lancet Oncol. 2017;18(6):732–42.

17. Krop IE, Kim SB, Gonzalez-Martin A, LoRusso PM, Ferrero JM, Smitt M et al. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014;15(7):689–99.

18. Krop IE, Kim SB, Martin AG, LoRusso PM, Ferrero JM, Badovinac-Crnjevic T et al. Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomised open-label phase 3 trial. Lancet Oncol. 2017;18(6):743–54.

19. Hurvitz SA, Martin M, Symmans WF, Jung KH, Huang CS, Thompson AM et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol. 2018;19(1):115–26.

20. A Study Evaluating Trastuzumab Emtansine Plus Pertuzumab Compared With Chemotherapy Plus Trastuzumab and Pertuzumab for Participants With Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancer (ClinicalTrials.gov Identifier: NCT02131064) [website]. Bethesda: U.S. National Library of Medicine; 2019. (https://clinicaltrials.gov/ct2/show/results/NCT02131064, accessed 29 September 2019).

21. von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2019;380(7):617–28.

22. Kadcyla: Summary of Product Characteristics. Amsterdam: Eurpean Medicines Agency. Available from https://www.ema.europa.eu/en/documents/product-information/kadcyla-epar-product-information_en.pdf.

23. Krop IE, Suter TM, Dang CT, Dirix L, Romieu G, Zamagni C et al. Feasibility and cardiac safety of trastuzumab emtansine after anthracycline-based chemotherapy as (neo)adjuvant therapy for human epidermal growth factor receptor 2-positive early-stage breast cancer. J Clin Oncol. 2015;33(10):1136–42.

24. The selection and use of essential medicines. Report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children) (WHO Technical Report Series, No. 1006). Geneva: World Health Organization; 2017. Available from https://apps.who.int/iris/bitstream/handle/10665/259481/9789241210157-eng.pdf, accessed 30 October 2019.

25. Hurvitz SA, Dirix L, Kocsis J, Bianchi GV, Lu J, Vinholes J et al. Phase II randomized study of trastuzumab emtansine versus trastuzumab plus docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. J Clin Oncol. 2013;31(9):1157–63.

26. Elsada A, Doss S, Robertson J, Adam EJ. NICE guidance on trastuzumab emtansine for HER2-positive advanced breast cancer. Lancet Oncol. 2016;17(2):143–4.

27. Trastuzumab emtansine for treating HER-2 positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane. Technology appraisal guidance (TA371) 2015. London: National Institute for Health and Care Excellence: 2015. Available from https://www.nice.org.uk/guidance/ta371/resources/trastuzumab-emtansine-for-treating-her2positive-unresectable-locally-advanced-or-metastatic-breast-cancer-after-treatment-with-trastuzumab-and-a-taxane-82602784201669, accessed 29 September 2019.

28. Squires H, Stevenson M, Simpson E, Harvey R, Stevens J. Trastuzumab Emtansine for Treating HER2-Positive, Unresectable, Locally Advanced or Metastatic Breast Cancer After Treatment with Trastuzumab and a Taxane: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. Pharmacoeconomics. 2016;34(7):673–80.

29. Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V et al. Trastuzumab containing regimens for early breast cancer. Cochrane Database Syst Rev. 2012;4:CD006243.

30. Ellis PA, Barrios CH, Eiermann W, Toi M, Im YH, Conte PF et al. Phase III, randomized study of trastuzumab emtansine (T-DM1) ± pertuzumab (P) vs trastuzumab + taxane (HT) for first-line treatment of HER2-positive MBC: Primary results from the MARIANNE study. 2015 ASCO Annual Meeting - Abstract 507 J Clin Oncol (Meeting Abstracts). 2015;33(Suppl).

31. Perez EA, Barrios C, Eiermann W, Toi M, Im YH, Conte P et al. Trastuzumab Emtansine With or Without Pertuzumab Versus Trastuzumab Plus Taxane for Human Epidermal Growth Factor Receptor 2-Positive, Advanced Breast Cancer: Primary Results From the Phase III MARIANNE Study. J Clin Oncol. 2017;35(2):141–8.

32. A Study of Trastuzumab Emtansine (T-DM1) Plus Pertuzumab/Pertuzumab Placebo Versus Trastuzumab [Herceptin] Plus a Taxane in Participants With Metastatic Breast Cancer (MARIANNE) (ClinicalTrials.gov Identifier: NCT01120184). Bethesda: U.S. National Library of Medicine: 2017. Available from https://clinicaltrials.gov/ct2/show/results/NCT01120184?term=01120184&rank=1&view=results.

33. Piwko C, Prady C, Yunger S, Pollex E, Moser A. Safety Profile and Costs of Related Adverse Events of Trastuzumab Emtansine for the Treatment of HER2-Positive Locally Advanced or Metastatic Breast Cancer Compared to Capecitabine Plus Lapatinib from the Perspective of the Canadian Health-Care System. Clin Drug Investig. 2015;35(8):487-93.

34. Trastuzumab emtansine for treating HER-2 positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane. Technology appraisal guidance (TA458) 2017. London: National Institute for Health and Care Excellence. Available from https://www.nice.org.uk/guidance/TA458, access 29 September 2019.

35. Trastuzumab emtansine for Metastatic Breast Cancer - Details. CADTH pan-Canadian Oncology Drug Review [website]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2014. (https://www.cadth.ca/trastuzumab-emtansine-metastatic-breast-cancer-details, accessed 29 September 2019).

36. Public Summary Document – November 2014 PBAC Meeting [website]. Canberra: Australian Government Department of Health; 2014. (http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2014-11/files/pertuzumab-trastuzumab-psd-11-2014.pdf, accessed 29 September 2019).

37. Trastuzumab emtansine (Kadcyla) is accepted for use within NHS Scotland [website]. Glasgow: Scottish Medicines Consortium; 2017. (https://www.scottishmedicines.org.uk/medicines-advice/trastuzumab-emtansine-kadcyla-resubmission-99014/, accessed 29 September 2019).

38. Trastuzumab emtansine (Kadcyla) Pharmacoeconomic Evaluations [website]. Dublin: National Centre for Pharmacoeconomics (NCPE) Ireland; 2015. (http://www.ncpe.ie/drugs/trastuzumab-emtansine-kadcyla/, accessed 29 September 2019).

39. Kadcyla (trastuzumab emtansine), anticorps ciblant le récepteur HER 2 couplé à un cytotoxique. Cancérologie – Nouveau Médicament et Avis d'efficience [website]. Saint-Denis La Plaine: Haute Autorité de santé (HAS); 2014. (https://www.has-sante.fr/jcms/c_1735595/fr/kadcyla-trastuzumab-emtansine-anticorps-ciblant-le-recepteur-her-2-couple-a-un-cytotoxique?xtmc=&xtcr=1, accessed 29 September 2019).

40. Kadcyla (trastuzumab-emtansin) [website]. Stockholm: Hälsoekonomiskt kunskapsunderlag. Tandvårds och läkemedelsförmånsverket (TLV); 2014. (https://www.tlv.se/download/18.467926b615d084471ac339c1/1510316400449/halsoekonomiskt-kunskapsunderlag-kadcyla.pdf, accessed 29 September 2019).

41. Welslau M, Dieras V, Sohn JH, Hurvitz SA, Lalla D, Fang L et al. Patient-reported outcomes from EMILIA, a randomized phase 3 study of trastuzumab emtansine (T-DM1) versus capecitabine and lapatinib in human epidermal growth factor receptor 2-positive locally advanced or metastatic breast cancer. Cancer. 2014;120(5):642–51.

42. ESMO-Magnitude of Clinical Benefit Scale. The ESMO-MCBS Score Card [website]. Lugano: European Society for Medical Oncology. (https://www.esmo.org/score/cards, accessed 29 September 2019).

43. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Breast Cancer Version 2; 2019. Available from https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf, accessed 29 September 2019.

44. Giordano SH, Temin S, Kirshner JJ, Chandarlapaty S, Crews JR, Davidson NE et al. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014; 32(19):2078–99.

45. Cardoso F, Costa A, Senkus E, Aapro M, Andre F, Barrios CH et al. 3rd ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3). Ann Oncol. 2017;28(1):16–33.

*Tyrosine-kinase inhibitors for non-small cell lung cancer – addition – EML*

| | |
|---|---|
| **Afatinib** | **ATC Code: L01XE13** |
| **Erlotinib** | **ATC Code: L01XE03** |
| **Gefitinib** | **ATC Code: L01XE02** |

**Proposal**

The application requested the addition of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) to the complementary list of the EML for first-line treatment of EGFR mutation positive, non-small cell lung cancer.

**Applicant**

Dr Sumitra Thongprasert

**WHO Technical Department**

Comments on the application were received from the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it supported the inclusion of EGFR TKIs on the EML, stating that there is sufficient evidence that these medicines are equivalent or superior to existing listed medicines, based on updated meta-analysis and real-world data, particularly in middle-income countries.

**EML/EMLc**

EML

**Section**

8.2.2 Targeted therapies

**Dose form(s) & strengths(s)**

Afatinib: capsule 20 mg, 40 mg, 50 mg
Erlotinib: capsule 100 mg, 150 mg
Gefitinib: capsule 250 mg

**Core/Complementary**

Complementary

**Individual/Square box listing**

Square box

**Background** (if relevant, eg. resubmission, previous EC consideration)

EGFR TKIs have been considered and rejected for inclusion on the EML on two previous occasions in 2015 and 2017. In each case, the Expert Committee acknowledged that individual patients with a drug-sensitive EGFR mutation may derive benefit from TKI therapy, which has been associated with similar efficacy and more favourable tolerability compared to cytotoxic chemotherapy. However, the requirements to screen patients for suitability for treatment must be taken into account by health systems (*1*, *2*).

Cytotoxic chemotherapy currently included on the EML for treatment of non-small cell lung cancer (NSCLC) includes carboplatin, cisplatin, etoposide, gemcitabine, paclitaxel and vinorelbine.

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**Public health relevance** (burden of disease)

Lung cancer is the most commonly diagnosed cancer globally, and the leading cause of cancer death, with estimated 2 million new cases and 1.7 related deaths in 2018. The economic impact of lung cancer has been estimated at around US$ 8 billion in lost productivity in the BRICS countries (Brazil, Russia, India, China and South Africa) (*3*).

Moreover, in the absence of wide coverage of effective screening programmes on a global scale, lung cancer diagnoses occur in advanced stage in more than 60% of cases, with highly regional variability (*4*, *5*). The mutational pattern of NSCLC varies across the different regions, with a higher prevalence in Asia Pacific (up to 76% of patients) and the lowest registered in Oceania (12%). Africa, Europe and North America registered the same rate of EGFR-mutated NSCLC, at around 20% (*6*–*8*).

Non-squamous NSCLC has been linked to gene mutations in EGFR. This disease, given its incidence, comprises a high burden and leads to a high mortality. However, with advances in cancer gene-directed treatment, the outcome of the disease has improved. The response rate doubled as compared to chemotherapy, the progression free survival (PFS) doubled and the median survival time increased to nearly three years if patients receive both the targeted medicines and chemotherapy together (the median survival time for patient receiving chemotherapy only is approximately 10 months, in historical series).

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**Summary of evidence: benefits** (from the application)

The application reported the findings and recommendations for EGFR-mutated NSCLC from the 2018 European Society For Medical Oncology (ESMO) Clinical Practice Guidelines for diagnosis, treatment and follow up of metastatic non-small cell lung cancer (*9*).

The ESMO guidelines state that EGFR-TKIs are the standard of care for first-line treatment for advanced EGFR-mutated NSCLC (level of evidence: I; grade of recommendation: A).

EGFR mutation as an oncogenic target has proven predictive power in NSCLC from multiple Phase III trials of EGFR-TKIs versus platinum-based chemotherapy (*10–15*). The improvement in objective response rate (ORR) and progression free survival (PFS) is consistent across all age groups, genders, smoking status and performance status. However, none of the above studies demonstrated an overall survival benefit for a EGFR-TKI over platinum-based chemotherapy, likely due to the high level of crossover (*16*).

The use of EGFR-TKI as first-line therapy has been associated with a greater benefit than as second-line treatment after chemotherapy for PFS (12.9 months vs 9.0 months (HR 0.78, 95%CI 0.61 to 0.98. p=0.034)), ORR (67.8% and 55.6%, respectively, p=0.001). Overall survival in patients receiving first-line TKI followed by second-line chemotherapy was longer than in patients receiving TKI second-line after chemotherapy (30.7 months vs 27.2 months (HR 0.69, 95%CI 0.50 to 0.94, p=0.02) (*17*).

Evidence supports the continuation of EGFR-TKI treatment beyond radiological progression in patients who are clinically stable (*18*). EGFR-TKI use in combination with local radiation therapy in patients with oligoprogressive disease, has also been shown to be associated with significantly longer PFS (*19*).

The IMPRESS trial tested the continuation of gefitinib plus chemotherapy with placebo plus chemotherapy in patients with EGFR mutation-positive advanced NSCLC with progression after first-line gefitinib (*20*). The trial failed to show a benefit of the continuation strategy of the EGFR-TKI as add-on strategy; the continuation of gefitinib plus cisplatin and pemetrexed was detrimental to OS when compared with placebo plus cisplatin and pemetrexed (hazard ratio [HR] 1.44, 95%CI 1.07 to 1.94; p=0.016; median OS, 13.4 v 19.5 months). Therefore, continuous use of EGFR-TKI in combination with chemotherapy is not recommended.

The NEJ009 trial evaluated the efficacy of a combination of gefitinib and carboplatin/pemetrexed in untreated advanced NSCLC patients with EGFR mutations (*21*). Carboplatin/pemetrexed/gefitinib demonstrated better PFS (mPFS: 20.9 vs 11.2 months, HR 0.49, 95%CI 0.39 to 0.62) and OS (mOS: 52.2 vs 38.8 months, HR 0.69, 95%CI 0.52 to 0.92) compared with gefitinib monotherapy in advanced EGFR mutated NSCLC, representing a first-line therapy option.

The choice between first- (gefitinib or erlotinib, (reversible)) and second-generation (afatinib, (irreversible)) EGFR-TKIs was investigated in two randomized studies. The Phase IIB LUX-Lung 7 trial compared afatinib with gefitinib (*22*). The study reported similar tumour ORR and a modest non-clinically meaningful difference in PFS (mPFS 11.0 vs 10.9 months; HR 0.73, 95%CI 0.57 to 0.95, p=0.0165). OS was not statistically different (*23*). There was no difference in OS in patients with EGFR exon 19 mutation, contrary to earlier claims of benefit in this sub-group from the pooled analysis of LUX-Lung 3 and LUX-Lung 6 studies (*24*).

ARCHER 1050 is a randomized Phase III study that compared dacomitinib (a second-generation EGFR-TKI) with gefitinib in stage IV EGFR-mutated lung cancer patients without central nervous system (CNS) metastasis (*25*, *26*). The study showed an improved PFS in the dacomitinib arm (mPFS 14.7 vs 9.2 months; HR 0.59, 95%CI 0.47 to 0.74, p<0.0001). The mOS was 34.1 months with dacomitinib vs 26.8 months with gefitinib (HR 0.76, 95%CI 0.58 to 0.993, p<0.04). The OS probabilities at 30 months were 56.2% and 46.3% with dacomitinib and gefitinib, respectively.

**Summary of evidence: harms** (from the application)

The toxicity profile of EGFR-TKIs is generally clinically manageable, with 6% of toxicity-related treatment discontinuation reported in one pooled analysis (*27*, *28*).

The use of EGFR-TKI was favoured over chemotherapy in quality of life (QoL) analyses, reporting a longer time to clinical deterioration and maintained overall QoL (*29–31*).

For afatinib, an extensive investigation of patient-reported symptoms and health-related QoL benefits have been reported, showing that afatinib delayed the time to deterioration for cough (HR 0.60, 95%CI 0.41 to 0.87; p=0.007) and dyspnoea (HR 0.68, 95%CI 0.50 to 0.93; p=0.015), with more patients on afatinib (64%) versus chemotherapy (50%) experiencing improvements in dyspnoea scores (p=0.010), the cardinal symptom for lung cancer patients (*32*). For erlotinib, a secondary analysis from the OPTIMAL (CTONG-0802) Phase III clinical trial, showed that patients receiving erlotinib experienced clinically relevant improvements in QoL compared with the chemotherapy group, across different scales to assess general outcome and lung-specific subscales (*33*). Data for gefitinib are still consistent with the findings for the other two EGFR-TKIs: time to deterioration in physical and life well-being favoured gefitinib over chemotherapy (HR of time to deterioration, 0.34, 95%CI 0.23 to 0.50; p<0.0001 and HR 0.43, 95%CI 0.28 to 0.65; p<0.0001, respectively) (*29*).

**Additional evidence** (not in the application)

N/A

**WHO Guidelines**

N/A

**Costs/cost-effectiveness**

A cost-effectiveness analysis performed by the Institute for Clinical and Economic Review showed that the use of each of the first-line EGFR-TKI regimens resulted in a 0.84 life-year gain in survival relative to chemotherapy. Quality-adjusted life-years (QALYs) gained versus chemotherapy were also very similar, ranging

from 0.60 for gefitinib to 0.62 for afatinib and erlotinib. Incremental costs versus chemotherapy were lower for gefitinib (approximately US$ 66 000) than for the other EGFR-TKIs, as a function of a shorter duration of time spent in the progression-free state (and a consequently shorter duration of treatment). Cost-effectiveness estimates were similar across the EGFR-TKIs, ranging from approximately US$ 110 000 to US$ 150 000 per QALY gained (*34*).

In another cost-effectiveness analysis, two different strategies were compared: the 'EGFR testing strategy', in which EGFR mutation testing was performed before treatment and patients with EGFR mutations received gefitinib while those without mutations received standard chemotherapy, to the 'no-testing strategy,' in which genetic testing was not conducted and all patients were treated with standard chemotherapy. The authors concluded that the combination use of gefitinib and EGFR testing can be considered a cost-effective first-line therapy compared to chemotherapy such as carboplatin-paclitaxel for the treatment for NSCLC in Japan (*35*).

Technology appraisal guidance issued by National Institute for Health and Care Excellence (NICE) for first-line EGFR-TKIs gefitinib, erlotinib and afatinib state that these medicines are recommended treatment options people with locally advanced or metastatic EGFR mutation-positive NSCLC if the manufacturers provide the drugs at agreed fixed or discounted prices (*36*–*38*).

**Availability**

Originator brands of afatinib, erlotinib and gefitinib are manufactured by Boehringer Ingelheim, Roche and AstraZeneca, respectively. Generic brands are becoming available.

**Other considerations**

Based on the results of the LUX-Lung 3 study (*14*, *32*), afatinib received a score of 4 on the ESMO-Magnitude of Clinical Benefit Scale (MCBS, v1.1) for first-line use in metastatic EGFR+ NSCLC (*39*).

Based on the results of the OPTIMAL (*40*) and EURTAC (*13*) studies, erlotinib received a score of 4 on the ESMO-MCBS v1.1 for use in metastatic EGFR+ NSCLC (*39*).

Based on the results of the IPASS study (*10*, *41*), gefitinib received a score of 4 on the ESMO-MCBS v1.1 for first-line use in metastatic EGFR+ NSCLC (*39*).

**Committee recommendations**

The Committee endorsed the recommendations of the EML Cancer Medicine Working Group with regard to the proposed threshold of four to six months of overall survival benefit as a guiding principle for prioritizing cancer medicines for inclusion on the EML, and applied this principle to the consideration of the tyrosine kinase inhibitors afatinib, erlotinib and gefitinib.

The Committee noted that afatinib, erlotinib and gefitinib were all scored as 4/5 on the ESMO-MCBS v1.1 for this indication.

The Expert Committee recommended the addition of erlotinib with a square box to the complementary list of the EML for first-line treatment of EGFR mutation-positive advanced non-small cell lung cancer. Afatinib and gefitinib should be considered as therapeutically equivalent alternatives. The Committee noted that these medicines are associated with relevant survival benefits for patients, acceptable toxicity and improvements in quality of life compared to chemotherapy.

The Committee also noted that since these medicines were considered for inclusion on the EML in 2015, generic versions of these medicines are more widely available, as are quality-assured diagnostic molecular tests for EGFR mutations.

## References

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children) (WHO Technical Report Series, No. 994). Geneva: World Health Organization; 2015. Available from https://apps.who.int/iris/bitstream/handle/10665/189763/9789241209946_eng.pdf, accessed 30 October 2019.
2. The selection and use of essential medicines. Report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children) (WHO Technical Report Series, No. 1006). Geneva: World Health Organization; 2017. Available from https://apps.who.int/iris/bitstream/handle/10665/259481/9789241210157-eng.pdf, accessed 30 October 2019.
3. Pearce A, Sharp L, Hanly P, Barchuk A, Bray F, de Camargo Cancela M et al. Productivity losses due to premature mortality from cancer in Brazil, Russia, India, China, and South Africa (BRICS): A population-based comparison. Cancer Epidemiol. 2018;53:27–34.
4. Cheng TY, Cramb SM, Baade PD, Youlden DR, Nwogu C, Reid ME. The International Epidemiology of Lung Cancer: Latest Trends, Disparities, and Tumor Characteristics. J Thorac Oncol. 2016; 11(10):1653–71.
5. Morgensztern D, Ng SH, Gao F, Govindan R. Trends in stage distribution for patients with non-small cell lung cancer: a National Cancer Database survey. J Thorac Oncol. 2010;5(1):29–33.
6. Midha A, Dearden S, McCormack R. EGFR mutation incidence in non-small-cell lung cancer of adenocarcinoma histology: a systematic review and global map by ethnicity (mutMapII). Am J Cancer Res. 2015;5(9):2892–911.
7. Benbrahim Z, Antonia T, Mellas N. EGFR mutation frequency in Middle East and African non-small cell lung cancer patients: a systematic review and meta-analysis. BMC Cancer. 2018;18(1):891.
8. Rosell R, Moran T, Queralt C, Porta R, Cardenal F, Camps C et al. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med. 2009;361(10):95867.
9. Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Supplement_4):iv192–iv237.

10. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361(10):947–57.
11. Han JY, Park K, Kim SW, Lee DH, Kim HY, Kim HT et al. First-SIGNAL: first-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. J Clin Oncol. 2012;30(10):1122–8.
12. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med. 2010;362(25):2380–8.
13. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012;13(3):239–46.
14. Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol. 2013;31(27):3327–34.
15. Wu YL, Zhou C, Hu CP, Feng J, Lu S, Huang Y et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol. 2014; 15(2):213–22.
16. Nan X, Xie C, Yu X, Liu J. EGFR TKI as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer. Oncotarget. 2017;8(43):75712–26.
17. Xu J, Zhang X, Yang H, Ding G, Jin B, Lou Y et al. Comparison of outcomes of tyrosine kinase inhibitor in first- or second-line therapy for advanced non-small-cell lung cancer patients with sensitive EGFR mutations. Oncotarget. 2016;7(42):68442–8.
18. Park K, Yu CJ, Kim SW, Lin MC, Sriuranpong V, Tsai CM et al. First-Line Erlotinib Therapy Until and Beyond Response Evaluation Criteria in Solid Tumors Progression in Asian Patients With Epidermal Growth Factor Receptor Mutation-Positive Non-Small-Cell Lung Cancer: The ASPIRATION Study. JAMA Oncol. 2016;2(3):305–12.
19. Jiang T, Chu Q, Wang H, Zhou F, Gao G, Chen X et al. EGFR-TKIs plus local therapy demonstrated survival benefit than EGFR-TKIs alone in EGFR-mutant NSCLC patients with oligometastatic or oligoprogressive liver metastases. Int J Cancer. 2018; 144(10):2605–2612.
20. Mok TSK, Kim SW, Wu YL, Nakagawa K, Yang JJ, Ahn MJ et al. Gefitinib Plus Chemotherapy Versus Chemotherapy in Epidermal Growth Factor Receptor Mutation-Positive Non-Small-Cell Lung Cancer Resistant to First-Line Gefitinib (IMPRESS): Overall Survival and Biomarker Analyses. J Clin Oncol. 2017;35(36):4027–34.
21. Nakamura A, Inoue A, Morita S, Hosomi Y, Kato T, Fukuhara T et al. Phase III study comparing gefitinib monotherapy (G) to combination therapy with gefitinib, carboplatin, and pemetrexed (GCP) for untreated patients (pts) with advanced non-small cell lung cancer (NSCLC) with EGFR mutations (NEJ009). J Clin Oncol. 2018;36(15_suppl):9005.
22. Park K, Tan EH, O'Byrne K, Zhang L, Boyer M, Mok T et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. Lancet Oncol. 2016;17(5):577–89.
23. Paz-Ares L, Tan EH, O'Byrne K, Zhang L, Hirsh V, Boyer M et al. Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial. Ann Oncol. 2017;28(2):270–7.

24. Yang JC, Wu YL, Schuler M, Sebastian M, Popat S, Yamamoto N, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol. 2015;16(2):141-51.
25. Mok TS, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S et al. Improvement in Overall Survival in a Randomized Study That Compared Dacomitinib With Gefitinib in Patients With Advanced Non-Small-Cell Lung Cancer and EGFR-Activating Mutations. J Clin Oncol. 2018;36(22):2244–50.
26. Wu YL, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. Lancet Oncol. 2017;18(11):1454–66.
27. Takeda M, Nakagawa K. Toxicity profile of epidermal growth factor receptor tyrosine kinase inhibitors in patients with epidermal growth factor receptor gene mutation-positive lung cancer. Mol Clin Oncol. 2017;6(1):3-6.
28. Takeda M, Okamoto I, Nakagawa K. Pooled safety analysis of EGFR-TKI treatment for EGFR mutation-positive non-small cell lung cancer. Lung Cancer. 2015;88(1):74–9.
29. Oizumi S, Kobayashi K, Inoue A, Maemondo M, Sugawara S, Yoshizawa H et al. Quality of life with gefitinib in patients with EGFR-mutated non-small cell lung cancer: quality of life analysis of North East Japan Study Group 002 Trial. Oncologist. 2012;17(6):863–70.
30. Metro G. EGFR targeted therapy for lung cancer: are we almost there? Transl Lung Cancer Res. 2018;7(Suppl 2):S142–s5.
31. Kohler J, Schuler M. Afatinib, erlotinib and gefitinib in the first-line therapy of EGFR mutation-positive lung adenocarcinoma: a review. Onkologie. 2013;36(9):510–8.
32. Yang JC, Hirsh V, Schuler M, Yamamoto N, O'Byrne KJ, Mok TS et al. Symptom control and quality of life in LUX-Lung 3: a phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations. J Clin Oncol. 2013;31(27):3342–50.
33. Chen G, Feng J, Zhou C, Wu YL, Liu XQ, Wang C et al. Quality of life (QoL) analyses from OPTIMAL (CTONG-0802), a phase III, randomised, open-label study of first-line erlotinib versus chemotherapy in patients with advanced EGFR mutation-positive non-small-cell lung cancer (NSCLC). Ann Oncol. 2013;24(6):1615–22.
34. Treatment options for advanced non-small cell lung cancer: Effectiveness, value and value-based price benchmarks. Evidence Report. Boston: Institute for Clinical and Economic Review; 2016. Available from: https://icer-review.org/wp-content/uploads/2016/08/MWCEPAC_NSCLC_Evidence_Report_Plus_Supplement_101716.pdf, accessed 10 November 2019.
35. Narita Y, Matsushima Y, Shiroiwa T, Chiba K, Nakanishi Y, Kurokawa T, et al. Cost-effectiveness analysis of EGFR mutation testing and gefitinib as first-line therapy for non-small cell lung cancer. Lung Cancer. 2015;90(1):71–7.
36. Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer. Technology appraisal guidance [TA192]. London: National Institute for Health and Care Excellence; 2010. Available from https://www.nice.org.uk/guidance/ta192, accessed 29 September 2019.
37. Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer. Technology appraisal guidance [TA310] 23 April 2014. London: National Institute for Health and Care Excellence; 2014. Available from https://www.nice.org.uk/guidance/TA310, accessed 29 September 2019.

38. Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer. Technology appraisal guidance [TA258]. London: National Institute for Health and Care Excellence; 2012. Available from https://www.nice.org.uk/guidance/TA258, accessed 29 September 2019.

39. ESMO-Magnitude of Clinical Benefit Scale. The ESMO-MCBS Score Card. Lugano: European Society for Medical Oncology. Available from https://www.esmo.org/score/cards, accessed 29 September 2019.

40. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 2011;12(8):735–42.

41. Fukuoka M, Wu YL, Thongprasert S, Sunpaweravong P, Leong SS, Sriuranpong V et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). J Clin Oncol. 2011;29(21):2866–74.

*Medicines for multiple myeloma – addition – EML*

| | |
|---|---|
| **Bortezomib** | **ATC Code: L01XX32** |
| **Lenalidomide** | **ATC Code: L01AX04** |
| **Thalidomide** | **ATC Code: L04AX02** |

**Proposal**

The application requested the addition of bortezomib, lenalidomide and thalidomide to the EML for the treatment of newly diagnosed multiple myeloma patients in non-transplant settings.

**Applicant**

Dr Vanessa Piechotta, Dr Marius Goldkuhle, Prof Christof Scheid, Dr Nicole Skoetz

**WHO Technical Department**

Comments on the application were received from the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it supported the inclusion of these medicines on the EML. The technical united noted that use of these medicines is either as part of pre-autologous stem cell transplantation treatment in fit patients, or as an alternative treatment in transplant-ineligible patients, although the difference in transplant eligible and ineligible patients was not addressed in the application.

**EML/EMLc**

EML

**Section**

8.2.2 Targeted therapies (bortezomib)
8.2.3 Immunomodulators (lenalidomide, thalidomide)

**Dose form(s) & strengths(s)**

Bortezomib: lyophilized powder for injection 3.5 g
Lenalidomide: capsule 25 mg
Thalidomide: capsule 50 mg

**Core/Complementary**

Complementary

**Individual/Square box listing**

Individual listing for each medicine.

**Background** (if relevant, eg. resubmission, previous EC consideration)

Treatments for multiple myeloma had not previously been considered by the Expert Committee for addition to the EML.

[Abbreviations: M = melphalan, P = prednisone, C = cyclophosphamide, D = dexamethasone, V = bortezomib, R = lenalidomide, T = thalidomide].

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**Public health relevance** (burden of disease)

Multiple myeloma (MM) is the second most common haematological malignancy and accounts for 2.1% of all cancer deaths in the United States (*1*, *2*). In 2018, 159 985 new MM cases and 106 105 MM deaths were estimated worldwide (*3*). Globally, myeloma caused 2.1 million disability-adjusted life-years (DALYs) in 2016 (*4*). Globally, the incidence rate increased by 126% between 1990 and 2016 and is strongly related to age (*4*, *5*). The largest increase has been observed in low- and middle-income countries (LMICs) (*4*). Based on the latest statistics in the United States, the median age of myeloma diagnosis across all races and both genders is 69 years (*2*).

In high-income countries (HIC), autologous stem cell transplantation (ASCT) is routinely used for younger patients with a good general state of health. However, ASCT is not available in many LMICs (*3*). Lack of access to general and specialized health care leads to wide disparities in survival rates between HICs and LMICs. In the United Kingdom, for example, 47% of diagnosed MM patients are predicted to survive at least five years (32.5% at least 10 years) (*5*). In comparison, a five-year survival rate of only 7.6% was recently reported in Nigeria, as a result of constraints in access to ASCT, unavailability of medicines for MM and delayed diagnosis with more advanced presentations and related organ failures (*6*). Of patients diagnosed with MM in Nigeria, up to one-third qualify for renal dialysis as a result of MM-related end-stage nephropathy (*7*).

In non-transplant settings (no transplant-accessibility or transplant-ineligibility), the introduction of immunomodulatory drugs and proteasome inhibitors has led to an improvement in the overall survival of patients. A retrospective analysis of 631 patients, who received an initial therapy of bortezomib, lenalidomide or thalidomide, reported a median OS of 7.3 years (95%CI 5.9 to not reached). In comparison, a median OS of 3.8 years (95%CI 3.1 to 4.6) was reported for 425 patients, whose initial therapy did not include these agents (*8*). The lack of availability ASCT services is more common in LMICs. Some regions of the world lack access to stem cell transplantation entirely; for example, in sub-Saharan Africa there is no facility to deliver ASCT care for MM patients outside of South Africa (*4*). This raises the issue of a public health urgency requiring diversified actions including ensuring access to effective medicines, and building capacity for transplant services. The application focused on the transplant-ineligible/inaccessible setting, more applicable in LMICs, proposing

the inclusion in the EML of bortezomib, lenalidomide and thalidomide to address an unmet medical need.

**Summary of evidence: benefits** (from the application)

The application presented the findings of a rapid Cochrane network meta-analysis conducted to compare the efficacy and safety of bortezomib, lenalidomide and thalidomide versus the former standard treatment of melphalan and prednisone (still used in many LMICs) for transplant-ineligible MM patients. Twenty-six randomized controlled trials (11 403 participants) were eligible for inclusion in the NMA: (Myeloma XI (*9*), EMN01 (*10*), FIRST (*11*), ECOG E1A06 (*12*), MM-015 (*13*), HOVON 87 (*14*), Myeloma IX (*15*), GBRAM0002 (*16*), Kim 2007 (*17*), Ludwig 2009 (*18*), TMSG (*19*), HOVON 49 (*20*), IFM 99-06 (*21*), GISMM2001-A (*22*), MM03 (*23*), IFM 01/01 (*24*), NMSG #12 (*25*), Katsuoka 2013 (*26*), UPFRONT (*27*), VISTA (*28*), GEM2005 (*29*), Mookerje 2017 (*30*), SWOG S0777 (*31*), E1A05 (*32*), GIMEMA-MM-03-05 (*33*), NCT01274403 (*34*)). Included participants were randomized to 21 different treatment regimens involving fixed or continuous therapy with combination regimens involving melphalan (M), prednisone (P), cyclophosphamide (C), dexamethasone (D), bortezomib (V), lenalidomide (R) and thalidomide (T).

Overall survival was measured for all 21 treatment regimens and a total of 11 071 patients. The network was not fully connected and consisted of three sub-networks comprising 30 pairwise comparisons. Compared to MP, four regimens showed a significant, clinically meaningful improvement in overall survival: Continuous VRDc (bortezomib, lenalidomide, dexamethasone) (HR 0.49, 95%CI 0.26 to 0.92), continuous VTMPc (bortezomib, thalidomide, melphalan, prednisone) (HR 0.49, 95%CI 0.26 to 0.93), fixed RD (HR 0.63, 95%CI 0.40 to 0.99), and fixed TMP (thalidomide, melphalan, prednisone) (HR 0.75, 95%CI 0.58 to 0.97). The estimated differences in median OS compared to MP were 37.4 months for VRDc and VTMPc, 21.1 months for RD and 12.0 months for TMP. The confidence in estimates for overall survival could be rated for RD, TMP, VMP, and VRDc. The use of RD, TMP, and VRDc for first-line treatment of multiple myeloma patients likely results in a large increase in overall survival (moderate confidence in estimates). The use of VMP as initial myeloma therapy may result in a large increase in overall survival (low confidence in estimates).

The clinical benefit of the treatments was assessed in the application according to the ESMO-MCBS v1.1 (*35*). The application graded the magnitude of clinical benefit as 4 (survival benefit compared to comparator >nine months (*36*)) for VRDc, VTMPc, RD, RDc, VMP, RCPc and TMP. The Committee noted that to date, the ESMO-MCBS v1.1 has been validated only for solid tumours and that a version validated for haematological malignancies is in development. (Unpublished data of ESMO-MCBS ratings for the proposed medicines were shared with the Expert Committee).

Progression-free survival (PFS) was measured for all 21 treatment regimens and a total of 10 389 patients. The network was not fully connected and consisted of four sub-networks comprising 29 pairwise comparisons. In general, continuous treatment regimens were superior to fixed MP, and 7 out of 11 compared bortezomib, lenalidomide or thalidomide combinations showed a significant improvement of PFS compared to MP. The confidence in estimates for PFS could be rated for RD, TMP, and VRDc, but could not be rated for VMP, because VMP was not connected to MP in the network. The use of RD, TMP, and VRDc for first-line treatment of MM patients likely results in a large increase in PFS (moderate confidence in estimates).

**Summary of evidence: harms** (from the application)

Adverse events of Grade 3 and 4 were reported in nine studies for 13 treatment regimens in 3318 patients, however the studies were not comparable in NMA.

Serious adverse events (SAEs) were reported in eight studies for 14 treatment regimens in 7306 patients. The relative risk (RR) for at least one SAE was similar across treatment regimens. The confidence in estimates could only be rated for VMP. There was moderate confidence in the estimates that VMP likely increases occurrence of SAEs (RR 1.28, 95%CI 1.06 to 1.54).

Infections were reported in 15 studies for 17 treatment regimens in 7470 patients. The RR for infections tended to be slightly higher for patients receiving lenalidomide-based therapies compared to patients receiving thalidomide-based therapies. The RR for infections was also significantly higher in patients receiving continuous therapies compared to fixed MP.

Polyneuropathies were reported in 18 studies for 19 treatment regimens in 8978 patients. The RR for polyneuropathies was the highest in patients receiving bortezomib-based therapies compared to MP (RR 88.22, (95%CI 5.36 to 1451.11) to 441.08 (95%CI 7.74 to 25 145.52)). The RR for polyneuropathy appeared to be smaller for patients receiving lenalidomide-based therapies, compared to patients receiving thalidomide-based therapies.

Thromboembolism was analysed from 13 studies for 13 treatment regimens in 4 277 patients. The RR for thromboembolism was higher for patients receiving continuous therapy compared to fixed duration MP (RR 3.91, (95%CI 0.41 to 37.12) to 13.09 (95%CI 1.03 to 167.25)). Patients receiving a thalidomide-based therapy had a greater risk for thromboembolism compared to patients receiving bortezomib- or lenalidomide-based therapies, or MP.

Withdrawals due to adverse events were reported in 16 studies for 19 treatment regimens in 7 052 patients. The RR to discontinue assigned therapy was greater for patients receiving double or triple drug combinations compared to MP alone (RR 1.06, (95%CI 0.63 to 1.81) to 8.92 (95%CI 3.82 to 20.84)). Study withdrawal was similar across bortezomib-, lenalidomide-, and

thalidomide-based regimens. There was no difference between double versus triple drug combinations, or between fixed duration versus continuous therapy. The confidence in estimates for withdrawals due to AEs was rated for RD, TMP, VMP, and VRDc. Compared to MP, use of RD, TMP, and VRDc results in a large increase in withdrawals due to AEs (high confidence in estimates). Use of VMP probably results in little or no difference in withdrawals due to AEs (moderate confidence in estimates).

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**Additional evidence** (not in the application)

The Committee also considered additional evidence, not presented in the application, for the treatment of MM in the ASCT-eligible/accessible settings.

The standard treatment for ASCT-eligible MM patients involves induction therapy followed by high-dose melphalan and ASCT with lenalidomide maintenance.

A meta-analysis of four studies (1572 patients) compared bortezomib-based induction therapy prior to ASCT with non-bortezomib-based induction therapy. The studies compared bortezomib-dexamethasone with vincristine-doxorubicin-dexamethasone (IFM 2005-01 trial); bortezomib-doxorubicin-dexamethasone with vincristine-doxorubicin-dexamethasone (HOVON-65); and bortezomib-thalidomide-dexamethasone with thalidomide-dexamethasone (PETHEMA GEM05MENOS65 and GIMEMA MM-BO2005). The bortezomib-based therapies were associated with longer PFS (+7.3 months; HR 0.75), longer OS (+5% at 3 years, HR 0.80) and greater activity (complete response rates: +14%, OR 2.05), compared to non-bortezomib-based therapies. Peripheral neuropathy was reported more frequently in bortezomib treated patients compared to non-bortezomib treated patients: 19% vs 7% (all Grade), and 3.3% vs 2% (≥ Grade 3) (*37*).

A randomized controlled trial involving 525 patients with newly-diagnosed MM evaluated the efficacy and safety of the addition of bortezomib to lenalidomide and dexamethasone (SWOG S0777). Findings were consistent with the thalidomide-containing regimens: the addition or bortezomib to lenalidomide-dexamethasone was associated with gains in both PFS (+13 months, HR 0.71) and OS (+11 months, HR 0.71). Adverse events of Grade 3 or higher, and treatment discontinuations were also more common in the bortezomib-treated group (*38*).

The Committee also considered the role of lenalidomide after ASCT, as maintenance up to relapse and maximal tolerance. A meta-analysis of three RCTs (CALGB/Alliance 100104 study, IFM 2005-02 Trial and the Italian GIMEMA RV-MM-PI-209) involving 1208 patients evaluated the effect of lenalidomide maintenance after ASCT in newly diagnosed MM. Lenalidomide maintenance demonstrated a significant gain in both PFS and OS: PFS in

patients receiving lenalidomide was 29.3 months longer (HR 0.48, 95%CI 0.41 to 0.55). The 7-year survival rate was 62% with lenalidomide maintenance and 50% with placebo or observation (HR 0.75, 95%CI 0.63 to 0.90). The use of lenalidomide resulted in more major adverse events than placebo. In particular, an increased risk of secondary malignancies was observed, 6.1% vs 2.8% with placebo/ no maintenance (*39*). The long-term follow-up data of CALGB (Alliance) 100104 study showed a meaningful and significant OS gain in patients receiving lenalidomide maintenance. After three interim analyses, the study was unblinded at a median follow-up of 18 months, at which point 86 (67%) of 128 patients without progressive disease in the placebo group chose to cross over to the lenalidomide group. The analysis of survival on the intention-to-treat population demonstrated an increase in 3-year OS of 8%, with 88% (95%CI 84 to 93) among patients in the lenalidomide group and 80% (95%CI 74 to 86) among patients in the placebo group (HR 0.62, 95%CI 0.40 to 0.95) (*40*).

The Myeloma XI study more recently provided results consistent with the previous clinical trials of lenalidomide maintenance, confirming a gain in median PFS (39 months vs 20 months; HR 0.46, 95%CI 0.41 to 0.53; p<0,0001) but not in OS (78.6% vs 75.8%; p=0,15). The analysis was published at 31 months of median follow up (*41*). Notably, mature data for OS in ASCT-eligible settings require long-term follow up. For this reason, PFS and myeloma response rates have been agreed as valuable surrogate endpoints for OS and PFS is used as primary endpoint to assess the benefit of anti-myeloma medicines (*42*).

**WHO Guidelines**

None available.

**Costs/cost-effectiveness**

The application summarized the findings of a scoping review undertaken for economic evidence that addressed treatment regimens based on bortezomib, thalidomide or lenalidomide as first-line therapy in MM. The scoping review identified two cost-analyses (*43*, *44*), one cost-impact analysis (*45*) and one retrospective study of claims data (*46*). Also identified was a health technology assessment report by the National Institute for Health and Care Excellence (NICE) (*47*).

Reported incremental cost-effective ratios in the NICE technology appraisal ranged from £ 2234 per quality adjusted life year (QALY) to over £ 300 000, compared to MP depending on the intervention (*47*).

A United States cost-analysis found the monthly on-treatment costs (drug cost, medical costs and AE management costs) were lowest for MP alone and highest for MPT. The total cost over 20 years for treatment with VMP and MPT were almost or over twice as high than with MP alone. Compared to VMP,

MP was more effective with regard to costs per life-year and cost per QALY, while compared to MPT, VMP was cost-saving (*44*).

A cost-impact model addressed the total costs associated with first-line treatment of newly diagnosed MM who were ineligible for stem cell transplant in France, Germany, Italy, Spain and the United Kingdom, modelled over five years. Three scenarios were evaluated and compared. A baseline-scenario represented the 2017 uptake of lenalidomide in the assessed countries. The market shares in this scenario were 64% for bortezomib, 25% for thalidomide and 11% for lenalidomide. The second scenario involved a steady increase of the uptake of lenalidomide to 50% of the market in year five. The third scenario evaluated a 20% increased uptake of the triple regimen carfilzomib, lenalidomide, and dexamethasone as a second-line of treatment. Direct drug costs were averaged from the listing prices across the five countries. The assumed annual treatment costs for the baseline scenario ranged between € 40 692 and € 40 781 per patient per year, while the total costs for an increased uptake of lenalidomide ranged between € 41 559 and € 44 139 per patient per year. The difference between both situations rose relatively steady from 2.13% of the total cost of the baseline scenario in year one to 8.23% of the baseline scenario in year five. Across all three scenarios the total treatment cost in the fifth year of treatment were lowest for the baseline scenario. For the increased uptake of lenalidomide in first-line therapy, the annual costs per patient in year five were € 44 139. For the 20% uptake of the triplet regimen as second-line treatment, the total increase in year five in total cost per patient and year was € 52 528 (*45*).

A retrospective study based on United States claims data from 2006 to 2013 assessed patient monthly direct costs and cost patterns over quarterly time periods for patients with newly diagnosed MM treated with either bortezomib or lenalidomide based regimens. Costs were evaluated for 444 patients with newly diagnosed MM treated first-line with lenalidomide and 737 with bortezomib, for which data from treatment initiation until next treatment was available. For patients with first-line treatment with lenalidomide, the monthly treatment cost decreased steadily from US$ 15 090 in the first to the third month since start of treatment to US$ 5266 in month 19 or longer. In patients treated with first-line bortezomib the monthly costs fell from US$ 16 126 in the first three months of treatment to US$ 4833 in the 19th month or longer. Multivariable regression unadjusted for factors such as age, sex, number of prescriptions before index date for the beginning of first-line treatment, previous cancer history, etc. showed mean total cost of US$ 7534 (standard deviation (SD) 3207) for patients treated first-line with lenalidomide, compared to US$ 10 763 (SD 3938) in patients receiving first-line bortezomib. Monthly pharmacy costs included in the total monthly cost in the unadjusted analysis were US$ 4101 (SD 1931) and US$ 4855 (SD 2431) for lenalidomide and bortezomib, respectively (*46*).

**Availability**

Bortezomib, lenalidomide and thalidomide have worldwide regulatory approval for use in the treatment of MM. Originator and generic brands of all three medicines are available.

**Other considerations**

N/A

**Committee recommendations**

The Committee acknowledged the treatment of MM to be complex and recognized the need to provide the best available care within the context of both non-transplant and transplant settings.

The Committee recommended the addition of bortezomib, lenalidomide and thalidomide to the complementary list of the EML for the treatment of multiple myeloma patients in both non-transplant and transplant eligible/available settings, on the basis of good evidence showing large improvement in survival outcomes with acceptable safety for patients with newly diagnosed multiple myeloma.

With regard to MM treatment in transplant-eligible populations, the Committee noted the additional evidence presented as part of the review process supporting standard regimens used in the induction phase before ASCT involving three-drug combinations: VTD (bortezomib, thalidomide, dexamethasone), VCD (bortezomib, cyclophosphamide, dexamethasone), PAD (bortezomib, doxorubicin, dexamethasone) and RVD (lenalidomide, bortezomib, dexamethasone); and of the benefit of lenalidomide maintenance therapy following ASCT.

In the non-transplant setting, the Committee acknowledged that the proposed medicines are administered as part of treatment regimens involving companion cytotoxic agents and/or steroids (melphalan, cyclophosphamide, prednisone, dexamethasone). Accordingly, the Committee recommended the addition of melphalan to the complementary list of the EML for treatment of multiple myeloma, and that the current listings for cyclophosphamide, doxorubicin, prednisone and dexamethasone be extended to include multiple myeloma as an indication.

## References

1. Kazandjian D. Multiple myeloma epidemiology and survival: A unique malignancy. Semin Oncol. 2016;43(6):676–81.
2. Cancer Stat Facts: Myeloma. Bethesda: National Cancer Institute; 2018. Available from: https://seer.cancer.gov/statfacts/html/mulmy.html, accessed 29 September 2019.

3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
4. Cowan AJ, Allen C, Barac A, Basaleem H, Bensenor I, Curado MP et al. Global Burden of Multiple Myeloma: A Systematic Analysis for the Global Burden of Disease Study 2016. JAMA oncology. 2018; 4(9):1221–1227.
5. Myeloma statistics 2018. London: Cancer Research UK; 2018. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma, accessed 29 September 2019.
6. Nwabuko OC, Igbigbi EE, Chukwuonye, II, Nnoli MA. Multiple myeloma in Niger Delta, Nigeria: complications and the outcome of palliative interventions. Cancer Manag Res. 2017;9:189–96.
7. Madu AJ, Ocheni S, Nwagha TA, Ibegbulam OG, Anike US. Multiple myeloma in Nigeria: an insight to the clinical, laboratory features, and outcomes. Niger J Clin Pract. 2014;17(2):212–7.
8. Kumar SK, Dispenzieri A, Lacy MQ, Gertz MA, Buadi FK, Pandey S et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia. 2014;28(5):1122–8.
9. Pawlyn C, Davies F, Cairns D, Striha A, Best P, Sigsworth R et al. Continuous treatment with lenalidomide improves outcomes in newly diagnosed myeloma patients not eligible for autologous stem cell transplant: results of the myeloma xi trial. Blood Conference: 59th annual meeting of the american society of hematology, ASH 2017 United States. 2017;130(Supplement 1).
10. Magarotto V, Bringhen S, Offidani M, Benevolo G, Patriarca F, Mina R et al. Triplet vs doublet lenalidomide-containing regimens for the treatment of elderly patients with newly diagnosed multiple myeloma. Blood. 2016;127(9):1102–8.
11. Bahlis N, Corso A, Mugge L, Shen Z, Desjardins P, Stoppa A et al. Benefit of continuous treatment for responders with newly diagnosed multiple myeloma in the randomized FIRST trial. Leukemia. 2017;31(11):2435–42.
12. Stewart AK, Jacobus S, Fonseca R, Weiss M, Callander NS, Chanan-Khan AA et al. Melphalan, prednisone, and thalidomide vs melphalan, prednisone, and lenalidomide (ECOG E1A06) in untreated multiple myeloma. Blood. 2015;126(11):1294–301.
13. Palumbo A, Hajek R, Delforge M, Kropff M, Petrucci MT, Catalano J et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma.[Erratum appears in N Engl J Med. 2012 Jul 19;367(3):285]. N Engl J Med. 2012;366(19):1759–69.
14. Zweegman S, Holt B, Mellqvist U, Salomo M, Bos G, Levin M et al. Melphalan, prednisone, and lenalidomide versus melphalan, prednisone, and thalidomide in untreated multiple myeloma. Blood. 2016;127(9):1109–16.
15. Morgan G, Davies F, Gregory W, Russell N, Bell S, Szubert A et al. Cyclophosphamide, thalidomide, and dexamethasone (CTD) as initial therapy for patients with multiple myeloma unsuitable for autologous transplantation. Blood. 2011;118(5):1231–8.
16. Hungria V, Crusoe E, Maiolino A, Bittencourt R, Fantl D, Maciel J, et al. Phase 3 trial of three thalidomide-containing regimens in patients with newly diagnosed multiple myeloma not transplant-eligible. Ann Hematol. 2016;95(2):271-8.
17. Kim Y, Lee J, Sohn S, Shin H, Lee S, Shim H et al. Efficacy and safety of thalomide and dexamethasone combination with or without cyclophosphamide in patients with newly diagnosed multiple myeloma. Haematologica. 2007;92(Suppl 1):411–2.

18. Ludwig H, Hajek R, Tothova E, Drach J, Adam Z, Labar B et al. Thalidomide-dexamethasone compared with melphalan-prednisolone in elderly patients with multiple myeloma. Blood. 2009;113(15):3435–42.

19. Beksac M, Haznedar R, Firatli-Tuglular T, Ozdogu H, Aydogdu I, Konuk N et al. Addition of thalidomide to oral melphalan/prednisone in patients with multiple myeloma not eligible for transplantation: results of a randomized trial from the Turkish Myeloma Study Group. Eur J Haematol. 2011; 86(1):16–22.

20. Wijermans P, Schaafsma M, Termorshuizen F, Ammerlaan R, Wittebol S, Sinnige H et al. Phase III study of the value of thalidomide added to melphalan plus prednisone in elderly patients with newly diagnosed multiple myeloma: the HOVON 49 Study. J Clin Oncol. 2010;28(19):3160–6.

21. Facon T, Mary J, Hulin C, Benboubker L, Attal M, Pegourie B et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. Lancet. 2007;370(9594):1209–18.

22. Palumbo A, Bringhen S, Caravita T, Merla E, Capparella V, Callea V et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. Lancet. 2006;367(9513): 825–31.

23. Sacchi S, Marcheselli R, Lazzaro A, Morabito F, Fragasso A, Di Renzo N et al. A randomized trial with melphalan and prednisone versus melphalan and prednisone plus thalidomide in newly diagnosed multiple myeloma patients not eligible for autologous stem cell transplant. Leuk Lymphoma. 2011;52(10):1942–8.

24. Hulin C, Facon T, Rodon P, Pegourie B, Benboubker L, Doyen C, et al. Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. J Clin Oncol. 2009; 27(22):3664–70.

25. Waage A, Gimsing P, Fayers P, Abildgaard N, Ahlberg L, Björkstrand B et al. Melphalan and prednisone plus thalidomide or placebo in elderly patients with multiple myeloma. Blood. 2010;116(9):1405–12.

26. Katsuoka Y, Kato Y, Omoto E, Sasaki O, Kimura H, Meguro K et al. Phase II trial of bortezomib based regimen for transplant-ineligible multiple myeloma-tomato study. Clinical lymphoma, myeloma and leukemia. 2013;13:S148.

27. Niesvizky R, Flinn I, Rifkin R, Gabrail N, Charu V, Clowney B et al. Community-Based Phase IIIB Trial of Three UPFRONT Bortezomib-Based Myeloma Regimens. J Clin Oncol. 2015;33(33):3921–9.

28. San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med. 2008;359(9):906–17.

29. Mateos MV, Oriol A, Martinez-Lopez J, Gutierrez N, Teruel AI, de Paz R et al. Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. Lancet Oncol. 2010;11(10):934–41.

30. Mookerjee A, Gupta R, Jasrotia S, Sahoo R, Kumar R, Thulkar S et al. Bortezomib, lenalidomide and low-dose dexamethasone (VRD) versus lenalidomide and low-dose dexamethasone (LD) for newly-diagnosed multiple myeloma-a randomized phase III study. Blood. 2017;130(Supplement 1).

31. Durie GM, Hoering A, Abidi MH, Rajkumar SV, Epstein J, Kahanic SP et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet. 2017; 389(10068):519–527.
32. Jacobus SJ, Rajkumar SV, Weiss M, Stewart AK, Stadtmauer EA, Callander NS et al. Randomized phase III trial of consolidation therapy with bortezomib-lenalidomide-Dexamethasone (VRd) vs bortezomib-dexamethasone (Vd) for patients with multiple myeloma who have completed a dexamethasone based induction regimen. Blood Cancer J. 2016;6(7):e448.
33. Palumbo A, Bringhen S, Larocca A, Rossi D, Di Raimondo F, Magarotto V et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: updated follow-up and improved survival. J Clin Oncol. 2014;32(7):634–40.
34. A Randomized Study With Oral Melphalan + Prednisone (MP) Versus Melphalan, + Prednisone + Thalidomide (MPT) for Newly Diagnosesd Elderly Patients With Multiple Myeloma [Internet]. Bethesda: National Library of Medicine (ClinicalTrials.gov); 2011. Available from https://clinicaltrials.gov/ct2/show/NCT01274403, accessed 29 September 2019.
35. ESMO-Magnitude of Clinical Benefit Scale. The ESMO-MCBS Score Card [website]. Lugano: European Society for Medical Oncology. (https://www.esmo.org/score/cards, accessed 29 September 2019).
36. ESMO Magnitude of Clinical Benefit Scale v1.1. Form 2a: for therapies that are not likely to be curative with primary endpoint of OS 2018. Lugano: European Society for Medical Oncology. Available from https://www.esmo.org/content/download/117388/2059152/file/ESMO-MCBS-Version-1-1-Evaluation-Form-2a-OS-24-Months.pdf, accessed 29 September 2019.
37. Sonneveld P, Goldschmidt H, Rosinol L, Blade J, Lahuerta JJ, Cavo M et al. Bortezomib-based versus nonbortezomib-based induction treatment before autologous stem-cell transplantation in patients with previously untreated multiple myeloma: a meta-analysis of phase III randomized, controlled trials. J Clin Oncol. 2013;31(26):3279–87.
38. Durie BG, Hoering A, Abidi MH, Rajkumar SV, Epstein J, Kahanic SP et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet. 2017;389(10068):519–27.
39. McCarthy PL, Holstein SA, Petrucci MT, Richardson PG, Hulin C, Tosi P et al. Lenalidomide Maintenance After Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Meta-Analysis. J Clin Oncol. 2017;35(29):3279–89.
40. Holstein SA, Jung SH, Richardson PG, Hofmeister CC, Hurd DD, Hassoun H et al. Updated analysis of CALGB (Alliance) 100104 assessing lenalidomide versus placebo maintenance after single autologous stem-cell transplantation for multiple myeloma: a randomised, double-blind, phase 3 trial. Lancet Haematol. 2017;4(9):e431–e42.
41. Jackson GH, Davies FE, Pawlyn C, Cairns DA, Striha A, Collett C et al. Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (Myeloma XI): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2019;20(1):57–73.
42. Committee for Medicinal Products for Human Use (CHMP). Guideline on the use of minimal residual disease as a clinical endpoint in multiple myeloma studies (EMA/CHMP/459559/2018). Amsterdam: European Medicines Agency; 2018. Available from https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-use-minimal-residual-disease-clinical-endpoint-multiple-myeloma-studies_en.pdf, accessed 29 September 2019.

43. Picot J, Cooper K, Bryant J, Clegg AJ. The clinical effectiveness and cost-effectiveness of bortezomib and thalidomide in combination regimens with an alkylating agent and a corticosteroid for the first-line treatment of multiple myeloma: a systematic review and economic evaluation. Health Technol Assess. 2011;15(41):1–204.

44. Garrison LP, Jr., Wang ST, Huang H, Ba-Mancini A, Shi H, Chen K et al. The cost-effectiveness of initial treatment of multiple myeloma in the U.S. with bortezomib plus melphalan and prednisone versus thalidomide plus melphalan and prednisone or lenalidomide plus melphalan and prednisone with continuous lenalidomide maintenance treatment. Oncologist. 2013;18(1):27–36.

45. Schey S, Montero LFC, Stengel-Tosetti C, Gibson CJ, Dhanasiri S. The Cost Impact of Lenalidomide for Newly Diagnosed Multiple Myeloma in the EU5. Oncol Ther. 2017;5(1):31–40.

46. Arikian SR, Milentijevic D, Binder G, Gibson CJ, Hu XH, Nagarwala Y et al. Patterns of total cost and economic consequences of progression for patients with newly diagnosed multiple myeloma. Curr Med Res Opin. 2015;31(6):1105–15.

47. Bortezomib and thalidomide for the first-line treatment of multiple myeloma. Technology appraisal guidance [TA228]. London: National Institute for Health and Care Excellence; 2011. Available from https://www.nice.org.uk/guidance/ta228

*Anti PD-1/PD-L1 Immune checkpoint inhibitors – addition – EML and EMLc*

| | |
|---|---|
| **Atezolizumab** | **ATC Code: L01XC32** |
| **Nivolumab** | **ATC Code: L01XC17** |
| **Pembrolizumab** | **ATC Code: L01XC18** |

**Proposal**

The application requested the addition of atezolizumab, nivolumab and pembrolizumab to the complementary list of the EML for the following indications:

| | Melanoma | Non-small cell lung cancer |
|---|---|---|
| Atezolizumab | N/A | As second-line therapy in locally advanced or metastatic non-small cell lung carcinoma (NSCLC) after chemotherapy. |
| Nivolumab | Early and advanced stage | As second-line therapy after chemotherapy failure in locally advanced or metastatic NSCLC, regardless of PD-L1 status |
| Pembrolizumab | Early and advanced stage | As first-line therapy in NSCLC expressing PD-L1≥50%, in second-line after chemotherapy failure for NSCLC PD-L1≥1% |

**Applicant**

Jean-Yves Douillard, Chief Medical Officer, European Society for Medical Oncology (ESMO)

**WHO Technical Department**

Comments on the application were received from the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it not support inclusion of these medicines on the EML at this time, though noting with great interest the emerging data on long-term outcomes in this clinically relevant class of medicines.

**EML/EMLc**

EML

**Section**

8.2.3 Immunomodulators

**Dose form(s) & strengths(s)**

Atezolizumab: concentrate solution for infusion 1.2 g/20 mL
Nivolumab: concentrate solution for infusion 10 mg/mL
Pembrolizumab: powder for injection 50 mg

**Core/Complementary**

Complementary

**Individual/Square box listing**

Individual listings requested

**Background** (if relevant, eg. resubmission, previous EC consideration)

Atezolizumab, nivolumab and pembrolizumab belong to the class of PD-1/ PD-L1 immune-checkpoint inhibitors (ICI) and had not previously been considered for inclusion on the EML.

The EML currently includes cytotoxic chemotherapies for NSCLC, but there are no alternative medicines currently on the EML for the treatment of metastatic melanoma.

**Public health relevance** (burden of disease)

Lung cancer is the most diagnosed and the leading cause of death for cancer worldwide, with an estimated 2 million new cases and 1.7 million deaths in 2018 (*1*). Lung cancer is a highly lethal malignancy, with an economic impact estimated around US$ 8 billion productivity lost in the BRICS countries (*2*). Moreover, in the absence of a wide coverage of an effective screening programme in place on global scale, lung cancer diagnoses occur in advanced stage in more than 60% of cases, with highly regional variability (*3–5*). Over 80% of lung cancers are classified as non-small cell lung cancer (NSCLC). Although targeted therapies have redefined the therapeutic landscape for some patients, these therapies are ineffective in patients whose tumours lack the particular genetic mutations/ alterations, constituting the majority of NSCLC patients. For this reason, ICI therapy is becoming part of the treatment of such patients, in an attempt to improve survival and quality of life. The ICIs targets are the immune-competent cells, such as T-lymphocytes and antigen-presenting cells, releasing a tumour-induced immunosuppressant milieu (e.g. PD-1, PD-L1) or strengthening the immune-activating signals of the immune response (e.g. GITR, pro- inflammatory interleukins, interferon-gamma) (*6*). The availability of ICIs in NSCLC addresses an unmet need for patients considered to have a poor prognosis in advanced stages, in the absence of an indication of targeted therapy.

Melanoma is the most lethal form of skin cancer. In 2018, nearly 300 000 new cases were diagnosed worldwide, with over 60 000 deaths (*1*). As a cancer

related to the exposure to sunlight, melanoma demonstrates greater variation in incidence rates across different ethnic groups and is more commonly found among fair-skinned Caucasian populations. Incidence of melanoma peaks at the 7th decade of life; however, though half of the diagnoses are in patients aged between 55 and 74 years, melanoma is the most common cancer diagnosed in adolescents and young adults 20–29 years and the most commonly diagnosed cancers in young adults worldwide (*7*). Early detection and resection of melanoma is the most effective treatment strategy, with a traditionally poor prognosis for metastatic disease (*8*).

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**Summary of evidence: benefits** (from the application)

**NSCLC (first-line)**

***Pembrolizumab***

The Phase III KEYNOTE-024 study evaluated pembrolizumab as first-line treatment in patients with advanced NSCLC showing PD-L1 expression ≥50%, in the absence of epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) translocations (non-oncogene-driven NSCLC) (9). Approximately 30% of screened patients had tumour PD-L1 expression ≥50%. 305 patients were randomized to receive 200 mg pembrolizumab every three weeks (up to two years) or 4-6 cycles of standard platinum-doublet chemotherapy. Patients in the chemotherapy group were permitted to cross over to the pembrolizumab group if they experienced disease progression. In the intention-to-treat population, progression-free survival (PFS) and overall survival (OS) were significantly longer in the pembrolizumab group than the chemotherapy group (PFS: hazard ratio (HR) 0.50, 95%CI 0.37 to 0.68; p<0.001; OS: HR 0.60, 95%CI 0.41 to 0.89; p=0.005). Health-related quality of life measures also favoured pembrolizumab (*10*).

An updated survival report with a 25.2 months median follow up, confirmed the superiority of pembrolizumab over chemotherapy: the HR for OS was 0.63 (95%CI 0.47 to 0.86), with a median OS of 30.0 months (95%CI 18.3–not reached) in the pembrolizumab arm and 14.2 months (95%CI 9.8 to 19.0) in the chemotherapy arm; the Kaplan-Meier estimate of OS at 12 months was 70.3% (95%CI 62.3% to 76.9%) for the pembrolizumab group and 54.8% (95%CI 46.4% to 62.4%) for the chemotherapy group (*11*). Eighty-two patients, allocated to the chemotherapy arm, crossed over to receive pembrolizumab upon meeting eligibility criteria. In term of magnitude of benefit, pembrolizumab provided a gain of median OS of +15.8 months and +15.5% at one year.

Based on the KEYNOTE-024 trial results, the clinical benefit of pembrolizumab in the first-line setting measured with the European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 received a score of 4 (*12*).

The first-line use of pembrolizumab was investigated in NSCLC other than PD-L1>50%, to assess if the benefit was conserved in unselected populations of patients. The Phase III KEYNOTE-042 trial randomized patients with NSCLC EGFR/ALK wild type showing PD-L1≥1%, both adenocarcinoma and squamous NSCLC, to receive either pembrolizumab 200 mg every three weeks or standard chemotherapy (paclitaxel plus carboplatin or pemetrexed plus carboplatin), stratifying per PD-L1 expression at three thresholds of PD-L1: ≥50%, ≥20% and ≥1% (13). 1274 patients were randomized: 637 to each arm. 599 patients (47.0%) had PD-L1 ≥50%, 818 (64.2%) had ≥20%. Pembrolizumab improved OS in NSCLC patients with PD-L1≥50% (HR 0.69, 95%CI 0.56 to 0.85), consistent with the results of Keynote-024 for the PD-L1 enriched population. The median OS (up to approximately 38 months) with the PD-L1 inhibitor was 20.0 months vs 12.2 months with chemotherapy. The HR for OS was 0.77 (95%CI 0.64 to 0.92) and 0.81 (95%CI 0.71 to 0.93) for PD-L1 ≥20% and ≥1%, respectively. In patients with limited expression of PD-L1 (1–49%) the stratified analysis of survival showed that OS reached 17.7 vs 13.0 months in PD-L1 ≥20% and 16.7 and 12.1 in PD-L1 ≥1%, respectively in these sub-populations. However, an exploratory analysis of KEYNOTE-042 showed that the survival advantage associated with pembrolizumab vs chemotherapy in patients with a tumour proportion score between 1% to 49% was not relevant (median OS: 13.4 vs 12.1 months; HR 0.92, 95%CI 0.77 to 1.11). The overall benefit might be driven by the enriched population with high expression of PD-L1 as the preponderance of the OS benefit was seen in patients with ≥50%, the only sub-group gaining more than six months overall survival.

**NSCLC (second-line)**

***Pembrolizumab***

The KEYNOTE-010 trial randomized 1034 patients with previously-treated squamous (22% of the population) and non-squamous (70%) NSCLC with PD-L1 expression of at least 1% of tumour cells to receive pembrolizumab (2 mg/kg or 10 mg/kg, every three weeks) or docetaxel 75 mg/m² every three weeks (*14*). Approximately two thirds of NSCLC patients screened met the PD-L1 threshold of 1%, and 28% showed high expression (≥50%), consistent with previous findings in Keynote-024. Patients were stratified in PD-L1 1–49% and PD-L1 ≥50%. OS was longer for pembrolizumab versus docetaxel (2 mg/kg, HR 0.71, 95%CI 0.58 to 0.88; 10 mg/kg, HR 0.61, 95%CI 0.49 to 0.75). Median overall survival was 10.4 months (95%CI 9.4 to 11.9) for the pembrolizumab 2 mg/kg group, 12.7 months (10.0 to 17.3) for the pembrolizumab 10 mg/kg group, and 8.5 months (95%CI 7.5 to 9.8) for the docetaxel group. One-year overall survival was 43.2% vs 52.3% vs 34.6%.

Based on the KEYNOTE-010 trial results, the clinical benefit of pembrolizumab in the second-line setting measured with the ESMO-MCBS v1.1 was scored at 5/5 (*12*).

In patients with a PD-L1 tumour proportion score of ≥ 50%, the greatest benefit was observed for OS for pembrolizumab 2 mg/kg vs docetaxel with HR 0.54 (95%CI 0.38 to 0.77; p=0.0002), and for pembrolizumab 10 mg/kg vs docetaxel HR 0.50 (95%CI 0.36 to 0.70; p<0.0001). Median OS was 14.9 months and 17.3 months for the 2 mg/kg and 10 mg/kg arms respectively, longer than the chemotherapy arm (8.2 months). After the primary analysis, crossover from docetaxel to pembrolizumab was allowed. 36 months overall survival rate was 23% for the pembrolizumab groups (pooling the two dose arms) vs 11% for docetaxel (*15*).

### *Nivolumab*

The role of nivolumab as second-line treatment of NSCLC has been investigated two Phase III clinical trials: CheckMate-017 and CheckMate-057. In CheckMate-017, 272 patients with squamous NSCLC were randomized to receive nivolumab 3 mg/kg every two weeks, or docetaxel, at a dose of 75 mg/m² every three weeks (*16*). The median OS was 9.2 months (95%CI 7.3 to 13.3) in the nivolumab group vs 6.0 months (95%CI 5.1 to 7.3) in the docetaxel group. The OS rate at one year was 42% (95%CI 34 to 50) in the nivolumab group vs 24% (95%CI 17 to 31) in the docetaxel group. OS was improved in those who received nivolumab (HR 0.59, 95%CI 0.44 to 0.79, p<0.001). The rate of confirmed objective response was higher with nivolumab than with docetaxel (20%, 95%CI 14 to 28 vs 9%, 95%CI 5 to 15), p=0.008). The median PFS was 3.5 months (95%CI 2.1 to 4.9) in the nivolumab group and 2.8 months (95%CI 2.1 to 3.5) in the docetaxel group, consistent with the mechanism of action of ICIs, where atypical patterns of response are described (pseudo progression) and long-lasting post-progression benefit persisting (*17*). The level of PD-L1 expression was neither prognostic nor predictive of any of the efficacy endpoints.

Based on the CheckMate-017 trial results, the clinical benefit of nivolumab in the second-line setting in squamous cell NSCLC measured with the ESMO-MCBS v1.1 was scored at 5/5 (*12*).

In CheckMate-057, 582 patients with non-squamous NSCLC (e.g. adenocarcinoma) were randomized to nivolumab or docetaxel (*18*). Nivolumab improved OS compared to docetaxel: at the time of interim analysis, median OS was 12.2 months (95%CI 9.7 to 15.0) for nivolumab and 9.4 months (95%CI 8.1 to 10.7) for docetaxel, with a HR of 0.73 (95%CI 0.59 to 0.89; p=0.002). One-year OS rates were 51% (95%CI 45 to 56) and 39% (95%CI 33 to 45) for nivolumab and docetaxel, respectively. The survival HRs per sub-group

analysis did not favour nivolumab over docetaxel in the EGFR-mutated NSCLC population (oncogene-driven disease, HR 1.18) (*19*). Moreover, the EGFR wild-type populations seemed to derive the greatest benefit, with HR 0.66 (95%CI 0.51 to 0.86).

Based on the CheckMate-057 trial results, the clinical benefit of nivolumab in the second-line setting in non-squamous cell NSCLC measured with the ESMO-MCBS v1.1 was scored at 5/5 (*12*).

In an updated analysis of CheckMate-017 and CheckMate-057, pooled two-year OS favoured nivolumab in both squamous and non-squamous NSCLC (squamous: 29%, 95%CI 24% to 34% vs 16%, 95%CI 12% to 20%; non-squamous: 23%, 95%CI 16% to 30% vs 8%, 95%CI 4% to 13%) (*20*). In the pooled analysis of OS in the intention-to-treat population (n = 854) with squamous (n = 272 (31.9%)) and non-squamous (n = 582 (68.1%)) NSCLC, median OS was 11.1 months (95%CI 9.2 to 13.1 months) with nivolumab vs 8.1 months (95%CI 7.2 to 9.2 months) with docetaxel (HR 0.72, 95%CI 0.62 to 0.84). Higher PD-L1 expression levels were associated with greater OS benefit with nivolumab (HR 0.42, 95%CI 0.28 to 0.63) in patients with ≥50% PD-L1 expression, but a benefit was still observed in patients with <1% PD-L1 expression (HR 0.78, 95%CI 0.61 to 0.99). Among nivolumab-treated patients, 37% of confirmed responders with squamous NSCLC and 34% with non-squamous NSCLC had ongoing responses after two years' minimum follow up and no patient in docetaxel group had an ongoing response. Consistent with the primary analyses, two-year OS benefit with nivolumab versus docetaxel was observed in patients with squamous NSCLC regardless of PD-L1 expression level. However, in patients with non-squamous NSCLC, higher levels of PD-L1 were associated with a greater magnitude of OS benefit with nivolumab. NSCLC with PD-L1<1% still derived greater benefit from ICI than chemotherapy: in patients with ≥50% PD-L1 expression, the HR for OS on the basis of two years' minimum follow-up was 0.38 (95%CI 0.24 to 0.60) for patients with non-squamous NSCLC.

#### *Atezolizumab*

The Phase III OAK trial randomized 850 immuno-oncology naive patients with advanced squamous and non-squamous NSCLC previously treated with one or two lines of chemotherapy to receive atezolizumab 1200 mg fixed dose every three weeks or standard docetaxel 75 mg/m² every three weeks (*21*). Treatment was administered until unacceptable toxicity or disease progression. Atezolizumab could be continued beyond disease progression if clinical benefit was demonstrated despite evidence of radiological disease progression on computerized tomography (CT) scan, to rule out atypical pattern of response (i.e. pseudo progression). No crossover to atezolizumab was allowed. Patients were stratified by PD-L1 expression. OS was improved in the ITT study population

with atezolizumab, reaching a median OS of 13.8 months (95%CI 11.8 to 15.7) vs docetaxel (9.6 months, 95%CI 8.6 to 11.2), with HR 0.73 (95%CI 0.62 to 0.87, p=0.0003).

Based on the OAK trial results, the clinical benefit of atezolizumab in the second-line setting measured with the ESMO-MCBS v1.1 was scored at 5/5 (12).

Sub-group analysis showed a greater magnitude of benefit in patients with higher PD-L1 expression, both assessed on tumour cells (TC) or immune-infiltrating cells (IC): the net benefit gain in TC1/2/3 or IC1/2/3 population was +5.4 months (HR 0.74, 95%CI 0.58 to 0.93, p=0.0102) and +5.5 months in TC2/3 or IC2/3 population (HR 0.67, 95%CI 0.49 to 0.90, p=0.0080).

### Metastatic melanoma

#### *Pembrolizumab*

The role of pembrolizumab was investigated in randomized trials and cohort studies for metastatic or unresectable locally-advanced melanoma as monotherapy, both in BRAF-mutated and wild-type tumours.

The Phase I Keynote-001 trial evaluated pembrolizumab 2 mg/kg and 10 mg/kg every two weeks in patients with advanced melanoma (*22*). Around one third of the population was pre-treated with ipilimumab. The overall response rate during receipt of therapy, across all doses, based on assessment by the investigator according to immune-related response criteria was 38%. An updated analysis showed an estimated five-year OS rate of 34% in all patients enrolled (pre-treated with chemotherapy, targeted agents or ipilimumab) and 41% in treatment-naive patients (*23*). Median OS was 23.8 months (95%CI 20.2 to 30.4) and 38.6 months (95%CI 27.2–not reached) in pre-treated and treatment-naive patients, respectively with a five-year PFS rates of 21% and 29%.

The Phase II Keynote-002 trial assessed the efficacy and safety of pembrolizumab 2 mg/kg or 10 mg/kg every three weeks vs investigator-choice chemotherapy (paclitaxel plus carboplatin, paclitaxel, carboplatin, dacarbazine, or oral temozolomide) in patients with ipilimumab-refractory melanoma (1:1 randomization, n=540 patients) (*24*, *25*). Median OS was 13.4 months for 2 mg/kg, 14.7 months for 10 mg/kg, and 11.0 months for chemotherapy. 18-months OS rates were 40%, 44%, and 36%; 24-months rates were 36%, 38%, and 30%. HR for OS was 0.86 (95%CI 0.67 to 1.10) for 2 mg/kg and 0.74 (95%CI 0.57 to 0.96) for 10 mg/kg, with no difference between doses (0.87, 95%CI 0.67 to 1.12). The benefit was consistent across the sub-groups, of age (younger or older than 65 years), plasma lactate dehydrogenase (LDH) normal or elevated, sex and BRAF status (mutant or wild-type).

Based on the Keynote-002 trial results, the clinical benefit of pembrolizumab for melanoma in the second-line setting measured with the ESMO-MCBS v1.1 was scored at 3/5 (*12*).

The Phase III Keynote 006 trial assessed pembrolizumab (10 mg/kg every two weeks or every three weeks) as first-line therapy for advanced melanoma, versus ipilimumab (3 mg/kg), the standard of care at the time of the investigation (*26*, *27*). Median OS was not reached in either pembrolizumab group and was 16.0 months with ipilimumab (HR 0.68, 95%CI 0.53 to 0.87 for pembrolizumab every two weeks vs ipilimumab and 0.68, 95%CI 0.53 to 0.86 for pembrolizumab every 3 weeks vs ipilimumab). 24-month OS rate was 55% in the two- and three-week group, and 43% in the ipilimumab group, showing limited differences between pembrolizumab dosing schedules.

### *Nivolumab*

The CheckMate 037 trial assessed the efficacy and safety of nivolumab (3 mg/kg every two weeks) in ipilimumab-progressing patients, compared with standard chemotherapy (dacarbazine, paclitaxel combined with carboplatin every three weeks) (*28*). Confirmed objective responses were reported in 31.7% (95%CI 23.5 to 40.8) in the nivolumab group versus 10.6% (95%CI 3.5 to 23.1) in the chemotherapy arm. However overall survival did not differ between arms, being 15.74 (12.88 to 19.88) in the nivolumab group and 14.39 (11.66 to 18.17) in the investigator's choice group (HR 0.95, 95%CI 0.73 to 1.24) (*29*).

CheckMate 066 tested nivolumab first-line versus dacarbazine, showing a gain in OS of 73% vs 42% at 1 year (*30*, *31*). Response rates also favoured nivolumab, 40% vs 14%. Three-year OS survival rates were 51.2% (95%CI 44.1% to 57.9%) and 21.6% (95%CI 16.1% to 27.6%), respectively. The median OS was 37.5 months (95%CI 25.5 months to not reached) in the nivolumab group and 11.2 months (95%CI 9.6 to 13.0 months) in the dacarbazine group (HR 0.46, 95%CI 0.36 to 0.59), with a net benefit of OS of +26.3 months.

CheckMate 067 tested the combination treatment of the two ICIs nivolumab and ipilimumab against nivolumab monotherapy and ipilimumab alone in a 1:1:1 ratio (32, 33). Median PFS was 11.5 months (95%CI 8.9 to 16.7) with nivolumab plus ipilimumab, compared with 2.9 months (95%CI 2.8 to 3.4) with ipilimumab (HR 0.42; 99.5% CI, 0.31 to 0.57) and 6.9 months (95%CI 4.3 to 9.5) with nivolumab (HR for the comparison with ipilimumab, 0.57, 99.5%CI 0.43 to 0.76, $p<0.001$). A subgroup analysis according to PD-L1 expression was performed. Patients with tumours positive for PD-L1, achieved a median PFS of 14.0 months in the nivolumab-plus-ipilimumab group and in the nivolumab group, but in patients with PD-L1–negative tumours, PFS was longer with the combination therapy than with nivolumab alone (11.2 months (95%CI 8.0 to not reached) vs 5.3 months (95%CI 2.8 to 7.1)). The four-year follow-up updated results confirmed the earlier findings: median OS was not reached (95%CI 38.2 to not reached) in the nivolumab plus ipilimumab group, 36.9 months (95%CI 28.3 to not reached) in the nivolumab group, and 19.9 months (95%CI 16.9 to 24.6) in the ipilimumab group. The results of sub-group analyses suggested that

the greatest benefit with the combination of nivolumab and ipilimumab versus nivolumab alone may occur in the context of negative PD-L1 tumour expression. In the subgroup of patients with PD-L1–positive tumours, both nivolumab alone and nivolumab plus ipilimumab resulted in a similar prolongation of PFS compared to ipilimumab alone. This finding suggested the role of immunotherapy as monotherapy in "inflamed tumours", showing high expression of PD-L1 and a role of combination therapy for "non-inflamed" tumours, for which the combination ICI could derive a major benefit, acting synergistically on different steps of immune activation.

The clinical benefit of nivolumab for first-line treatment of metastatic melanoma measured with the ESMO-MCBS v1.1 was scored at 4/5 (*12*).

#### Early stage (resected) melanoma

The discussion around the role of immunotherapy in the adjuvant setting of melanoma is ongoing, with data of OS expected to confirm the optimal strategy of care, particularly between the ipilimumab and the PD-1 blockers, including the safety profile.

##### *Pembrolizumab*

Pembrolizumab was assessed as an adjuvant agent in the Phase III Keynote 054 trial, for patients with stage III resected melanoma. Patients were randomized to receive pembrolizumab 200 mg every three weeks for 18 doses or placebo (n=1019) (*34*). Pembrolizumab showed a superior relapse-free survival rate, from 61% to 75.4% at 12 months (HR 0.57, 95%CI 0.43 to 0.74); the data were consisted across the PD-L1 pre-specified sub-groups.

##### *Nivolumab*

The CheckMate-238 trial compared high-dose ipilimumab versus nivolumab 3 mg/kg every two weeks up to 12 months (35). Patients with resected stage III and IV, with no evidence of disease (NED) derived major benefit from nivolumab: relapse-free survival at 12 months was 70.5% and 60.8%, respectively (HR 0.65, 95%CI 0.51 to 0.83). At 24-months follow-up, nivolumab was shown to be superior with +13% of relapse-free survival (*35*, *36*). The benefit was consistent across the sub-groups of PD-L1 expression, in PD-L1 less than 5% or 5% and more.

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**Summary of evidence: harms** (from the application)

#### NSCLC first-line

##### *Pembrolizumab*

In Keynote 024, treatment-related adverse events (TRAE) occurred in 73.4% of the patients in the pembrolizumab group and in 90.0% of the patients in the chemotherapy group, of which 53.3% vs 26.6% were Grade 3 (moderate-severe)

to Grade 5 (toxic death) in the chemotherapy and pembrolizumab groups, respectively. The treatment discontinuation rate was slightly higher in the chemotherapy arm (10.7%) than the ICI arm (7.1%) due to these TRAEs (*9*). TRAEs for pembrolizumab were consistent with an immune-mediated process, meaning an autoimmune event or an immune-activation syndrome, the most common being hypo- and hyper-thyroidism (9% and 8%, all Grade 1 and 2, non-severe events not leading to discontinuation of therapy and registered as laboratory transient and not clinically relevant alterations of plasma thyroid hormones), diarrhoea (in 14.3% of the patients), fatigue (10.4%), and pyrexia (10.4%) in the pembrolizumab group; for chemotherapy, the bone marrow toxicity (anaemia in 44.0%) and traditional systemic TRAEs were observed (nausea in 43.3% and fatigue in 28.7%); anti-emetic pre-medication was allowed per protocol, consistent with institutional and international guidelines for moderately to highly-emetogenic platinum-containing CT regimens in the standard of care arm.

In Keynote 042, despite a longer duration of treatment exposure, Grades 3 to 5 TRAEs occurred much less often with pembrolizumab than with chemotherapy (17.8% vs 41.0%) (*13*). Grades 3 to 5 immune-related adverse events and infusion reactions occurred more frequently among patients treated with pembrolizumab than with chemotherapy (8.0% vs 1.5%). The respective rates of treatment discontinuation (9.0% vs 9.4%) and treatment-related deaths (2.0% vs 2.3%) were comparable between treatment arms.

#### NSCLC second-line

##### *Pembrolizumab*

In the Keynote-010 trial the safety profile favoured pembrolizumab with less Grade 3–5 adverse events, namely 16% vs 35% in the chemotherapy arm, and decreased appetite (14%) and fatigue (14%) for ICI and neutropenia (14%), alopecia (33%), anaemia (13%) and oral mucositis (14%) for chemotherapy (*14*). There was no difference in the efficacy or safety of pembrolizumab at 2 or 10 mg/kg.

##### *Nivolumab*

In the CheckMate-017, treatment-related adverse events, including haematologic and non-haematologic events, occurred less frequently with nivolumab than with docetaxel. In the nivolumab group, 58% of the patients had events of any Grade, of which 7% were Grade 3 or 4; in the docetaxel group, this occurred in 86% of the patients of which 55% were Grade 3 or 4 (*16*). The safety profile was consistent with the class side-effects, with no new signals of safety, namely the most frequently reported TRAEs with nivolumab were fatigue and asthenia and for docetaxel were neutropenia (33%; 10% febrile neutropenia), fatigue (33%), alopecia (22%), nausea (23%) and peripheral neuropathy (11%). Respectively

3% and 10% of patients discontinued the treatment for an adverse event in the ICI and CT arm.

In the CheckMate-057, the safety profile and pattern of adverse events in non-squamous NSCLC patients were consistent with the data from squamous population: treatment-related adverse events were observed in 69%/10%/5% in nivolumab arm and 88%/54%/15% in docetaxel arm for any Grade/Grade 3-4/ discontinuation rate, respectively (*18*).

#### *Atezolizumab*

In the Phase III OAK trial, tolerability was better with atezolizumab, with 15% of 609 patients treated with atezolizumab experiencing a Grade 3–4 treatment-related toxicity compared with 43% of 578 patients treated with docetaxel (*21*). Fatigue (87 patients (14%)), nausea (53 patients (9%)), decreased appetite (52 patients (9%)), and asthenia (51 patients (8%)) were the most common atezolizumab-related adverse events of any grade.

### Metastatic melanoma

#### *Pembrolizumab*

Safety analysis showed a higher incidence of Grade 3–4 TRAEs in patients receiving chemotherapy (26%) vs pembrolizumab (11% in the 2mg/kg group, 14% in the 10 mg/kg group) (*24*). The most common serious TRAEs observed in the combined pembrolizumab treatment groups were diarrhoea and pneumonitis. There were no treatment-related deaths. Treatment interruption as a result of TRAEs was needed in 15 (8%) of 178 patients treated with pembrolizumab 2 mg/kg, 15 (8%) of 179 patients treated with pembrolizumab 10 mg/kg, and 30 (18%) of 171 patients treated with chemotherapy. TRAEs led to permanent treatment discontinuation in five (3%) patients given pembrolizumab 2 mg/kg, 12 (7%) given pembrolizumab 10 mg/kg, and 10 (6%) patients given chemotherapy.

In the Keynote 006 trial, around two thirds of the study population experienced a TRAE; however, Grade 3 to 5 adverse events that were attributed to a study drug by investigators occurred in 13.3% of patients receiving pembrolizumab every two weeks, 10.1%, every three weeks and 19.9% of patients receiving ipilimumab, respectively, with a safety profile favourable of the PD-1 blocker over CTLA-4 inhibitor (*26*). The rate of permanent discontinuation of a study drug because of TRAEs was lower in each pembrolizumab group than in the ipilimumab group (4.0%, 6.9%, and 9.4%, respectively).

#### *Nivolumab*

In the CheckMate 066 trial, treatment-related Grade 3/4 adverse events occurred in 15.0% (31 of 206) of nivolumab-treated patients and in 17.6% (36 of 205) of dacarbazine-treated patients (*30*, *31*).

In the CheckMate 238 trial, nivolumab showed a major tolerability and better safety profile with 14.4%/9.7% Grade 3 and 4 adverse events/treatment-related discontinuation, compared with 45.6%/42.6% in the ipilimumab arm (*32*, *33*).

#### Early stage (resected) melanoma

No data were presented in the application regarding the safety of immune checkpoint inhibitors for melanoma in the early/resected stage setting.

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**Additional evidence** (not in the application)

N/A

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**WHO Guidelines**

None available.

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**Costs/cost-effectiveness**

#### NSCLC

The application presented a cost-effectiveness analysis of first-line pembrolizumab in advanced non-oncogene driven NSCLC expressing high levels of PD-L1 (*37*). Data of safety and efficacy were derived from the Keynote 024 trial (*13*). The analysis was conducted from the perspective of a United States third-party public health care payer (updated to US$, year 2016 values). Pembrolizumab would be expected to result in an incremental cost of US$ 98 281 per quality adjusted life year (QALY) gained or an incremental cost of US$ 78 873 per life year (LY) gained. Including cost of PD-L1 testing had a very small impact on the model results. With a five-year time horizon, the ICER was US$ 99 998/LY and US$ 122 024/QALY; with a 10-year time horizon, the ICER was US$ 83 065 and US$ 103 101/QALY. Base-case results indicated that, compared with standard of care over a 20-year time horizon, pembrolizumab would be expected to result in an additional 1.31 LYs and an additional 1.05 QALYs gained.

In the second-line setting, a cost-effectiveness analysis was presented for pembrolizumab versus docetaxel in the enriched population with PD-L1>50%. Base case results for PD-L1 positive (TPS ≥50%) patients treated with pembrolizumab showed a mean survival of 2.25 years (*38*). For docetaxel, a mean survival time of 1.07 years was estimated. Expected QALYs were 1.71 and 0.76 for pembrolizumab and docetaxel, respectively. The incremental cost per QALY gained with pembrolizumab vs docetaxel is US$ 168 619/QALY, which is cost-effective in the United States using a threshold of three times GDP per capita.

#### Melanoma

The cost-effectiveness of nivolumab for the treatment of advanced melanoma patients has been investigated in the United Kingdom. A Markov state-transition

model was developed to estimate the lifetime costs and benefits of nivolumab versus ipilimumab and dacarbazine for BRAF mutation-negative patients and versus ipilimumab, dabrafenib, and vemurafenib for BRAF mutation-positive patients (*39*). Nivolumab was the most cost-effective treatment option in BRAF mutation-negative and mutation-positive patients, with incremental cost-effectiveness ratios of £ 24 483 and £ 17 362 per QALY, respectively. A similar analysis was performed for pembrolizumab in advanced melanoma in Portugal (*40*). A cost-effectiveness model was developed to analyse the costs and consequences of treatment with pembrolizumab compared to treatment with ipilimumab in patients with advanced melanoma not previously treated with ipilimumab. Pembrolizumab increased life expectancy in 1.57 undiscounted life-years (LYs) and was associated with an increase in costs versus that of ipilimumab. The estimated incremental cost-effectiveness ratio was € 47 221 per QALY and € 42 956 per LY. The authors concluded that considering the usually accepted thresholds in oncology, pembrolizumab is a cost-effective alternative for treating patients with advanced melanoma in Portugal.

**Availability**

Atezolizumab (trade name Tecentriq, Genetech Inc.) is available as a 60 mg/mL injection solution for intravenous use as 840 mg/14 mL and 1,200 mg/20 mL single-dose vials.

Nivolumab (trade name Opdivo, Bristol-Myers Squibb) is available as a 10 mg/mL injection solution for intravenous use as 40 mg/4 mL, 100 mg/10 mL and 240 mg/24 mL single-dose vials.

Pembrolizumab (trade name Keytruda, Merck Sharp & Dohme) is available as 50 mg lyophyilized powder for intravenous injection and as a 25 mg/mL injection solution for intravenous use as 100 mg/4mL single-dose vial.

**Other considerations**

As a result of the Keynote-024 trial, pembrolizumab was approved by the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) as first-line therapy for patients with NSCLC with high PD-L1 expression (PD-L1≥50%) as assessed by immunohistochemistry. In the approval trial, the PD-L1 expression was assessed in FFPE tumour samples at a central laboratory with the use of the commercially available PD-L1 IHC 22C3 pharmDx assay (Dako) on histology specimens. However, the assessment of PD-L1 IHC of cytology cell-block was as reliable as the histology assessment, in independent assessments (*20–22*). The PD-L1 IHC 22C3 pharmDx assay is the companion diagnostic of pembrolizumab first-line with the threshold of "high expression" PD-L1 tumour proportion score of ≥50%. This finding is clinically relevant since the collection of a histology sample may be challenging in lung cancer diagnosis, particularly when bronchoscopy with fine-needle aspirations is used. In detail,

cell block cytology is a technique used in cytopathology (in addition to smears) for evaluation of tissue from fine needle aspirations or fluid aspiration for which the cells in solution are then concentrated via centrifuge from cytological specimens into paraffin blocks that can be cut and stained by the same methods used for histopathology. Based on this evidence, the use of the cell-block is considered as a reliable specimen to assess the PD-L1 status, reducing the need of more invasive procedures and increasing the likelihood to have an informative specimen in term of prediction to treatment response with few cytology materials.

Pembrolizumab as monotherapy is indicated in the first-line treatment of advanced EGFR and ALK wild type NSCLC showing PD-L1 hyperexpression i.e. PD-L1≥50% and for the second-line treatment of advanced NSCLC with a PD-L1 tumour expression ≥1% after platinum-containing chemotherapy failure, and in association with chemotherapy for the first-line treatment of NSCLC, regardless of PD-L1 status. Moreover, pembrolizumab is indicated for the first-line treatment of metastatic melanoma, with no biomarker for patients' selection. Patients are treated with pembrolizumab until disease progression or unacceptable toxicity.

**Committee recommendations**

The Committee endorsed the recommendations of the EML Cancer Medicine Working Group with regard to the proposed threshold of four to six months of overall survival benefit as a guiding principle for prioritizing cancer medicines for inclusion on the EML, and applied this principle to the consideration of the immune checkpoint inhibitors.

The Committee noted that there were no treatment options for metastatic melanoma currently included on the Model List. The Committee recommended the addition of nivolumab and pembrolizumab to the complementary list of the EML, for use as first-line monotherapy for treatment of patients with unresectable and metastatic melanoma on the basis of evidence of significantly increased overall survival for patients that met the recommended threshold for benefit, and in the absence of other EML-listed treatment options. Listing should be for nivolumab with a square box indicating pembrolizumab as a therapeutically equivalent alternative. The Committee noted that nivolumab was scored as 4/5 on the ESMO-MCBS v1.1 for this indication.

The Committee considered that more mature data would be necessary before listing of these medicines could be considered for use in adjuvant indications of radically resected melanoma.

The Committee did not recommend listing of atezolizumab, nivolumab or pembrolizumab for treatment of patients with metastatic NSCLC at this time, as the Committee considered that their precise place in the treatment/immunotherapy of this condition is still evolving. The Committee noted the

evidence of efficacy in the treatment of patients with metastatic NSCLC with these agents. The Committee observed that the duration of follow up of the single studies for first-line and second-line immunotherapy in trials for lung cancer was generally shorter than three years, and considered that data from longer follow up would better capture the actual magnitude of benefit. By the time of the next Committee meeting in 2021, more mature data will be available for metastatic NSCLC and also for use of these agents in locally advanced non-resectable disease, and as adjuvant therapy.

Furthermore, the Committee noted that the landscape of clinical development of cancer immunotherapy still has some areas of uncertainty with regard to the optimal time for introduction of treatment (first- or second-line), appropriate patient selection, and whether or not use of ICIs in combination with other medicines is superior.

The Committee expressed concern about the potential budget impact of oncology medicines, which could be an impediment to access, and countries may not be able to list these medicines on their national EMLs. Therefore, the Committee recommended that WHO engage stakeholders to find ways to facilitate better access and affordability as a high priority through avenues such as the Medicines Patent Pool, WHO prequalification and collaborative registration procedures. The Committee also recommended ongoing activities of the EML Cancer Medicines Working Group to include identification of obstacles to access and affordability of cancer medicines, and pricing data collection.

## References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68(6):394–424.
2. Pearce A, Sharp L, Hanly P, Barchuk A, Bray F, de Camargo Cancela M et al. Productivity losses due to premature mortality from cancer in Brazil, Russia, India, China, and South Africa (BRICS): A population-based comparison. Cancer Epidemiol. 2018;53:27–34.
3. Walters S, Maringe C, Coleman MP, Peake MD, Butler J, Young N et al. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004-2007. Thorax. 2013;68(6):551–64.
4. Gaafar R. SC17.05 Lung Cancer in Africa: Challenges and Perspectives. J Thorac Oncol. 2017;12(1):S115–S6.
5. Parikh PM, Ranade AA, Govind B, Ghadyalpatil N, Singh R, Bharath R et al. Lung cancer in India: Current status and promising strategies. South Asian J Cancer. 2016;5(3):93–5.
6. Park YJ, Kuen DS, Chung Y. Future prospects of immune checkpoint blockade in cancer: from response prediction to overcoming resistance. Exp Mol Med. 2018;50(8):109.
7. Matthews NH, Li WQ, Qureshi AA, Weinstock MA, Cho E. Epidemiology of Melanoma. In: Ward WH, Farma JM, editors. Cutaneous Melanoma: Etiology and Therapy. Brisbane: Codon Publications; 2017.

8. Dickson PV, Gershenwald JE. Staging and prognosis of cutaneous melanoma. Surg Oncol Clin N Am. 2011;20(1):1–17.
9. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016;375(19): 1823–33.
10. Brahmer JR, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A et al. Health-related quality-of-life results for pembrolizumab versus chemotherapy in advanced, PD-L1-positive NSCLC (KEYNOTE-024): a multicentre, international, randomised, open-label phase 3 trial. Lancet Oncol. 2017;18(12):1600–9.
11. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A et al. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. J Clin Oncol. 2019:Jco1800149.
12. ESMO-Magnitude of Clinical Benefit Scale. The ESMO-MCBS Score Card [website]. Lugano: European Society for Medical Oncology. (https://www.esmo.org/score/cards, accessed 29 September 2019).
13. Lopes G, Wu Y-L, Kudaba I, Kowalski D, Cho BC, Castro G et al. Pembrolizumab (pembro) versus platinum-based chemotherapy (chemo) as first-line therapy for advanced/metastatic NSCLC with a PD-L1 tumor proportion score (TPS) ≥ 1%: Open-label, phase 3 KEYNOTE-042 study. J Clin Oncol. 2018;36(18_suppl):LBA4–LBA.
14. Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia JL, Han JY et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387(10027):1540–50.
15. Herbst RS, Garon EB, Kim D-W, Chul Cho B, Pérez Gracia JL, Han J-Y et al. Long-term survival in patients (pts) with advanced NSCLC in the KEYNOTE-010 study overall and in pts who completed two years of pembrolizumab (pembro). Ann Oncol. 2018;29(suppl_8).
16. Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med. 2015;373(2):123–35.
17. Park SE, Lee SH, Ahn JS, Ahn MJ, Park K, Sun JM. Increased Response Rates to Salvage Chemotherapy Administered after PD-1/PD-L1 Inhibitors in Patients with Non-Small Cell Lung Cancer. J Thorac Oncol. 2018;13(1):106–11.
18. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med. 2015;373(17):1627–39.
19. Lee CK, Man J, Lord S, Links M, Gebski V, Mok T et al. Checkpoint Inhibitors in Metastatic EGFR-Mutated Non-Small Cell Lung Cancer-A Meta-Analysis. J Thorac Oncol. 2017;12(2):403–7.
20. Horn L, Spigel DR, Vokes EE, Holgado E, Ready N, Steins M et al. Nivolumab Versus Docetaxel in Previously Treated Patients With Advanced Non-Small-Cell Lung Cancer: Two-Year Outcomes From Two Randomized, Open-Label, Phase III Trials (CheckMate 017 and CheckMate 057). J Clin Oncol. 2017;35(35):3924–33.
21. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017;389(10066):255–65.
22. Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N Engl J Med. 2013;369(2):134–44.

23. Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, et al. Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. Ann Oncol. 2019;30(4):582–588.
24. Ribas A, Puzanov I, Dummer R, Schadendorf D, Hamid O, Robert C et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol. 2015;16(8):908–18.
25. Hamid O, Puzanov I, Dummer R, Schachter J, Daud A, Schadendorf D et al. Final overall survival for KEYNOTE-002: pembrolizumab (pembro) versus investigator-choice chemotherapy (chemo) for ipilimumab (ipi)-refractory melanoma. Ann Oncol. 2016;27(suppl_6):11070.
26. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015;372(26):2521–32.
27. Schachter J, Ribas A, Long GV, Arance A, Grob JJ, Mortier L et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). Lancet. 2017;390(10105):1853–62.
28. Weber JS, D'Angelo SP, Minor D, Hodi FS, Gutzmer R, Neyns B et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2015;16(4):375–84.
29. A Study to Compare BMS-936558 to the Physician's Choice of Either Dacarbazine or Carboplatin and Paclitaxel in Advanced Melanoma Patients That Have Progressed Following Anti-CTLA-4 Therapy (CheckMate 037) (ClinicalTrials.gov Identifier: NCT01721746). Bethesda: U.S. National Library of Medicine; 2017. Available from https://clinicaltrials.gov/ct2/show/results/NCT01721746, accessed 209 September 2019
30. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372(4):320–30.
31. Ascierto PA, Long GV, Robert C, Brady B, Dutriaux C, Di Giacomo AM et al. Survival Outcomes in Patients With Previously Untreated BRAF Wild-Type Advanced Melanoma Treated With Nivolumab Therapy: Three-Year Follow-up of a Randomized Phase 3 Trial. JAMA Oncol. 2019; 5(2):187–194.
32. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015;373(1):23–34.
33. Hodi FS, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Cowey CL et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. Lancet Oncol. 2018;19(11):1480–92.
34. Eggermont AMM, Blank CU, Mandala M, Long GV, Atkinson V, Dalle S et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. N Engl J Med. 2018;378(19):1789–801.
35. Weber JS, Mandalà M, Vecchio MD, Gogas H, Arance AM, Cowey CL et al. Adjuvant therapy with nivolumab (NIVO) versus ipilimumab (IPI) after complete resection of stage III/IV melanoma: Updated results from a phase III trial (CheckMate 238). J Clin Oncol. 2018;36(15_suppl):9502.
36. Weber J, Mandala M, Del Vecchio M, Gogas HJ, Arance AM, Cowey CL et al. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. N Engl J Med. 2017;377(19):1824–35.
37. Huang M, Lou Y, Pellissier J, Burke T, Liu FX, Xu R et al. Cost Effectiveness of Pembrolizumab vs. Standard-of-Care Chemotherapy as First-Line Treatment for Metastatic NSCLC that Expresses High Levels of PD-L1 in the United States. Pharmacoeconomics. 2017;35(8):831–44.
38. Huang M, Lou Y, Pellissier J, Burke T, Liu FX, Xu R et al. Cost-effectiveness of pembrolizumab versus docetaxel for the treatment of previously treated PD-L1 positive advanced NSCLC patients in the United States. J Med Econ. 2017;20(2):140–50.

39. Meng Y, Hertel N, Ellis J, Morais E, Johnson H, Philips Z et al. The cost-effectiveness of nivolumab monotherapy for the treatment of advanced melanoma patients in England. Eur J Health Econ. 2018;19(8):1163–72.

40. Miguel LS, Lopes FV, Pinheiro B, Wang J, Xu R, Pellissier J et al. Cost Effectiveness of Pembrolizumab for Advanced Melanoma Treatment in Portugal. Value Health. 2017;20(8):1065–73.

*Medicines for prostate cancer – addition – EML*

| | |
|---|---|
| **Abiraterone** | **ATC Code: L02BX03** |
| **Enzalutamide** | **ATC Code: L02BB04** |

**Proposal**

The application requested the addition of abiraterone and enzalutamide to the EML for use in the treatment of metastatic castration-resistant prostate cancer.

**Applicant**

Knowledge Ecology International

**WHO Technical Department**

Comments on the application were received from the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it did not support the inclusion of abiraterone or enzalutamide on the EML for management of castration-resistant prostate cancer at this time, though noting with interest ongoing studies and more mature data that may demonstrate significant benefit, particularly for overall survival.

**EML/EMLc**

EML

**Section**

8.2.4 Hormones and antihormones

**Dose form(s) & strengths(s)**

Abiraterone: tablet 250 mg, 500 mg
Enzalutamide: capsule 40 mg

**Core/Complementary**

Complementary

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

In 2017, the Committee considered an application requesting inclusion of enzalutamide on the EML for the treatment of prostate cancer, but did not recommend inclusion, instead recommending a comprehensive review of prostate cancer medicines including abiraterone to be considered at its next meeting (*1*).

**Public health relevance** (burden of disease)

Prostate cancer is the second most common cancer in men and the fourth most common cancer overall. In 2018, approximately 1.3 million men were diagnosed with prostate cancer (*2*). When patients are diagnosed with prostate cancer, if they are treated early and tumours are localized, the prognosis is often favourable. However, some patients will relapse, which in nearly all cases, leads to castration-resistant prostate cancer (CRPC). At the CRPC stage, the disease is no longer responsive to androgen deprivation therapy (ADT), thus limiting the available treatment options.

There are currently six treatments being used to treat CRPC. Enzalutamide and abiraterone acetate have several advantages over the other treatments. Four of the other treatments are invasive and require IV administration, leukapheresis, or the use of radiopharmaceuticals. Enzalutamide and abiraterone acetate are the only daily oral tablets.

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**Summary of evidence: benefits** (from the application)

*Enzalutamide*

The application described the findings of two randomized placebo-controlled Phase III studies of enzalutamide for treatment of mCRPC.

The AFFIRM trial randomly assigned 1199 men with metastatic CRPC (mCRPC) who had previously taken docetaxel to 160 mg enzalutamide or placebo daily (*3*). Both groups received continuing androgen deprivation therapy. Overall survival (OS) favoured enzalutamide (18.4 months vs 13.6 months; HR 0.63, 95%CI 0.53 to 0.75; p<0.001). Progression-free survival (PFS) also favoured enzalutamide (8.3 months vs 2.9 months; HR 0.40, 95%CI 0.35 to 0.47, p<0.001). 54% of enzalutamide-treated patients experienced a 50% or greater decrease in prostate specific antigen (PSA) levels compared to only 2% in the control arm (p<0.001).

The PREVAIL trial investigated enzalutamide in a first-line setting in men with mCRPC who were chemotherapy naive. 1717 patients were randomized to receive 160 mg enzalutamide or placebo daily (*4*). The study was stopped after a planned interim analysis showed benefit for enzalutamide. Significantly fewer deaths were reported in the treatment arm compared to placebo (28% vs 35%; HR 0.71, 95%CI 0.60 to 0.84l p<0.001).

*Abiraterone acetate*

The application described the findings of two randomized placebo-controlled Phase III studies of abiraterone for treatment of mCRPC.

The COU-AA-301 trial randomly assigned 1195 patients who had failed prior docetaxel therapy to receive prednisone 5 mg twice daily with either abiraterone 1000 mg daily or placebo (*5*). The primary endpoint was

overall survival and was significantly longer in the abiraterone-prednisone arm compared to the control arm (14.8 months vs 10.9 months; HR 0.65, 95%CI 0.54 to 0.77; p<0.001). Abiraterone was also associated with significant benefit compared to placebo for the secondary endpoints of time to PSA progression (10.2 months vs 6.6 months; HR 0.58, 95%CI 0.46 to 0.73; p<0.001), and PFS (5.6 months vs 3.6 months; HR 0.67, 95%CI 0.59 to 0.78; p<0.001).

The COU-AA-302 trial randomly assigned 1088 chemotherapy naive patients with prostate cancer to receive abiraterone 1000 mg daily plus prednisone 5 mg twice daily or placebo plus prednisone (*6*). Median overall survival was observed to be longer in abiraterone treated patients compared to the placebo group (34.7 months vs 30.3 months; HR 0.81, 95%CI 0.70 to 0.93; p=0.0033).

#### *Enzalutamide versus abiraterone acetate*

The application described the findings of three studies in which enzalutamide and abiraterone were compared.

A network meta-analysis of eight RCTs involving 8666 patients with mCRPC compared the efficacy of abiraterone, enzalutamide and orteronel (*7*). Pooled hazard ratios for the primary endpoint of overall survival were 0.71 and 0.78 for enzalutamide and abiraterone, respectively compared to control groups. Enzalutamide also significantly improved PFS (HR 0.36), whereas abiraterone was not associated with a significant improvement. Enzalutamide and abiraterone were both associated with significant improvements in time to PSA progression compared to controls (HR 0.20 and 0.56, respectively). There were no significant associations for either drug with regard to the development of adverse events.

A retrospective study of patients with mCRPC receiving treatment with enzalutamide (n=807) or abiraterone (n=2591) compared real-world treatment patterns and adherence to therapy (*8*). Abiraterone-treated patients were found to have higher medication possession ratios (MPRs) than enzalutamide-treated patients, suggesting greater medication adherence to abiraterone. Abiraterone-treated patients also had lower Kaplan-Meier rates of dose reduction.

A second retrospective study compared the combined duration of prostate cancer treatments of mCRPC patients initiated on abiraterone (n=2591) or enzalutamide (n=807) (*9*). Compared with patients initiated on enzalutamide, patients initiated on abiraterone had fewer discontinuations of mCRPC treatments (HR 0.73, p=0.004) or of any prostate cancer treatments (HR 0.61, p=0.002) at three months and the result was maintained up to 24 months. The median duration of mCRPC treatments was 4.1 months longer for patients initiated on abiraterone compared with those initiated on enzalutamide (18.3 vs 14.2 months, p<0.001). Similarly, the median duration of any prostate cancer treatment was longer for patients initiated on abiraterone compared with those initiated on enzalutamide (not reached vs 22.2 months, p<0.001).

**Summary of evidence: harms** (from the application)

*Enzalutamide*

From the PROSPECT trial in patients with non-metastatic disease, adverse events of Grade 3 or higher occurred in 31% of enzalutamide-treated patients compared with 23% receiving placebo. The most commonly reported adverse events occurring more frequently in the enzalutamide group included fatigue, hot flush, hypertension, nausea and constipation (*10*).

From the AFFIRM trial in previously treated patients with mCRPC, adverse events of Grade 3 or above were reported in 45.3% of patients in the enzalutamide arm compared to 53.1% of placebo-treated patients. Enzalutamide-treated patients experienced a higher incidence of any grade fatigue, diarrhoea, hot flashes, musculoskeletal pain, headache and seizures compared to placebo-treated patients. Adverse events causing death occurred in 3% and 4% of enzalutamide- and placebo-treated patients, respectively (*3*).

From the PREVAIL trial in chemotherapy naive patients with mCRPC, adverse events of Grade 3 or more were reported in 43% of the patients in the enzalutamide group, and 37% in the placebo group. Common adverse events occurring at least 2% more frequently in the enzalutamide group included fatigue, back pain, constipation and arthralgia (*4*).

*Abiraterone*

In the COU-AA-301 trial, there were more deaths, treatment discontinuations, and treatment discontinuations due to adverse events in the placebo arm versus the abiraterone arm. Common adverse events occurring at similar frequency between treatment groups were fatigue, back pain, nausea, constipation, bone pain and arthralgia. Urinary tract infection was observed more frequently in the abiraterone arm (*5*). The most common Grade 3 or greater adverse events of special interest reported in the COU-AA-302 trial occurring more frequently in the abiraterone arm were cardiac disorders (8% vs 4%), increased alanine aminotransferase (6% vs <1%) and hypertension (5% vs 3%) (*6*).

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**Additional evidence** (not in the application)

A recent prospective randomized Phase II study (n=72) investigated the effect of the administration of low dose abiraterone (250 mg daily) with a low-fat meal, compared to standard dose abiraterone (1000 mg daily) administered under fasting conditions (*11*). At 12 weeks, a greater effect on PSA was observed in the low-dose arm compared with the standard dose arm (mean log change −1.59 vs −1.19) meeting the predefined non-inferiority criteria. The PSA response rate was 58% and 50% in the low-dose and standard-dose arms, respectively. Median PFS was approximately nine months in both groups. Androgen levels decreased similarly in both arms. Abiraterone concentrations were higher in the

standard-dose group, yet there was no difference in PSA response or PFS. The study authors considered these data could have significant pharmacoeconomic implications and deserve consideration by prescribers, payers and patients. However, the study also concludes that additional studies are required to determine the long-term efficacy of this dosing strategy.

**WHO Guidelines**

None available.

**Costs/cost-effectiveness**

Many of the cost-benefit studies have been done using the prices from originator companies. Both drugs are now also available from generic suppliers, and as competition among generic suppliers expands, prices should decline considerably.

Before generic entry, some publicly quoted prices for the active pharmaceutical ingredient enzalutamide were in the range of US$ 6000 to US$ 13 000 per kg. At US$ 6000 per kg, the cost of the active pharmaceutical ingredient (API) for one 40 mg capsule of enzalutamide would be US$ 0.24 (US$ 0.006 per mg).

Prices of generic abiraterone acetate vary. One company offers 120 x 250 mg abiraterone acetate tablets for approximately US$ 238.40. The price for a unit of the API is US$ 7947 per kg and US$ 0.007947 per mg.

It is anticipated that API costs could decline to between US$ 300 and US$ 900 per kg over time for both products, in line with prices for tamoxifen (US$ 271 per kg), capecitabine (US$ 393 per kg) and prednisolone (US$ 962 per kg). A decline of that magnitude would result in API costs of US$ 0.012 to US$ 0.036 per 40 mg capsule, or US$ 0.048 to US$ 0.144 per day, for enzalutamide, and US$ 0.075 to US$ 0.225 per 250 mg tablet or US$ 0.30 to US$ 0.90 per day for abiraterone acetate (without prednisone).

Technology appraisal guidance issued by the National Institute for Health and Care Excellence (NICE) for enzalutamide and abiraterone state that these medicines are recommended treatment options people with metastatic hormone-relapsed prostate cancer if the manufacturers provide the drugs at agreed fixed or discounted prices (*12*, *13*). Similarly, the National Centre for Pharmacoeconomics in Ireland approved reimbursement for enzalutamide and abiraterone only after price negotiations were conducted.

The application summarized numerous studies that investigated the cost-effectiveness of enzalutamide and abiraterone, noting that many study authors were affiliated with the pharmaceutical manufacturers at the time of publication. The studies cited used the high originator prices and are of limited use when considering whether these medicines would be cost-effective in resource-limited settings, when and where the medicines available at lower prices from generic suppliers.

**Availability**

Enzalutamide and abiraterone acetate have worldwide regulatory approval. There are many generic versions of abiraterone acetate available, while only a single generic version of enzalutamide.

**Other considerations**

N/A

**Committee recommendations**

The Committee endorsed the recommendations of the EML Cancer Medicine Working Group with regard to the proposed threshold of four to six months of overall survival benefit as a guiding principle for prioritizing cancer medicines for inclusion on the EML, and applied this principle to the consideration of abiraterone and enzalutamide.

The Committee recommended the addition of abiraterone to the complementary list of the EML for use in the treatment of metastatic castration-resistant prostate cancer.

The Expert Committee acknowledged the significant public health burden of prostate cancer, which afflicts an increasing number of people in all countries, irrespective of income. The Committee recalled that the EML currently includes docetaxel, bicalutamide and leuprorelin for use in the treatment of metastatic prostate cancer. However, a significant proportion of patients will not respond to these medicines and patients will ultimately develop resistance.

The Committee noted that abiraterone and enzalutamide have each been shown to be effective treatments for metastatic castration-resistant prostate cancer, both in chemotherapy-naive and in pre-treated patients. The Committee noted that abiraterone had not shown any relevant clinical advantage over enzalutamide in terms of efficacy outcomes or safety. However, the Committee recognized the potential advantages offered by abiraterone in terms of emerging dosing strategies (lower doses may be possible when administered with food), reduced pill burden potentially improving adherence, wider availability of generics and potential associated cost savings. Given that metastatic prostate cancer often requires treatment over longer periods of time (i.e. above one year) and that low dosing and availability of generics would be associated with substantial cost savings, the Committee decided not to recommend listing abiraterone with a square box indicating enzalutamide as an alternative. While enzalutamide remains an effective therapeutic option for mCRPC, its use instead of abiraterone could result in considerable additional expenditure at country level, without additional clinical benefit. The Committee considered that addition of abiraterone alone on the EML serves to support its use, promoting competition between brand and generic medicines, and improving access and affordability.

## References


1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children) (WHO Technical Report Series, No. 1006). Geneva: World Health Organization; 2017. Available from https://apps.who.int/iris/bitstream/handle/10665/259481/9789241210157-eng.pdf, accessed 30 October 2019.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
3. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012;367(13):1187–97.
4. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014;371(5):424–33.
5. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011;364(21):1995–2005.
6. Ryan CJ, Smith MR, Fizazi K, Saad F, Mulders PF, Sternberg CN et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2015;16(2):152–60.
7. Kang M, Jeong CW, Kwak C, Ku JH, Kim HH. Comparing the clinical efficacy of abiraterone acetate, enzalutamide, and orteronel in patients with metastatic castration-resistant prostate cancer by performing a network meta-analysis of eight randomized controlled trials. Oncotarget. 2017;8(35):59690–7.
8. Behl AS, Ellis LA, Pilon D, Xiao Y, Lefebvre P. Medication Adherence, Treatment Patterns, and Dose Reduction in Patients with Metastatic Castration-Resistant Prostate Cancer Receiving Abiraterone Acetate or Enzalutamide. Am Health Drug Benefits. 2017;10(6):296–303.
9. Pilon D, Behl AS, Ellis LA, Emond B, Lefebvre P, Dawson NA. Duration of Treatment in Prostate Cancer Patients Treated with Abiraterone Acetate or Enzalutamide. J Manag Care Spec Pharm. 2017;23(2):225–35.
10. Hussain M, Fizazi K, Saad F, Rathenborg P, Shore N, Ferreira U et al. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2018;378(26):2465–74.
11. Szmulewitz RZ, Peer CJ, Ibraheem A, Martinez E, Kozloff MF, Carthon B et al. Prospective International Randomized Phase II Study of Low-Dose Abiraterone With Food Versus Standard Dose Abiraterone In Castration-Resistant Prostate Cancer. J Clin Oncol. 2018;36(14):1389–95.
12. Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen. Technology appraisal guidance [TA316]. London: National Institute for Health and Care Excellence; 2014. Available from https://www.nice.org.uk/guidance/ta316, accessed 29 September 2019.
13. Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated. Technology appraisal guidance [TA387]. London: National Institute for Health and Care Excellence; 2016. Available from https://www.nice.org.uk/guidance/ta387, accessed 29 September 2019.

# Section 10: MEDICINES AFFECTING THE BLOOD

## 10.2 Medicines affecting coagulation

*Direct oral anticoagulants (DOACs) – dabigatran, rivaroxaban, apixaban, edoxaban – addition – EML*

| Direct oral anticoagulants | |
|---|---|
| Apixaban | ATC Code: B01AF02 |
| Dabigatran etexilate | ATC Code: B01AE07 |
| Edoxaban | ATC Code: B01AF03 |
| Rivaroxaban | ATC Code: B01AF01 |

**Proposal**

Two applications requested the inclusion of direct oral anticoagulants (DOACs) on the EML for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF) and for treatment of venous thromboembolism.

**Applicants**

1. Dr Mariachiara DiCesare, Dr Xinyi Leng, Dr Ezequiel Zaidel
2. Dr Ignacio Neumann, Dr Holger J Schunemann

**WHO Technical Department**

Comments on the applications were received from the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it supported the addition of DOACs to the complementary list of the EML as they are effective medicines for which EML listing may improve equity by making them more accessible to patients, and driving costs down.

**EML/EMLc**

EML

**Section**

10.2 Medicines affecting coagulation

**Dose form(s) & strengths(s)**

Apixaban: tablet 2.5 mg, 5 mg
Dabigatran etexilate: capsule 110 mg, 150 mg
Edoxaban: tablet 30 mg, 60 mg
Rivaroxaban: tablet 15 mg, 20 mg

**Core/Complementary**

Core

**Individual/Square box listing**

1. Square box listing of dabigatran
2. Individual listing for each medicine

**Background** (if relevant, eg. resubmission, previous EC consideration)

In 2015, the Committee rejected an application seeking inclusion of dabigatran, rivaroxaban and apixaban as a therapeutic group on the EML for the treatment of nonvalvular atrial fibrillation (NVAF). The Committee considered that although the evidence presented indicated a favourable overall clinical benefit of DOACs over warfarin, the absolute magnitude of benefit was limited, inconsistent across trials and may be influenced by a number of factors, such as the quality of oral anticoagulation (time in therapeutic range). The Committee considered that in order for countries to maximize use of available resources, further research was necessary to explore the unmet need in terms of anticoagulation in people unable to be stabilized with warfarin and in clinical settings where access to warfarin monitoring is not readily available. The Committee expressed some concern regarding safety of DOACs, noting that there were currently no specific antidotes that would reverse anticoagulant effects in case of emergency. The Committee also acknowledged that the large difference in cost between DOACs and warfarin was not proportional to the observed incremental clinical benefit. Full details are available in the technical report of the 2015 Expert Committee meeting (*1*).

**Public health relevance** (burden of disease)

Atrial fibrillation (AF) is the most commonly diagnosed cardiac arrhythmia (*2*) and a major public health issue affecting 37.6 million individuals globally in 2017 (*3*). The incidence and prevalence of AF are expected to increase over the next 30 years (*4–6*).

Without antithrombotic treatment, the risk of stroke in patients with atrial fibrillation is around 5% per year, but it can be as high as 10% per year if other risk factors are present (*7*). In a cohort of 15 400 individuals with atrial fibrillation in 47 countries, the highest number of strokes occurred in patients in Africa (incidence 89/1137 (8%) per year), China (incidence 143/2023 (7%) per year), and Southeast Asia (incidence 88/1331 (7%) per year) (*8*).

In low and middle-income countries (LMICs), stroke is associated with an increased mortality and significant disability, particularly in disadvantaged populations (*9–11*). Additionally, according to a recent WHO survey of 177 countries, provisions for the treatment and rehabilitation of patients with stroke are available in less than a quarter of public health care facilities in LMICs (*12*).

Deep venous thrombosis and pulmonary embolism are major contributors to global disease burden. Their estimated annual incidence ranges from 0.7 to 2.7 per 1000 population in Western Europe, 1.1 to 2.4 per 1000 population in North America and 0.2 to 1.6 per 1000 population in Latin America and Asia (*13*). Additionally, venous thromboembolism markedly increases with age, with incidences as high as 4.29 to 5.64 per 1000 population in individuals older than 70 years (*14*, *15*). Thus, venous thromboembolism is likely to become an even more prominent problem with aging populations.

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**Summary of evidence: benefits** (from the application)

***Application 1 – NVAF:***

This application presented the results of a meta-analysis that updated a published meta-analysis of four randomized controlled trials (RCTs) by Ruff et al (*16*) with data from the J-ROCKET AF trial (*17*) involving a total of 59 819 participants. Compared with warfarin, DOACs were associated with a significantly reduced risk of stroke and systemic embolism in patients with NVAF (risk ratio (RR) 0.80, 95%CI 0.71 to 0.91, p=0.003; absolute effect: 8 fewer events per 1000 (95%CI 3 fewer to 11 fewer). The quality of evidence was rated as high using GRADE.

This application also presented the results of a systematic literature review of observational studies reporting real-world data for DOACs versus vitamin K antagonists for the primary efficacy outcome of stroke and systemic embolism. Of 23 studies included in the quantitative data synthesis, 12 studies provided data for the primary efficacy outcome of stroke and systemic embolism (*18–29*). In these studies, NOACs were associated with a reduced risk of stroke and systemic embolism compared with warfarin in patients with NVAF RR 0.79, 95%CI 0.71 to 0.89, p<0.001; absolute effect: 5 fewer events per 1000 (95%CI 3 fewer to 7 fewer). The quality of evidence was rated as very low using GRADE, due to the evidence being based on observational studies with heterogenous findings.

When compared individually with warfarin, dabigatran, rivaroxaban and apixaban were each associated with a lower risk of stroke and systemic embolism than warfarin. No real-world data were available for edoxaban.

***Application 2 – NVAF:***

This application conducted a meta-analysis of eight systematic reviews (*30–37*) and 13 randomized trials involving a total of 75 543 participants with AF and one or two additional risk factors for stroke (*17*, *38–49*). Participants were randomized to a DOAC or warfarin (target international normalized ratio 2.0 to 3.0) and were followed for two to three years. Individuals with estimated creatinine clearance of less than 30 mL per minute or a high risk of bleeding were excluded.

Use of DOACs instead of vitamin K antagonists in individuals with NVAF was associated with decreased mortality (RR 0.90, 95%CI 0.85 to 0.94, high certainty evidence) and decreased risk of stroke (RR 0.83, 95%CI 0.72 to 0.96; absolute effect: 7 fewer events per 1000 (95%CI 11 fewer to 4 fewer), high certainty evidence). Also, DOACs were found to probably decrease the risk of systemic embolism (RR 0.74, 95%CI 0.48 to 1.13; absolute effect: 1 fewer event per 1000 (95%CI 1 fewer to 0 fewer), moderate certainty evidence) and major bleeding (RR 0.81, 95%CI 0.66 to 0.98; absolute effect: 11 fewer events per 1000 (95%CI 20 fewer to 1 fewer), moderate certainty evidence).

*Application 2 – venous thromboembolism:*

This application conducted a meta-analysis of 24 systematic reviews (*50*–*73*) and 12 randomized trials involving 28 876 participants with an objectively confirmed symptomatic proximal deep venous thrombosis or pulmonary embolism (*74*–*85*). Participants were randomized to a DOAC or to an initial treatment with low molecular weight heparin (five to ten days) followed by dose-adjusted warfarin (target international normalized ratio 2.0 to 3.0). Dabigatran was also administered after an initial treatment of five to ten days with low molecular weight heparin, while rivaroxaban, apixaban and edoxaban were administered without initial parenteral anticoagulants. The length of the anticoagulation varied across trials from three to twelve months. Individuals with estimated creatinine clearance of less than 30 mL per minute or a high risk of bleeding were excluded.

The analysis showed that the use of DOACs instead of vitamin K antagonists in individuals with deep venous thrombosis or pulmonary embolism likely has a small effect on mortality (RR 0.99, 95%CI 0.85 to 1.15; absolute effect: 0 fewer events per 1000 (95%CI 6 fewer to 6 more), moderate certainty evidence) and the risk of subsequent pulmonary embolism (RR 0.97, 95%CI 0.77 to 1.23; absolute effect: 1 fewer event per 1000 (95%CI 5 fewer to 5 more), moderate certainty evidence). DOACs probably decrease the risk of a recurrent deep venous thrombosis (RR 0.80, 95%CI 0.59 to 1.09; absolute effect: 5 fewer events per 1000 (95%CI 11 fewer to 2 more), moderate certainty evidence) and major bleeding (RR 0.63, 95%CI 0.47 to 0.84; absolute effect: 6 fewer events per 1000 (95%CI 9 fewer to 3 fewer), high certainty evidence).

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**Summary of evidence: harms (from the application)**

*Application 1:*

From the updated meta-analysis of five RCTs (*16*, *17*), DOACs were found to be associated with a significantly lower risk of major bleeding compared with warfarin (RR 0.86, 95%CI 0.74 to 0.99, p=0.04; absolute effect: 8 fewer events per 1000 (95%CI 1 fewer to 16 fewer). The quality of the evidence was rated as moderate using GRADE, downgraded due to inconsistency.

This application also presented the results of a systematic literature review of observational studies reporting real-world data for DOACs versus vitamin K antagonists for the primary safety outcome of major bleeding. Of 23 studies included in the quantitative data synthesis, 17 studies provided data for the primary safety outcome (*18*, *20*, *22–29*, *86–92*). In these studies, DOACs were associated with a lower risk of bleeding compared with warfarin in NVAF patients (RR 0.72, 95%CI 0.64 to 0.80. p<0.001; absolute effect 9 fewer events per 1000 (95%CI 6 fewer to 11 fewer). The quality of evidence was rated as very low using GRADE, due to the evidence being based on observational studies with heterogenous findings.

When compared individually with warfarin, dabigatran, rivaroxaban apixaban and edoxaban were each associated with a lower risk of major bleeding than warfarin. No real-world data were available for edoxaban.

***Application 2:***

As reported above, randomized trial evidence suggests that DOACs are probably associated with a lower risk of major bleeding than vitamin K antagonists in the treatment of NVAF (RR 0.81, 95%CI 0.66 to 0.98; absolute effect: 11 fewer events per 1000 (95%CI 20 fewer to 1 fewer), moderate certainty evidence) and venous thromboembolism (RR 0.63, 95%CI 0.47 to 0.84; absolute effects 6 fewer events per 1000 (95%CI 9 fewer to 3 fewer), high certainty evidence).

Large observational studies on real-world populations suggest that the risk of bleeding with DOACs may be equivalent to or lower than the risk with vitamin K antagonists.

- A large cohort of 156 005 adults with atrial fibrillation and venous thromboembolism in the United Kingdom suggested a lower risk of bleeding with apixaban in comparison with warfarin (HR 0.69, 95%CI 0.54 to 0.79 in individuals with atrial fibrillation; HR 0.60, 95%CI 0.46 to 0.79 in individuals without atrial fibrillation). Also, investigators observed no significant differences in the risk of bleeding for the comparisons of rivaroxaban vs warfarin (HR 1.12, 95%CI 0.99 to 1.26 in individuals with atrial fibrillation; HR 0.95, 95%CI 0.82 to 1.10 in individuals without atrial fibrillation) and dabigatran vs warfarin (HR 0.87, 95%CI 0.72 to 1.04 in individuals with atrial fibrillation; HR 0.98, 95%CI 0.71 to 1.35 in individuals without atrial fibrillation) (*25*).
- A propensity-matched analysis of 76 940 individuals with non-valvular atrial fibrillation of an administrative database from the United States suggested a lower risk of bleeding with apixaban in comparison to warfarin (HR 0.60, 95%CI 0.54 to 0.65) (*29*).

- A community-based population study of 59 525 adults with venous thromboembolism in Canada and the United States showed a similar risk of bleeding with DOAC and VKA (HR 0.99, 95%CI 0.84 to 1.16) (*93*).
- A propensity score matched analysis of 45 361 patients with non-valvular atrial fibrillation of an administrative database from the United States, showed a lower risk of bleeding with dabigatran (HR 0.69 95%CI 0.50 to 0.96) and apixaban (HR 0.53, 95%CI 0.39 to 0.71) in comparison to warfarin. In patients using rivaroxaban, investigators observed a similar risk of bleeding in comparison to warfarin (HR 0.98, 95%CI 0.83 to 1.17) (*94*).
- A propensity-matched cohort of 29 963 adults with venous thromboembolism in Denmark, also suggested a similar risk of bleeding with DOAC and VKA (HR 1.19, 95%CI 0.66 to 2.13) (*95*).

The application also reported data from recent and ongoing trials involving specific antidotes for emergency reversal of anticoagulation in patients receiving DOACs.

Idarucizumab is a monoclonal antibody fragment that has been investigated for use in reversing the anticoagulant effect of dabigatran in the RE-VERSE AD trial in 503 patients with life-threatening bleeding or about to undergo an urgent procedure (*96*). Following administration of 5 g of IV idarucizumab, anticoagulation was completely reversed in 98% of patients within four hours.

Andexanet alfa has recently been approved as an antidote for rivaroxaban and apixaban based on results of two open label randomized trials of rivaroxaban or apixaban compared to placebo (ANNEXA-R and ANNEXA-A). The primary outcome of both trials was anti-factor Xa activity measured with a chromogenic assay. The results showed a reduction of anti-factor Xa activity of 92±11% with andexanet vs 18±15% with placebo in the rivaroxaban study and a reduction of 94±2% with andexanet vs 21±9% with placebo in the apixaban study (*97*). There is an ongoing open-label, non-randomized trial (ANNEXA-4) evaluating the effects of andexanet on clinical endpoints in patients with acute bleeding under treatment with rivaroxaban or apixaban. In an interim report of this study, of the 47 patients available for analysis, 37 were judged as having good haemostasis by an independent adjudication committee (*98*).

**Additional evidence (not in the application)**

N/A

**WHO Guidelines**

There are no WHO guidelines currently available for the treatment of NVAF or venous thromboembolism.

Oral anticoagulation with warfarin or DOACs (apixaban, dabigatran, rivaroxaban) in patients with atrial fibrillation (AF) at high risk of stroke based on a CHA2DS2-VASc score of 2 or more is recommended in multiple international guidelines (*99–102*).

For management of venous thromboembolism, recent, yet to be published, American and Latin American guidelines are reported to support short-term anticoagulation in individuals at low risk of recurrence and indefinite anticoagulation in individuals at high risk (e.g. unprovoked events). DOACs are the preferred alternative over warfarin.

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**Costs/cost-effectiveness**

Reported monthly costs of DOACs in the two applications indicate that the costs for DOACs range widely between countries: from US$ 20–50 per month in Latin American countries, to US$ 90 per month in the United Kingdom, to up to US$ 600 per month in the United States and Canada.

*Application 1:*

A 2016 systematic review of 54 studies from 21 countries reporting cost-effectiveness analyses of DOACs (*103*) concluded that DOACs are cost-effective in several countries, independent of their health system, direct costs of DOACs and vitamin K antagonists, and costs of diseases. The authors defined a drug as cost-effective when the incremental cost-effectiveness ratio was below the willingness to pay value. Most studies used a conventional Markov decision analysis model, and the rate of events was gathered from the RCTs of DOACs.

This application updated the systematic review, including 64 cost-effectiveness analyses from 28 high- and middle-income countries. Most of them used same criteria, but newer cost-effectiveness analyses from the United States included costs from health care resource use and real-world data from health systems to determine rate of stroke and bleeding rather than data solely from randomized trials. All studies to date demonstrated that DOACs were a cost-effective strategy. The studies included in the updated systematic review are referenced in the application.

*Application 2 – NVAF:*

The application identified two systematic reviews of economic evaluation of any DOAC versus vitamin K antagonists in patients with AF.

The first article identified was a systematic review of cost-utility analyses of dabigatran, rivaroxaban or apixaban versus warfarin. This review included

18 primary studies conducted in North America and Europe. All but one used a Markov model to extrapolate long-term data basing the calculation on the effectiveness and safety results from landmark trials. The majority of the models used the perspective of the payer. Thirteen models compared dabigatran versus warfarin, four rivaroxaban versus warfarin and four apixaban versus warfarin. Although there was some inconsistency among the conclusions of the individual models, the large majority showed that DOACs were cost-effective with ICERs below the willingness-to-pay thresholds and sometimes dominant over warfarin (*104*).

The second article identified was a systematic review of cost-utility analyses of apixaban versus warfarin. This review identified 26 primary studies conducted in North America, Latin America and Europe. All the studies except of one used a Markov model to extrapolate long-term data with the effectiveness and safety results from landmark trials. The majority of the models used the perspective of the payer with a lifetime horizon. The results showed that apixaban was cost-effective with incremental cost effectiveness ratios (ICERs) below the willingness-to-pay thresholds (*105*).

*Application 2 – venous thromboembolism:*

The application identified five cost comparisons between DOACs and VKA for patients with venous thromboembolism. Four reports suggested that DOACs are cost-saving compared with warfarin (*106–109*) and one study found an equivalent cost between DOACs and vitamin K antagonists (*110*).

In addition, the application identified 14 economic evaluations that compared the cost and effectiveness of DOACs versus vitamin K antagonists (*107*, *111–123*). All suggested that DOACs are cost-effective compared to warfarin.

**Availability**

Dabigatran, manufactured by Boehringer Ingelheim, apixaban, manufactured by Bristol-Myers Squibb, and rivaroxaban, manufactured by Bayer, all have wide global regulatory approval.

Edoxaban, manufactured by Daiichi Sanyko Company, has regulatory approval from regulatory authorities in the United States, Europe, Japan, Canada and Nigeria.

**Other considerations**

N/A

**Committee recommendations**

The Committee recommended the addition of dabigatran with a square box to the core list of the EML for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation and for treatment of venous

thromboembolism based on favourable efficacy and acceptable safety. The square box refers to apixaban, edoxaban and rivaroxaban as therapeutically equivalent alternatives.

The Committee noted that the DOACs demonstrated clinical benefits in terms of reduced mortality, reduced risk of stroke or systemic embolism, and were associated with fewer severe/major bleeding episodes compared to well-controlled warfarin in patients with NVAF.

In the treatment of patients with venous thromboembolism, DOACs were associated with small reductions in mortality, risk of subsequent/recurrent thromboembolic events and major bleeding compared to low-molecular weight heparin and vitamin K antagonists.

The use of DOACs may also have relevant health system benefits related to the infrastructure required for warfarin treatment monitoring, as they do not require laboratory monitoring. The Committee noted that DOACs have higher daily treatment costs than warfarin, but have been found to be a cost-effective intervention. It is recommended that countries take all these factors into consideration when selecting anticoagulants to best suit their national and local needs and circumstances.

The Committee recommended that WHO take action to facilitate access to these medicines through the WHO prequalification programme, and through collaboration with partners such as the Medicines Patent Pool.

## References


1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children) (WHO Technical Report Series, No. 994). Geneva: World Health Organization; 2015. Available from https://apps.who.int/iris/bitstream/handle/10665/189763/9789241209946_eng.pdf, accessed 30 October 2019.
2. Morillo CA, Banerjee A, Perel P, Wood D, Jouven X. Atrial fibrillation: the current epidemic. J Geriatr Cardiol. 2017;14(3):195–203.
3. Global Burden of Disease compare data visualization. Seattle: Institute for Health Metrics and Evaluation, University of Washington; 2016. Available from https://vizhub.Healthdata.Org/gbd-compare/, accessed 29 September 2019.
4. Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. European heart journal. 2013;34(35):2746–51.
5. Lip GYH, Brechin CM, Lane DA. The global burden of atrial fibrillation and stroke: a systematic review of the epidemiology of atrial fibrillation in regions outside North America and Europe. Chest. 2012;142(6):1489–98.
6. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation. 2006;114(2):119–25.

7. You JJ, Singer DE, Howard PA, Lane DA, Eckman MH, Fang MC et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic therapy and prevention of thrombosis, 9th ed: american college of chest physicians evidence-based clinical practice guidelines. Chest. 2012;141(2_suppl):e531S–e75S.
8. Healey JS, Oldgren J, Ezekowitz M, Zhu J, Pais P, Wang J et al. Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study. Lancet. 2016;388(10050):1161–9.
9. Joubert J, Prentice LF, Moulin T, Liaw ST, Joubert LB, Preux PM et al. Stroke in rural areas and small communities. Stroke. 2008;39(6):1920–8.
10. Lloyd-Sherlock P. Stroke in Developing Countries: Epidemiology, Impact and Policy Implications. Development Policy Review. 2010;28(6):693–709.
11. Pandian JD, Srikanth V, Read SJ, Thrift AG. Poverty and stroke in India: a time to act. Stroke. 2007;38(11):3063–9.
12. Assessing national capacity for the prevention and control of noncommunicable diseases. Geneva: World Health Organization; 2016.
13. Raskob GE, Angchaisuksiri P, Blanco AN, Buller H, Gallus A, Hunt BJ et al. Thrombosis: a major contributor to global disease burden. Arterioscler Thromb Vasc Biol. 2014;34(11):2363–71.
14. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med. 1998;158(6):585–93.
15. Nordstrom M, Lindblad B, Bergqvist D, Kjellstrom T. A prospective study of the incidence of deep-vein thrombosis within a defined urban population. J Intern Med. 1992;232(2):155–60.
16. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383(9921):955–62.
17. Hori M, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S et al. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation - the J-ROCKET AF study. Circ J. 2012;76(9): 2104–11.
18. Larsen TB, Skjoth F, Nielsen PB, Kjaeldgaard JN, Lip GY. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. BMJ. 2016;353:i3189.
19. Maura G, Blotiere PO, Bouillon K, Billionnet C, Ricordeau P, Alla F et al. Comparison of the short-term risk of bleeding and arterial thromboembolic events in nonvalvular atrial fibrillation patients newly treated with dabigatran or rivaroxaban versus vitamin K antagonists: a French nationwide propensity-matched cohort study. Circulation. 2015;132(13):1252–60.
20. Kohsaka S, Katada J, Saito K, Terayama Y. Safety and effectiveness of apixaban in comparison to warfarin in patients with nonvalvular atrial fibrillation: a propensity-matched analysis from Japanese administrative claims data. Curr Med Res Opin. 2018;34(9):1627–34.
21. Yoshimura S, Koga M, Sato S, Todo K, Yamagami H, Kumamoto M et al. Two-Year Outcomes of Anticoagulation for Acute Ischemic Stroke With Nonvalvular Atrial Fibrillation- SAMURAI-NVAF Study. Circ J. 2018;82(7):1935–42.
22. Sjogren V, Bystrom B, Renlund H, Svensson PJ, Oldgren J, Norrving B et al. Non-vitamin K oral anticoagulants are non-inferior for stroke prevention but cause fewer major bleedings than well-managed warfarin: A retrospective register study. PloS one. 2017;12(7):e0181000.

23. Lee HF, Chan YH, Tu HT, Kuo CT, Yeh YH, Chang SH et al. The effectiveness and safety of low-dose rivaroxaban in Asians with non-valvular atrial fibrillation. Int J Cardiol. 2018;261:78–83.
24. Chan YH, Kuo CT, Yeh YH, Chang SH, Wu LS, Lee HF et al. Thromboembolic, Bleeding, and Mortality Risks of Rivaroxaban and Dabigatran in Asians With Nonvalvular Atrial Fibrillation. J Am Coll Cardiol. 2016;68(13):1389–401.
25. Vinogradova Y, Coupland C, Hill T, Hippisley-Cox J. Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care. BMJ. 2018;362:k2505.
26. Laliberte F, Cloutier M, Nelson WW, Coleman CI, Pilon D, Olson WH et al. Real-world comparative effectiveness and safety of rivaroxaban and warfarin in nonvalvular atrial fibrillation patients. CurrMed Res Opin. 2014;30(7):1317–25.
27. Seeger JD, Bykov K, Bartels DB, Huybrechts K, Zint K, Schneeweiss S. Safety and effectiveness of dabigatran and warfarin in routine care of patients with atrial fibrillation. Thromb Haemost. 2015;114(6):1277–89.
28. Yao X, Abraham NS, Sangaralingham LR, Bellolio MF, McBane RD, Shah ND et al. Effectiveness and Safety of Dabigatran, Rivaroxaban, and Apixaban Versus Warfarin in Nonvalvular Atrial Fibrillation. J Am Heart Assoc. 2016;5(6).
29. Li XS, Deitelzweig S, Keshishian A, Hamilton M, Horblyuk R, Gupta K et al. Effectiveness and safety of apixaban versus warfarin in non-valvular atrial fibrillation patients in "real-world" clinical practice. A propensity-matched analysis of 76,940 patients. Thromb Haemost. 2017; 117(6):1072–82.
30. Almutairi AR, Zhou L, Gellad WF, Lee JK, Slack MK, Martin JR et al. Effectiveness and Safety of Non-vitamin K Antagonist Oral Anticoagulants for Atrial Fibrillation and Venous Thromboembolism: A Systematic Review and Meta-analyses. Clin Ther. 2017;39(7):1456-78.e36.
31. Bajaj NS, Kalra R, Patel N, Hashim T, Godara H, Ather S et al. Comparison of Approaches for Stroke Prophylaxis in Patients with Non-Valvular Atrial Fibrillation: Network Meta-Analyses of Randomized Controlled Trials. PloS one. 2016;11(10):e0163608.
32. Bruins Slot KM, Berge E. Factor Xa inhibitors versus vitamin K antagonists for preventing cerebral or systemic embolism in patients with atrial fibrillation. Cochrane Database Syst Rev. 2018;3:CD008980.
33. Cohen AT, Hill NR, Luo X, Masseria C, Abariga SA, Ashaye AO. A systematic review of network meta-analyses among patients with nonvalvular atrial fibrillation: A comparison of efficacy and safety following treatment with direct oral anticoagulants. Int J Cardiol. 2018;269:174–81.
34. Lowenstern A, Al-Khatib SM, Sharan L, Chatterjee R, LaPointe NMA, Shah B et al. Interventions for Preventing Thromboembolic Events in Patients With Atrial Fibrillation: A Systematic Review. Ann Intern Med. 2018;169(11):774–787.
35. Ntaios G PV, Diener HC, Makaritsis K, Michel P. Nonvitamin-K-antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and previous stroke or transient ischemic attack: An updated systematic review and meta-analysis of randomized controlled trials. Stroke. 2017;12(6):589–96.
36. Sterne JA, Bodalia PN, Bryden PA, Davies PA, Lopez-Lopez JA, Okoli GN et al. Oral anticoagulants for primary prevention, treatment and secondary prevention of venous thromboembolic disease, and for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis and cost-effectiveness analysis. Health Technol Assess. 2017;21(9):1–386.
37. Tawfik A, Bielecki JM, Krahn M, Dorian P, Hoch JS, Boon H et al. Systematic review and network meta-analysis of stroke prevention treatments in patients with atrial fibrillation. Clin Pharmacol. 2016;8:93–107.

38. Chung N, Jeon HK, Lien LM, Lai WT, Tse HF, Chung WS et al. Safety of edoxaban, an oral factor Xa inhibitor, in Asian patients with non-valvular atrial fibrillation. Thromb Haemost. 2011;105(3): 535–44.
39. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139–51.
40. Ezekowitz MD, Reilly PA, Nehmiz G, Simmers TA, Nagarakanti R, Parcham-Azad K et al. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). Am J Cardiol. 2007;100(9):1419–26.
41. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369(22):2093–104.
42. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981–92.
43. NCT00973245. BAY59-7939 in Atrial Fibrillation Once Daily (OD). 2014. Available from https://clinicaltrials.gov/ct2/show/NCT00973245, accessed 30 October 2019.
44. NCT00973323. BAY59-7939 Japanese in Atrial Fibrillation (2nd). 2014. Available from https://clinicaltrials.gov/ct2/show/NCT00973323, accessed 30 October 2019.
45. NCT01136408. A Dose Response Study of Dabigatran Etexilate(BIBR 1048) in Pharmacodynamics and Safety in Patients With Non-valvular Atrial Fibrillation in Comparison to Warfarin. 2014. Available from https://clinicaltrials.gov/ct2/show/NCT01136408, accessed 30 October 2019.
46. Ogawa S, Shinohara Y, Kanmuri K. Safety and efficacy of the oral direct factor xa inhibitor apixaban in Japanese patients with non-valvular atrial fibrillation. -The ARISTOTLE-J study. Circ J. 2011;75(8):1852–9.
47. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883–91.
48. Weitz JI, Connolly SJ, Patel I, Salazar D, Rohatagi S, Mendell J et al. Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation. Thromb Haemost. 2010;104(3):633–41.
49. Yamashita T, Koretsune Y, Yasaka M, Inoue H, Kawai Y, Yamaguchi T et al. Randomized, multicenter, warfarin-controlled phase II study of edoxaban in Japanese patients with non-valvular atrial fibrillation. Circ J. 2012;76(8):1840–7.
50. Adam SS, McDuffie JR, Ortel TL, Williams Jr JW. Comparative effectiveness of warfarin and new oral anticoagulants for the management of atrial fibrillation and venous thromboembolism: a systematic review. Ann Intern Med. 2012;157(11):796–807.
51. Almutairi AR, Zhou L, Gellad WF, Lee JK, Slack MK, Martin JR et al. Effectiveness and Safety of Non-Vitamin K Antagonist Oral Anticoagulants for Atrial Fibrillation and Venous Thromboembolism: A Systematic Review and Meta-Analyses. Clin Ther. 2017;39(7):1456–78.
52. Canadian Agency for D, Technologies in H. Rivaroxaban (Xarelto): Treatment of Venous Thromboembolic Events (Deep Vein Thrombosis [DVT], Pulmonary Embolism [PE]) and Prevention of Recurrent DVT and PE2015 2015/08/None. Available from https://www.ncbi.nlm.nih.gov/books/NBK344331/, accessed 30 October 2019.
53. Castellucci LA, Cameron C, Le Gal G, Rodger MA, Coyle D, Wells PS et al. Clinical and safety outcomes associated with treatment of acute venous thromboembolism: a systematic review and meta-analysis. JAMA. 2014;312(11):1122–35.

54. Cohen AT, Hamilton M, Mitchell SA, Phatak H, Liu X, Bird A et al. Comparison of the Novel Oral Anticoagulants Apixaban, Dabigatran, Edoxaban, and Rivaroxaban in the Initial and Long-Term Treatment and Prevention of Venous Thromboembolism: Systematic Review and Network Meta-Analysis. PloS one. 2015;10(12):e0144856.
55. Dentali F, Di Minno MN, Gianni M, Ambrosino P, Squizzato A, Ageno W. Non-vitamin K oral anticoagulants in patients with pulmonary embolism: a systematic review and meta-analysis of the literature. Intern Emerg Med. 2015;10(4):507–14.
56. Di Minno MN, Ambrosino P, Lupoli R, Di Minno A, Dentali F. Direct oral anticoagulants for the treatment of unprovoked venous thromboembolism: a meta-analysis of randomised controlled trials. Blood Transfus. 2015;13(3):391–5.
57. Fox BD, Kahn SR, Langleben D, Eisenberg MJ, Shimony A. Efficacy and safety of novel oral anticoagulants for treatment of acute venous thromboembolism: direct and adjusted indirect meta-analysis of randomised controlled trials. BMJ. 2012;345(7884):e7498.
58. Ganji R, Ala S, Aarabi M, Baghery B, Salehifar E. Comparison of Dabigatran vs. Warfarin in Acute Vnous Thromboemboly: Systematic Review. Iran J Pharm Res. 2016;15(2):611–7.
59. Gómez-Outes A, Suárez-Gea ML, Lecumberri R, Terleira-Fernández AI, Vargas-Castrillón E. Direct oral anticoagulants in the treatment of venous thromboembolism, with a focus on patients with pulmonary embolism: an evidence-based review. Vasc Health Risk Manag. 2014;10:627–39.
60. Gómez-Outes A, Terleira-Fernández AI, Lecumberri R, Suárez-Gea ML, Vargas-Castrillón E. Direct oral anticoagulants in the treatment of acute venous thromboembolism: a systematic review and meta-analysis. Thromb Res. 2014;134(4):774–82.
61. Hirschl M, Kundi M. New oral anticoagulants in the treatment of acute venous thromboembolism - a systematic review with indirect comparisons. VASA Zeitschrift für Gefässkrankheiten. 2014;43(5):353–64.
62. Kakkos SK, Kirkilesis GI, Tsolakis IA. Editor's Choice - Efficacy and Safety of the New Oral Anticoagulants Dabigatran, Rivaroxaban, Apixaban, and Edoxaban in the Treatment and Secondary Prevention of Venous Thromboembolism: A Systematic Review and Meta-analysis of Phase III Trials. Eur J Vasc Endovasc Surg. 2014;48(5):565–75.
63. Kang N, Sobieraj DM. Indirect treatment comparison of new oral anticoagulants for the treatment of acute venous thromboembolism. Thromb Res. 2014;133(6):1145–51.
64. Loffredo L, Perri L, Del Ben M, Angelico F, Violi F. New oral anticoagulants for the treatment of acute venous thromboembolism: are they safer than vitamin K antagonists? A meta-analysis of the interventional trials. Intern Emerg Med. 2015;10(4):499–506.
65. Mumoli N, Cei M, Pesavento R, Campanini M, Dentali F. Are direct oral anticoagulants equally effective in reducing deep vein thrombosis and pulmonary embolism? Int J Cardiol. 2015;187: 645–7.
66. Petrov VI, Shatalova OV, Gorbatenko VS, Smuseva ON, Maslakov AS. Efficacy and safety of the new oral anticoagulants in the treatment of venous thromboembolic complications: meta-analysis. Rational Pharmacotherapy in Cardiology. 2016;12(1):31–9.
67. Robertson L, Kesteven P, McCaslin JE. Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis. Cochrane Database Syst Rev. 2015;6(6):CD010956.
68. Robertson L, Kesteven P, McCaslin JE. Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of pulmonary embolism. Cochrane Database Syst Rev. 2015;12(12):CD010957.
69. Senoo K, Kondo Y, Miyazawa K, Isogai T, Chun YH, Kobayashi Y. Safety and efficacy of direct oral anticoagulants over warfarin in Japanese patients with acute venous thromboembolism: A meta-analysis. J Cardiol. 2017;69(5):763–8.

70. Tahir F, Riaz H, Riaz T, Badshah MB, Riaz IB, Hamza A et al. The new oral anti-coagulants and the phase 3 clinical trials - a systematic review of the literature. Thromb J. 2013;11(1):18.

71. van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. J Thromb Haemost. 2014;12(3):320–8.

72. Van Es N, Coppens M, Schulman S, Middeldorp S, Buller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: Evidence from phase 3 trials. Blood. 2014;124(12):1968–75.

73. Vedovati MC, Becattini C, Germini F, Agnelli G. Efficacy and safety of direct oral anticoagulants after pulmonary embolism: a meta-analysis. Int J Cardiol. 2014;177(2):601–3.

74. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013;369(9):799–808.

75. Agnelli G, Gallus A, Goldhaber SZ, Haas S, Huisman MV, Hull RD et al. Treatment of proximal deep-vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAY 59-7939): the ODIXa-DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients With Acute Symptomatic Deep-Vein Thrombosis) study. Circulation. 2007;116(2):180–7.

76. Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363(26):2499–510.

77. Buller H, Deitchman D, Prins M, Segers A. Efficacy and safety of the oral direct factor Xa inhibitor apixaban for symptomatic deep vein thrombosis. The Botticelli DVT dose-ranging study. J Thromb Haemost. 2008;6(8):1313–8.

78. Buller HR, Decousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013; 369(15):1406–15.

79. Buller HR, Lensing AW, Prins MH, Agnelli G, Cohen A, Gallus AS et al. A dose-ranging study evaluating once-daily oral administration of the factor Xa inhibitor rivaroxaban in the treatment of patients with acute symptomatic deep vein thrombosis: the Einstein-DVT Dose-Ranging Study. Blood. 2008;112(6):2242–7.

80. Buller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012;366(14):1287–97.

81. Nakamura M, Nishikawa M, Komuro I, Kitajima I, Uetsuka Y, Yamagami T et al. Apixaban for the Treatment of Japanese Subjects With Acute Venous Thromboembolism (AMPLIFY-J Study). Circ J. 2015;79(6):1230–6.

82. Piazza G MV, Grosso M, et al. A randomized, open-label, multicenter study of the efficacy and safety of edoxaban monotherapy versus low-molecular weight heparin/warfarin in patients with symptomatic deep vein thrombosis—edoxaban thrombus reduction imaging study (eTRIS) [abstract]. Circulation. 2014;130:A12074.

83. Schulman S, Kakkar AK, Goldhaber SZ, Schellong S, Eriksson H, Mismetti P et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation. 2014;129(7):764–72.

84. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009;361(24): 2342–52.

85. Yamada N, Hirayama A, Maeda H, Sakagami S, Shikata H, Prins MH, et al. Oral rivaroxaban for Japanese patients with symptomatic venous thromboembolism - the J-EINSTEIN DVT and PE program. Thromb J. 2015;13:2.

86. Lamberts M, Staerk L, Olesen JB, Fosbol EL, Hansen ML, Harboe L et al. Major Bleeding Complications and Persistence With Oral Anticoagulation in Non-Valvular Atrial Fibrillation: Contemporary Findings in Real-Life Danish Patients. J Am Heart Assoc. 2017;6(2).

87. Ramagopalan S, Allan V, Saragoni S, Esposti LD, Alessandrini D, Perrone V et al. Patient characteristics and bleeding events in nonvalvular atrial fibrillation patients treated with apixaban or vitamin K antagonists: real-world evidence from Italian administrative databases. J Comp Eff Res. 2018;7(11):1063–71.

88. Kohsaka S, Murata T, Izumi N, Katada J, Wang F, Terayama Y. Bleeding risk of apixaban, dabigatran, and low-dose rivaroxaban compared with warfarin in Japanese patients with non-valvular atrial fibrillation: a propensity matched analysis of administrative claims data. Current medical research and opinion. 2017;33(11):1955–63.

89. Lee SR, Choi EK, Han KD, Jung JH, Oh S, Lip GYH. Edoxaban in Asian Patients With Atrial Fibrillation: Effectiveness and Safety. J Am Coll Cardiol. 2018;72(8):838–53.

90. Yap LB, Eng DT, Sivalingam L, Rusani BI, Umadevan D, Muhammad Z et al. A Comparison of Dabigatran With Warfarin for Stroke Prevention in Atrial Fibrillation in an Asian Population. Clin Appl Thromb Hemost. 2016;22(8):792–7.

91. Halvorsen S, Ghanima W, Fride Tvete I, Hoxmark C, Falck P, Solli O et al. A nationwide registry study to compare bleeding rates in patients with atrial fibrillation being prescribed oral anticoagulants. Eur Heart J Cardiovasc Pharmacother. 2017;3(1):28–36.

92. Chan YH, Yen KC, See LC, Chang SH, Wu LS, Lee HF et al. Cardiovascular, Bleeding, and Mortality Risks of Dabigatran in Asians With Nonvalvular Atrial Fibrillation. Stroke. 2016;47(2):441–9.

93. Jun M, Lix LM, Durand M, Dahl M, Paterson JM, Dormuth CR et al. Comparative safety of direct oral anticoagulants and warfarin in venous thromboembolism: multicentre, population based, observational study. BMJ. 2017;359:j4323.

94. Lip GY, Keshishian A, Kamble S, Pan X, Mardekian J, Horblyuk R et al. Real-world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin. A propensity score matched analysis. Thromb Haemost. 2016;116(5):975–86.

95. Larsen TB, Skjoth F, Kjaeldgaard JN, Lip GYH, Nielsen PB, Sogaard M. Effectiveness and safety of rivaroxaban and warfarin in patients with unprovoked venous thromboembolism: a propensity-matched nationwide cohort study. Lancet Haematol. 2017;4(5):e237–e44.

96. Pollack CV, Jr., Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA et al. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. N Engl J Med. 2017;377(5):431–41.

97. Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL et al. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. N Engl J Med. 2015;373(25):2413–24.

98. Connolly SJ, Milling TJ, Jr., Eikelboom JW, Gibson CM, Curnutte JT, Gold A et al. Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. N Engl J Med. 2016;375(12):1131–41.

99. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr. et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation. 2014;130(23):2071–104.

100. Macle L, Cairns J, Leblanc K, Tsang T, Skanes A, Cox JL et al. 2016 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation. Can J Cardiol. 2016;32(10):1170–85.

101. Atrial fibrillation: management. Clinical guidline [CG180]. London: National Institute for Health and Care Excellence; 2014. Available from https://www.nice.org.uk/guidance/cg180, accessed 30 October 2019.

102. Brieger D, Amerena J, Attia J, Bajorek B, Chan KH, Connell C et al. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Diagnosis and Management of Atrial Fibrillation 2018. Heart Lung Circ. 2018;27(10):1209–66.

103. Liberato NL, Marchetti M. Cost-effectiveness of non-vitamin K antagonist oral anticoagulants for stroke prevention in non-valvular atrial fibrillation: a systematic and qualitative review. Expert Rev Pharmacoecon Outcomes Res. 2016;16(2):221–35.

104. Limone BL, Baker WL, Kluger J, Coleman CI. Novel anticoagulants for stroke prevention in atrial fibrillation: a systematic review of cost-effectiveness models. PloS one. 2013;8(4):e62183.

105. Pinyol C, Cepeda JM, Roldan I, Roldan V, Jimenez S, Gonzalez P et al. A Systematic Literature Review on the Cost-Effectiveness of Apixaban for Stroke Prevention in Non-valvular Atrial Fibrillation. Cardiol Ther. 2016;5(2):171–86.

106. Amin A, Bruno A, Trocio J, Lin J, Lingohr-Smith M. Real-World Medical Cost Avoidance When New Oral Anticoagulants are Used Versus Warfarin for Venous Thromboembolism in the United States. Clin Appl Thromb Hemost. 2016;22(1):5–11.

107. Amin A, Jing Y, Trocio J, Lin J, Lingohr-Smith M, Graham J. Evaluation of medical costs associated with use of new oral anticoagulants compared with standard therapy among venous thromboembolism patients. J Med Econ. 2014;17(11):763–70.

108. Margolis JM, Deitelzweig S, Kline J, Tran O, Smith DM, Crivera C, et al. Pulmonary Embolism Inpatients Treated With Rivaroxaban Had Shorter Hospital Stays and Lower Costs Compared With Warfarin. Clin Ther. 2016;38(11):2496–503.

109. Weeda ER, Kohn CG, Peacock WF, Fermann GJ, Crivera C, Schein JR et al. Rivaroxaban versus Heparin Bridging to Warfarin Therapy: Impact on Hospital Length of Stay and Treatment Costs for Low-Risk Patients with Pulmonary Embolism. Pharmacotherapy. 2016;36(10):1109–15.

110. Courtney W, Groarke E, Conway J, Conway E, Bourke D, Saunders J et al. A Direct Oral Anticoagulant as a Cost Effective Alternative to Warfarin for Treatment of Provoked Venous Thrombosis. Ir Med J. 2016;109(9):466.

111. Bamber L, Muston D, McLeod E, Guillermin A, Lowin J, Patel R. Cost-effectiveness analysis of treatment of venous thromboembolism with rivaroxaban compared with combined low molecular weight heparin/vitamin K antagonist. Thromb J. 2015;13:20.

112. Jimenez D, Jimenez S, Martinez-Lopez I, Monreal M, Vicente V, Perez-Alcantara F et al. Cost-effectiveness of rivaroxaban in the treatment of venous thromboembolism in Spain. Pharmacoeconomics. 2015;12(4):147–56.

113. Jugrin AV, Ustyugova A, Urbich M, Lamotte M, Sunderland T. The cost-utility of dabigatran etexilate compared with warfarin in treatment and extended anticoagulation of acute VTE in the UK. Thromb Haemost. 2015;114(4):778–92.

114. Lanitis T, Leipold R, Hamilton M, Rublee D, Quon P, Browne C et al. Cost-effectiveness of Apixaban Versus Other Oral Anticoagulants for the Initial Treatment of Venous Thromboembolism and Prevention of Recurrence. Clin Ther. 2016;38(3):478-93.e1–16.

115. Law S, Ghag D, Grafstein E, Stenstrom R, Harris D. A pharmacoeconomic study of traditional anticoagulation versus direct oral anticoagulation for the treatment of venous thromboembolism in the emergency department. CJEM. 2016;18(5):340–8.

116. Lefebvre P, Coleman C, Bookhart B, Wang S, Mody S, Tran K et al. Cost-effectiveness of rivaroxaban compared with enoxaparin plus a vitamin K antagonist for the treatment of venous thromboembolism. J Med Econ. 2014; 17(1):52–64.

117. Maervoet J, Verhamme P, Hainaut P, McLeod E, Bamber L, Raf P et al. Cost effectiveness of Rivaroxaban versus low molecular weight heparin and vitamin K antagonists for the treatment of deep-vein thrombosis in the Belgian healthcare setting. Eur J Cardiovasc Med. 2015;3(1):452–61.

118. Preblick R, Kwong WJ, White RH, Goldhaber SZ. Cost-effectiveness of edoxaban for the treatment of venous thromboembolism based on the Hokusai-VTE study. Hosp Pract (1995). 2015;43(5): 249–57.

119. Quon P, Le HH, Raymond V, Mtibaa M, Moshyk A. Clinical and economic benefits of extended treatment with apixaban for the treatment and prevention of recurrent venous thromboembolism in Canada. J Med Econ. 2016;19(6):557–67.

120. Rudakova AV. Cost-effectiveness of new oral anticoagulants in the treatment and secondary prevention of venous thromboembolism. Rational Pharmacotherapy in Cardiology. 2015;11(5): 496–503.

121. Santos IF, Pereira S, McLeod E, Guillermin AL, Chatzitheofilou I. Economic analysis of rivaroxaban for the treatment and long-term prevention of venous thromboembolism in Portugal. Acta Med Port. 2014;27(5):615–24.

122. Seaman CD, Smith KJ, Ragni MV. Cost-effectiveness of rivaroxaban versus warfarin anticoagulation for the prevention of recurrent venous thromboembolism: a U.S. perspective. Thromb Res. 2013;132(6):647–51.

123. Stevanovic J, De Jong LA, Kappelhoff BS, Dvortsin EP, Voorhaar M, Postma MJ. Dabigatran for the treatment and secondary prevention of venous thromboembolism; a cost-effectiveness analysis for the Netherlands. PLoS One. 2016;11 (10) (no pagination)(e0163550).

# Section 12: CARDIOVASCULAR MEDICINES

## 12.3 Antihypertensive medicines

*Fixed-dose combination antihypertensives – addition – EML*

| | |
|---|---|
| **Lisinopril + amlodipine** | **ATC Code: C09BB03** |
| **Lisinopril + hydrochlorothiazide** | **ATC Code: C09BA03** |
| **Telmisartan + amlodipine** | **ATC Code: C09DB04** |
| **Telmisartan + hydrochlorothiazide** | **ATC Code: C09DA07** |

**Proposal**

The application proposed the addition of four two-drug fixed-dose combinations (FDC) to the core list of the EML for use in the treatment of hypertension.

**Applicant**

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**WHO Technical Department**

Comments on the application were received from the WHO Department for Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention. The technical unit advised that it supported the inclusion of dual FDC antihypertensives to the EML, stating that most people with hypertension require more than one antihypertensive agent to achieve control and that FDCs are likely to improve adherence to treatment.

**EML/EMLc**

EML

**Section**

12.3 Antihypertensive Medicines

**Dose form(s) & strengths(s)**

Lisinopril + amlodipine: tablet 10 mg + 5 mg; 20 mg + 5 mg; 20 mg + 10 mg

Lisinopril + hydrochlorothiazide: tablet 10 mg + 12.5 mg; 20 mg + 12.5 mg; 20 mg + 25 mg

Telmisartan + amlodipine: tablet 40 mg + 5 mg; 80 mg + 5 mg; 80 mg + 10 mg

Telmisartan + hydrochlorothiazide: tablet 40 mg + 12.5 mg; 80 mg + 12.5 mg; 80 mg + 25 mg

**Core/Complementary**

Core

**Individual/Square box listing**

Square box listings as representative of the following pharmacological class combinations:

- ACE inhibitor + dihydropyridine calcium channel blocker
- ACE inhibitor + thiazide or thiazide-like diuretic
- Angiotensin receptor blocker + dihydropyridine calcium channel blocker
- Angiotensin receptor blocker + thiazide or thiazide-like diuretic

Square box listings of the components of the FDCs should be interpreted by countries as limited to:

- Lisinopril > any ACE inhibitor (ATC code C09AA--)
- Telmisartan > any angiotensin receptor blocker (ATC code C09CA--)
- Amlodipine > any once-daily dihydropyridine calcium channel blocker (intrinsically long-acting e.g. amlodipine, lercanidipine, lacidipine; or modified-release e.g. nifedipine, felodipine)
- HCTZ > chlortalidone or indapamide.

**Background** (if relevant, eg. resubmission, previous EC consideration)

The pharmacological classes of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, calcium channel blockers and thiazide diuretics are all represented on the EML with square box listings. The individual components of the proposed FDCs are included on the EML either specifically (amlodipine, hydrochlorothiazide) or as members of pharmacological classes represented by square box listings (lisinopril (represented by enalapril), telmisartan (represented by losartan)).

In 2017, an application for inclusion of an FDC of lisinopril + hydrochlorothiazide on the EML was not recommended by the Committee. The Committee considered that listing a single FDC of medicines for treatment of hypertension would limit choice from the variety of combinations, component medicines and dosages available that would be necessary to tailor therapy for individual patients.

However, the Committee acknowledged that appropriate FDCs for hypertension may have advantages over the single medicines given concomitantly, including increased adherence and reduced pill burden. An explanatory note to this effect was included in Section 12 of the EML (*1*).

To address the concerns of the 2017 Committee, the current application proposed four different combinations, with each component qualified with a square box, and with multiple dose options.

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**Public health relevance** (burden of disease)

Cardiovascular diseases are the leading cause of death globally, responsible for 31% of total deaths in 2016. Hypertension is the leading modifiable risk factor for cardiovascular disease. The global prevalence of hypertension (defined as systolic and/or diastolic blood pressure more than or equal to 140/90 mmHg) in adults was 24.1% in men and 20.1% in women in 2015. The number of adults with hypertension has increased by over half a billion to 1.13 billion in the 40 years to 2015, with the increase seen largely in low- and middle-income countries (LMICs) (*2*).

In LMICs, nearly three quarters of patients treated for hypertension in 2010 did not have adequate blood pressure control (*3*). Data from the ALLHAT trial (*4*) suggest that two or more antihypertensive medicines are required by the majority of patients in order to achieve blood pressure targets below 140/90 mmHg.

A meta-analysis of 42 trials involving almost 11 000 participants found that combination therapy using medicines from any two pharmacological classes of thiazide diuretics, beta-blockers, ACE-inhibitors and calcium channel blockers produces a greater blood pressure lowering effect than doubling the dose of monotherapy (*5*). Greater blood pressure lowering effects have been associated with greater reductions in cardiovascular events such as myocardial infarction and stroke (*6*–*9*).

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**Summary of evidence: benefits** (from the application)

**Dual versus monotherapy for initial treatment of hypertension**

A systematic review conducted for the application of dual versus monotherapy as initial treatment identified 33 randomized trials involving over 10 000 participants. Compared to patients receiving monotherapy, there was a 27% increase in the rate of achieving blood pressure control among patients receiving dual combination therapy.

The application also described the results of three studies that compared initial combination antihypertensive treatment with alternative initial treatment regimens including monotherapy, sequential monotherapy and stepped-care (*10*–*12*). In all comparisons, combination therapy was associated with greater improvements in blood pressure control, without an increase in adverse events.

### Effects of combination therapy versus placebo on cardiovascular events

As in the 2017 application, the current application presented the same findings of a review of 11 randomized controlled trials (RCTs) involving 35 208 patients comparing combination antihypertensive treatment with placebo/no treatment on cardiovascular outcomes and mortality (*13*–*23*). Combination therapy was found to significantly reduce the risk of cardiovascular outcomes and mortality for all studies combined, and to a greater extent when only the studies demonstrating a reduction in systolic pressure of more than 6 mmHg were considered.

### Review of RCTs assessing antihypertensive effects of the proposed FDCs

#### *Lisinopril + hydrochlorothiazide*

Two trials reported data for either the comparison of lisinopril + HCTZ versus placebo or versus component monotherapy (*24*, *25*). In both studies, combination therapy was associated with a significant reduction in both systolic and/or diastolic blood pressure.

Two trials reported data for the comparison of lisinopril + HCTZ with alternative dual combination therapy (sustained release verapamil + trandolapril, atenolol + chlorthalidone (*25*); and candesartan + HCTZ (*26*)). There were no significant differences in the adjusted mean change from baseline in sitting systolic or diastolic blood pressure between treatment groups.

#### *Telmisartan + amlodipine*

One trial reported data for various strength combinations of telmisartan (20–80 mg) + amlodipine (2.5–10 mg) versus placebo (*27*). Six trials reported data for various strengths of the combination compared with single component monotherapy at the same or higher dose (*28*–*33*). All studied comparisons favoured dual combination therapy for differences in mean systolic and diastolic blood pressure.

One trial compared telmisartan 80 mg + amlodipine 5 mg with olmesartan 40 mg + HCTZ 12.5 mg (*34*). At six months, both combinations were associated with significant reductions in mean systolic and diastolic blood pressure. There was no significant difference between treatment groups.

#### *Telmisartan + hydrochlorothiazide*

Two trials reported data for the comparison of telmisartan + HCTZ versus placebo (*35*, *36*). In both studies, there were significant differences in both systolic and diastolic blood pressure favouring combination therapy.

Three trials reported data for the comparison of telmisartan + HCTZ versus telmisartan monotherapy (*37*–*39*). Combination therapy was significantly more effective than the corresponding strength of telmisartan monotherapy in reducing mean systolic and diastolic blood pressure.

Four trials reported data for the comparison of telmisartan + HCTZ with the same combination at different doses of HCTZ (*40*), or different dual combinations (*36*, *41*, *42*). Both doses of telmisartan + HCTZ (12.5 mg and 25 mg) produced reductions from baseline in adjusted mean seated systolic and diastolic blood pressure, with the 25 mg HCTZ combination producing a greater blood pressure lowering effect (*40*). Comparisons of telmisartan + HCTZ with dual combination therapy with valsartan + HCTZ, showed that compared with placebo, both combinations produced substantial reductions in blood pressure. Patients treated with telmisartan + HCTZ had significantly greater reductions in systolic and diastolic blood pressure than patients treated with valsartan + HCTZ (*36*, *41*). In the comparison of telmisartan + HCTZ versus dual combination therapy with barnidipine (a calcium channel blocker) + losartan, blood pressure was reduced in both treatment arms, however, the blood pressure-lowering effect was greater in the barnidipine + losartan group (*42*).

*Lisinopril + amlodipine*

One small (n=15) cross-over trial compared lisinopril + amlodipine with single component monotherapy (*43*). After one month, combination therapy demonstrated a significant additional blood pressure-lowering effect compared with each component as monotherapy.

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**Summary of evidence: harms** (from the application)

The adverse event profiles of ACE inhibitors, angiotensin receptor blockers, thiazide diuretics, and dihydropyridine calcium channel blockers are well known. Safety data from the studies of the dual combination therapies presented with the application are consistent with the known adverse event profiles of these medicines.

An analysis of 33 placebo-controlled trials of antihypertensive therapy as monotherapy or dual combination therapy found that dual therapy was associated with adverse events at less than double the rate observed for monotherapy (7.5% vs 5.2%) (*44*), suggesting that there is not an additive effect of dual therapy in relation to adverse events.

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**Additional evidence** (not in the application)

N/A

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**WHO Guidelines**

The HEARTS technical package for cardiovascular disease management in primary care includes recommended treatment protocols for dual combination antihypertensive treatment as both first- and second-line interventions for hypertension (*45*, *46*).

Dual combination antihypertensive therapy is recommended for use in patients not controlled on monotherapy, and in selected patients as initial therapy in multiple international guidelines including Europe (*47*), the United States (*48*), India (*49*), Thailand (*50*) and China (*51*). Single pill FDCs are recommended in most guidelines as an alternative to separate pills to improve patient adherence. The 2018 European guidelines also recommended FDC therapy as initial therapy in most patients (*47*).

**Costs/cost-effectiveness**

The application presented a review of private sector prices in India of the proposed FDCs versus their component monotherapies, which showed the FDC prices to be similar or slightly lower than component monotherapies.

However, the Committee noted that this may not be the case in every jurisdiction. For example, a review of the MSH International Medical Products Price Guide (2015) reports the mean buyer prices to be US$ 0.1977, US$ 0.0233 and US$ 0.0077 for lisinopril + HCTZ 20 mg/12.5 mg, lisinopril 20 mg, and HCTZ 12.5mg, respectively.

The Committee agreed that medicine prices should be considered with regard to the potential cost-savings from improved hypertension control due to improved compliance (*52–54*), reduced need for repeat visits to achieve blood pressure control and with the use of FDC in settings where individuals requiring more than one blood pressure-lowering drug may have limited access to multiple drug classes (*55*, *56*). A price advantage of an FDC over its component monotherapies may be justified by a demonstrated advantage in clinical outcome or compliance.

FDC therapy may also be associated with reduced health system costs and out-of-pocket costs for patients. In a meta-analysis published in 2011 (*57*), the annual total health care costs from 44 336 patients in all included observational studies (n = 7) were lower for patients treated with FDC compared to individual monotherapy for hypertension (mean pooled difference US$ 1357; 95%CI US$ 778 to US$ 1935). An analysis using data from the 2004 Medical Expenditure Panel Survey in the United States (*58*) demonstrated that total monthly prescription expenditures were lower for 23 of 27 FDC medications examined compared to the separate individual drugs (mean decrease in monthly total costs US$ 20.89, 95%CI US$ 20.10 to US$ 21.68). Using pharmacy claims data in Japan, a study demonstrated transitioning to FDC therapy from separate drugs was associated with an annual saving of US$ 112 for patients (*59*). The cost savings of FDC therapy for patients also translate to the larger health system. In Canada, 60–100% of patients receiving two separate drugs transitioning to FDC therapy has been estimated to lead to a yearly cost-saving of US$ 27 million to US$ 45 million (*60*).

### Availability

The proposed FDCs are available globally, either in the stated combinations, or alternatives within pharmacological classes.

### Other considerations

N/A

### Committee recommendations

The Committee recommended the addition of four two-drug FDCs, each with multiple strength formulations to the core list of the EML for use in the treatment of hypertension. Each component of the combinations should be listed with a square box, indicating that other medicines within the respective pharmacological classes represent therapeutically equivalent alternatives. For the calcium channel blocker component, the square box should be limited to dihydropyridine class of calcium channel blockers.

The Committee accepted the efficacy of FDC antihypertensives compared to placebo or monotherapy for reducing blood pressure and cardiovascular events, but expressed concern that the application did not provide strong evidence of the claimed advantages of FDC therapy versus dual component monotherapy. However, the Committee accepted that many patients require multiple antihypertensive treatment to achieve blood pressure targets and recognized that FDCs may confer advantages for patients over single medicines given concomitantly in terms of better adherence and reduced pill burden.

The Committee considered that the ongoing availability of single agent antihypertensive medicines is critical to allow treatment modification where necessary, and that FDCs should not displace single components at country level.

The Committee also noted that the availability of multiple FDCs in varying strengths may be associated with significant supply chain and affordability issues for LMICs. The Committee noted that the cost of FDCs versus the sum of the cost of component monotherapies varies in different settings and is not always the same (or lower) than the sum of component monotherapies. The Committee stressed that the cost of FDCs should not be significantly higher than the sum of the cost of their component monotherapies. In particular, in resource-constrained settings where access is limited, the opportunity costs associated with treating patients with FDCs must be considered.

## References

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children) (WHO Technical Report Series, No. 1006). Geneva: World Health Organization; 2017. Available from https://apps.who.int/iris/bitstream/handle/10665/259481/9789241210157-eng.pdf, accessed 30 October 2019.

2. Zhou B, Bentham J, Di Cesare M, Bixby H, Goodarz D, Cowan MJ et al. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. Lancet. 2017;389(10064):37–55.
3. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K et al. Global Disparities of Hypertension Prevalence and Control: A Systematic Analysis of Population-Based Studies From 90 Countries. Circulation. 2016;134(6):441–50.
4. Cushman WC, Ford CE, Cutler JA, Margolis KL, Davis BR, Grimm RH et al. Success and predictors of blood pressure control in diverse North American settings: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). J Clin Hypertens (Greenwich). 2002; 4(6):393–404.
5. Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med. 2009;122(3):290–300.
6. Turnbull F. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet. 2003;362(9395): 1527–35.
7. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387(10022):957–67.
8. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009;338:b1665.
9. Xie X, Atkins E, Lv J, Bennett A, Neal B, Ninomiya T et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Lancet. 2016;387(10017):435–43.
10. Feldman RD, Zou GY, Vandervoort MK, Wong CJ, Nelson SA, Feagan BG. A simplified approach to the treatment of uncomplicated hypertension: a cluster randomized, controlled trial. Hypertension. 2009;53(4):646–53.
11. Mourad JJ, Waeber B, Zannad F, Laville M, Duru G, Andrejak M. Comparison of different therapeutic strategies in hypertension: a low-dose combination of perindopril/indapamide versus a sequential monotherapy or a stepped-care approach. J Hypertens. 2004;22(12):2379–86.
12. MacDonald TM, Williams B, Webb DJ, Morant S, Caulfield M, Cruickshank JK, et al. Combination Therapy Is Superior to Sequential Monotherapy for the Initial Treatment of Hypertension: A Double-Blind Randomized Controlled Trial. J Am Heart Assoc. 2017;6(11).
13. Lonn EM, Bosch J, Lopez-Jaramillo P, Zhu J, Liu L, Pais P et al. Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease. N Engl J Med. 2016;374(21):2009–20.
14. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358(24): 2560–72.
15. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet. 2001;358(9287):1033–41.
16. Hypertension-Stroke Cooperative Study Group. Effect of antihypertensive treatment on stroke recurrence. JAMA. 1974;229(4):409–18.
17. Carter AB. Hypotensive therapy in stroke survivors. Lancet. 1970;1(7645):485-9.

18. Dahlof B, Lindholm LH, Hansson L, Schersten B, Ekbom T, Wester PO. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). Lancet. 1991; 338(8778):1281–5.
19. Coope J, Warrender TS. Randomised trial of treatment of hypertension in elderly patients in primary care. Br Med J (Clin Res Ed). 1986;293(6555):1145–51.
20. Bulpitt CJ, Beckett NS, Peters R, Leonetti G, Gergova V, Fagard R et al. Blood pressure control in the Hypertension in the Very Elderly Trial (HYVET). J Hum Hypertens. 2012;26(3):157–63.
21. Smith WM. Treatment of mild hypertension: results of a ten-year intervention trial. Circ Res. 1977;40(5 Suppl 1):I98–105.
22. Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. JAMA. 1967;202(11):1028–34.
23. Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA. 1970;213(7):1143–52.
24. Chrysant SG. Antihypertensive effectiveness of low-dose lisinopril-hydrochlorothiazide combination. A large multicenter study. Lisinopril-Hydrochlorothiazide Group. Arch Intern Med. 1994;154(7):737–43.
25. de Leeuw PW, Notter T, Zilles P. Comparison of different fixed antihypertensive combination drugs: a double-blind, placebo-controlled parallel group study. J Hypertens. 1997;15(1):87–91.
26. McInnes GT, O'Kane KP, Istad H, Keinanen-Kiukaanniemi S, Van Mierlo HF. Comparison of the AT1-receptor blocker, candesartan cilexetil, and the ACE inhibitor, lisinopril, in fixed combination with low dose hydrochlorothiazide in hypertensive patients. J Hum Hypertens. 2000;14(4):263–9.
27. Littlejohn TW, 3rd, Majul CR, Olvera R, Seeber M, Kobe M, Guthrie R et al. Results of treatment with telmisartan-amlodipine in hypertensive patients. J Clin Hypertens (Greenwich). 2009;11(4): 207–13.
28. Zhu D, Gao P, Holtbruegge W, Huang C. A randomized, double-blind study to evaluate the efficacy and safety of a single-pill combination of telmisartan 80 mg/amlodipine 5 mg versus amlodipine 5 mg in hypertensive Asian patients. J Int Med Res. 2014;42(1):52–66.
29. Neutel JM, Mancia G, Black HR, Dahlof B, Defeo H, Ley L et al. Single-pill combination of telmisartan/amlodipine in patients with severe hypertension: results from the TEAMSTA severe HTN study. J Clin Hypertens (Greenwich). 2012;14(4):206–15.
30. Sharma AM, Bakris G, Neutel JM, Littlejohn TW, Kobe M, Ting N et al. Single-pill combination of telmisartan/amlodipine versus amlodipine monotherapy in diabetic hypertensive patients: an 8-week randomized, parallel-group, double-blind trial. Clin Ther. 2012;34(3):537–51.
31. Neldam S, Edwards C, Jones R. Switching patients with uncontrolled hypertension on amlodipine 10 mg to single-pill combinations of telmisartan and amlodipine: results of the TEAMSTA-10 study. Curr Med Res Opin. 2011;27(11):2145–53.
32. Neldam S, Lang M, Jones R. Telmisartan and amlodipine single-pill combinations vs amlodipine monotherapy for superior blood pressure lowering and improved tolerability in patients with uncontrolled hypertension: results of the TEAMSTA-5 study. J Clin Hypertens (Greenwich). 2011;13(7):459–66.
33. Sharma A, Bagchi A, Kinagi SB, Sharma YK, Baliga VP, Bollmall C. Results of a comparative, phase III, 12-week, multicenter, prospective, randomized, double-blind assessment of the efficacy and tolerability of a fixed-dose combination of telmisartan and amlodipine versus amlodipine monotherapy in Indian adults with stage II hypertension. Clin Ther. 2007;29(12):2667–76.

34. Jagodzinski A, Neumann JT, Ojeda F, Sorensen NA, Wild P, Munzel T et al. Cardiovascular Biomarkers in Hypertensive Patients with Medical Treatment-Results from the Randomized TEAMSTA Protect I Trial. Clin Chem. 2017;63(12):1877–85.
35. McGill JB, Reilly PA. Telmisartan plus hydrochlorothiazide versus telmisartan or hydrochlorothiazide monotherapy in patients with mild to moderate hypertension: a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial. Clin Ther. 2001;23(6):833–50.
36. White WB, Punzi HA, Murwin D, Koval SE, Davidai G, Neutel JM. Effects of the angiotensin II receptor blockers telmisartan vs valsartan in combination with hydrochlorothiazide 25 mg once daily for the treatment of hypertension. J Clin Hypertens (Greenwich). 2006;8(9):626–33.
37. Lacourciere Y, Tytus R, O'Keefe D, Lenis J, Orchard R, Martin K. Efficacy and tolerability of a fixed-dose combination of telmisartan plus hydrochlorothiazide in patients uncontrolled with telmisartan monotherapy. J Hum Hypertens. 2001;15(11):763–70.
38. Lacourciere Y, Martin K. Comparison of a fixed-dose combination of 40 mg telmisartan plus 12.5 mg hydrochlorothiazide with 40 mg telmisartan in the control of mild to moderate hypertension. Am J Ther. 2002;9(2):111–7.
39. Zhu DL, Bays H, Gao P, Mattheus M, Voelker B, Ruilope LM. Efficacy and tolerability of initial therapy with single-pill combination telmisartan/hydrochlorothiazide 80/25 mg in patients with grade 2 or 3 hypertension: a multinational, randomized, double-blind, active-controlled trial. Clin Ther. 2012;34(7):1613–24.
40. Neldam S, Edwards C. Results of increasing doses of hydrochlorothiazide in combination with an angiotensin receptor blocker in patients with uncontrolled hypertension. J Clin Hypertens (Greenwich). 2008;10(8):612–8.
41. White WB, Murwin D, Chrysant SG, Koval SE, Davidai G, Guthrie R. Effects of the angiotensin II receptor blockers telmisartan versus valsartan in combination with hydrochlorothiazide: a large, confirmatory trial. Blood Press Monit. 2008;13(1):21–7.
42. Derosa G, Querci F, Franzetti I, Dario Ragonesi P, D'Angelo A, Maffioli P. Comparison of the effects of barnidipine+losartan compared with telmisartan+hydrochlorothiazide on several parameters of insulin sensitivity in patients with hypertension and type 2 diabetes mellitus. Hypertens Res. 2015;38(10):690–4.
43. Cappuccio FP, Markandu ND, Singer DR, MacGregor GA. Amlodipine and lisinopril in combination for the treatment of essential hypertension: efficacy and predictors of response. J Hypertens. 1993;11(8):839–47.
44. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. BMJ. 2003;326(7404):1427.
45. HEARTS Technical Package for Cardiovascular Disease Management in Primary Health Care. Geneva: World Health Organization; 2016. Available from https://www.who.int/cardiovascular_diseases/hearts/Hearts_package.pdf, accessed 4 February 2019, accessed 29 September 2019.
46. HEARTS Technical package for cardiovascular disease management in primary health care: evidence-based treatment protocols. Geneva: World Health Organization; 2018. Available from https://apps.who.int/iris/bitstream/handle/10665/260421/WHO-NMH-NVI-18.2-eng.pdf;jsessionid=F7BBBE11E93C7AF4FB5799C127724A7B?sequence=1, accessed 29 September 2019.
47. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021–104.

48. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2018;138(17):e426–e83.

49. Indian guidelines on hypertension (I.G.H.) - III. 2013. J Assoc Physicians India. 2013;61(2 Suppl):6–36.

50. Buranakitjaroen P, Sitthisook S, Wataganara T, Ophascharoensuk V, Bunnag P, Roubsanthisuk W et al. 2015 Thai Hypertension Guideline. Available from http://www.thaihypertension.org/files/2015%20Thai%20Hypertension%20Guideline.pdf, accessed 29 September 2019.

51. Liu LS. [2010 Chinese guidelines for the management of hypertension]. Zhonghua xin xue guan bing za zhi. 2011;39(7):579–615.

52. Mallat SG, Tanios BY, Itani HS, Lotfi T, Akl EA. Free versus Fixed Combination Antihypertensive Therapy for Essential Arterial Hypertension: A Systematic Review and Meta-Analysis. PLoS One. 2016;11(8):e0161285.

53. Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. Hypertension. 2010;55(2):399–407.

54. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. Am J Med. 2007;120(8):713-9.

55. Attaei MW, Khatib R, McKee M, Lear S, Dagenais G, Igumbor EU et al. Availability and affordability of blood pressure-lowering medicines and the effect on blood pressure control in high-income, middle-income, and low-income countries: an analysis of the PURE study data. Lancet Public Health. 2017;2(9):e411–e9.

56. Khatib R, McKee M, Shannon H, Chow C, Rangarajan S, Teo K et al. Availability and affordability of cardiovascular disease medicines and their effect on use in high-income, middle-income, and low-income countries: an analysis of the PURE study data. Lancet. 2016;387(10013):61–9.

57. Sherrill B, Halpern M, Khan S, Zhang J, Panjabi S. Single-pill vs free-equivalent combination therapies for hypertension: a meta-analysis of health care costs and adherence. J Clin Hypertens (Greenwich). 2011;13(12):898–909.

58. Rabbani A, Alexander GC. Out-of-pocket and total costs of fixed-dose combination antihypertensives and their components. Am J Hypertens. 2008;21(5):509–13.

59. Akazawa M, Fukuoka K. Economic impact of switching to fixed-dose combination therapy for Japanese hypertensive patients: a retrospective cost analysis. BMC Health Serv Res. 2013;13:124.

60. Stankus V, Hemmelgarn B, Campbell NR, Chen G, McAlister FA, Tsuyuki RT. Reducing costs and improving hypertension management. Can J Clin Pharmacol. 2009;16(1):e151–5.

## 12.5 Antithrombotic medicines

### 12.5.2 Thrombolytic medicines

*Alteplase – addition – EML*

**Alteplase** **ATC Code: B01AD02**

**Proposal**

The application requested the inclusion of alteplase on the complementary list of the EML as a thrombolytic agent for use in patients diagnosed with acute ischaemic stroke (AIS) with a potentially handicapping neurological deficit at the time of thrombolysis, and treatment within 4.5 hours after onset of stroke symptoms (or after last proof of good health if unknown onset of symptoms).

**Applicants**

Patrik Michel, Michael Brainin on behalf of the World Stroke Organization

**WHO Technical Department**

Comments on the application were received from the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it supported the addition of alteplase to the EML, stating that it is a useful and effective drug and lowers morbidity and mortality associated with stroke when utilized correctly, and that cost-effectiveness had been demonstrated in various settings. The technical unit also noted that use of alteplase requires organized pre- and in-hospital care pathways in stroke-ready facilities, clinical training in diagnosing stroke, capacity to perform and interpret acute neuroimaging, continuous surveillance for at least 24 hours, and basic stroke management skills.

**EML/EMLc**

EML

**Section**

12.5.2 Thrombolytic medicines

**Dose form(s) & strengths(s)**

Powder for injection: 10 mg, 20 mg, 50 mg

**Core/Complementary**

Complementary

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Alteplase had not been previously considered for inclusion on the EML.

**Public health relevance** (burden of disease)

Globally, stroke is the second leading cause of death and disability, with the bulk of the burden (almost 80%) residing in low- and middle-income countries (LMICs) (*1*, *2*). In 2016, there were almost 14 million new cases of stroke, 5.5 million deaths associated with stroke and about 81 million stroke survivors. 30% of strokes are fatal in the first year and a further 70% of survivors are left with some level of disability. Although stroke incidence, mortality and disability burden rates have declined since 1990, in 2016 the absolute number of people who died from stroke, remained disabled from stroke, were affected by stroke (as measured by incidence of new strokes), or survived stroke had almost doubled largely due to aging of the population and population growth (*2*).

In well a well-developed stroke system, about 25% of all AIS patients who arrive to a stroke centre within 24 hours of last proof of usual health are eligible for intravenous thrombolysis (*3*). In Europe the current true rate is only 7.3% for all AIS *patients* (*4*), in the United States this number is probably similar (*5*). Very few patients in LMICs receive intravenous thrombolysis (*6*, *7*).

**Summary of evidence: benefits** (from the application)

A 2014 Cochrane systematic review of 27 trials involving 10 187 participants assessed the effectiveness and safety of thrombolytic therapy for treatment of acute ischaemic stroke (AIS) (*8*). Ten trials in the review assessed alteplase in 6886 participants. Compared to control, intravenous alteplase administered within 6 hours, was associated with a significant reduction in death or dependence (odds ratio (OR) 0.84, 95%CI 0.77 to 0.93, p=0.0006), corresponding to death or dependence in 40 fewer participants per 1000 treated (95%CI 20 fewer to 65 fewer). When a random-effects model analysis was performed due to the significant heterogeneity of treatment effect among the trials, the OR was 0.80 (95%CI 0.66 to 0.97, p=0.03).

For participants receiving alteplase within 3 hours (6 trials, 1779 participants), there was a significant reduction in death or dependence compared to control (59.3% vs 68.3%; OR 0.65, 95%CI 0.54 to 0.80, p<0.0001), with no significant heterogeneity, corresponding to death or dependence in 90 fewer participants per 1000 treated (95%CI 46 to 135).

There was a non-significant reduction of death in the long-term follow up of patients treated within 3 hours with an OR of 0.91 (95%CI 0.73 to 1.13,

p=0.39), with no statistically significant heterogeneity (p=0.22) and 14 fewer per 1000 deaths (95%CI 26 fewer to 55 fewer). For patients treated between 3 to 6 hours, the OR for this outcome was 0.97 (95%CI 0.85 to 1.09).

A meta-analysis of individual patient data from 6756 patients in nine randomized trials (RCTs) comparing alteplase with placebo or open control (*9*) found alteplase to be associated with increased odds of a good stroke outcome at three to six months (defined as a modified Rankin Score of 0 or 1) when administered within 4.5 hours of stroke onset, with earlier treatment (within 3 hours) associated with greater proportional benefit, irrespective of patient age or stroke severity.

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**Summary of evidence: harms** (from the application)

The application presented a summary of the key safety outcomes reported in the 2014 Cochrane systematic review (*8*).

Alteplase was associated with a greater proportion of patients experiencing early death (all causes, within seven to 10 days) compared to control (OR 1.44, 95%CI 1.18 to 1.76, p=0.0003; 5535 participants) corresponding to 25 more deaths per 1000 participants treated in absolute terms (95%CI 11 more to 40 more).

Alteplase was associated with a significant increase in the rate of fatal intracranial haemorrhage (ICH) within seven to 10 days compared to control (OR 4.18, 95%CI 2.99 to 5.84, p<0.00001; 6683 participants) corresponding to 30 additional ICH per 1000 treated participants in absolute terms (95%CI 20 to 40).

Early death due to causes other than fatal ICH occurred in 5.2% of alteplase treated patients compared with 5.7% of the control group (OR 0.93, 95%CI 0.73 to 1.18, p=0.54, 5303 participants).

There was no significant effect observed on deaths from all causes during follow-up (three to six months) between alteplase and control (OR 1.06, 95%CI 0.94 to 1.20; 7012 participants), corresponding to 7 more deaths per 1000 participants treated (95%CI 2 fewer to 25 more).

Orolingual angioedema associated with alteplase administration has been reported in case series studies (*10*, *11*).

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**Additional evidence** (not in the application)

N/A

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**WHO Guidelines**

WHO does not have approved guidelines for the management of AIS.

"Treatment of acute ischaemic stroke with intravenous thrombolytic therapy" was included as a policy option and cost-effective intervention in the

draft updated Appendix 3 of the *Global Action Plan for the prevention and control of non-communicable diseases 2013–2020*, to assist Member States in implementing actions to achieve targets for prevention and control of NCDs (*12*).

Use of IV alteplase within 4.5 hours of stroke onset is recommended in multiple national and international guidelines (*13–18*).

### Costs/cost-effectiveness

The application reports the price for a single IV dose of 63 mg alteplase for a 70 kg patient to range from US$ 260 (Brazil, public hospital) to US$ 6400 (average billing amount in the United States) (*19*, *20*).

Implementing and administering alteplase within the recommended 4.5 hours requires some initial investments in pre-hospital and intrahospital services. Many of these investments (such as stroke unit surveillance and care) will benefit stroke patients anyway, independently of thrombolysis being offered or not. These additional costs have to be balanced by generally shorter hospital stays, reduced rehabilitation needs, and reduced long-term care (including nursing homes and home care), given the reduction of handicap from thrombolysis (*21*).

The UK National Institute for Health and Care Excellence (NICE) concluded the cost for all treatment windows up to 4.5 hours were below accepted willingness-to-pay thresholds for alteplase (*19*). In another United Kingdom-based model, the authors concluded that any strategy that increases thrombolysis rates will result in cost savings and improved patient quality of life (*22*).

Studies from China and Brazil have also found alteplase treatment to be a cost-effective intervention (*23*, *24*).

A review of 16 studies of the cost-effectiveness of IV alteplase thrombolysis from Australia, Canada, China, Denmark, New Zealand, Spain, the United States and the United Kingdom, found that alteplase was a dominant or cost-effective strategy compared with traditional treatment in all but one of the studies (*25*).

### Availability

Alteplase has marketing approval in 104 countries globally. The 10 mg and 20 mg strengths may not be available in all jurisdictions.

### Other considerations

The Committee noted the use in practice of alteplase in acute myocardial infarction (MI) and considered that it is likely that alteplase would be used for this indication in some settings. The Committee noted that the EML currently includes streptokinase for MI and would welcome a future application reviewing the evidence for streptokinase and alteplase for this indication.

### Committee recommendations

The Committee recommended the addition of alteplase on the complementary list of the EML as a thrombolytic agent for use in patients diagnosed with acute ischaemic stroke on the basis of the evidence presented of improved patient outcomes in terms of reduced death or dependence when alteplase is administered within 4.5 hours of the onset of stroke symptoms.

The Committee acknowledged the significant global burden of stroke in terms of death and disability, and particularly in low- and middle-income countries. The Committee noted that optimal use of alteplase would require timely and highly organized care pathways, in facilities that are equipped and capable of managing stroke patients.

## References


1. Feigin VL, Roth GA, Naghavi M, Parmar P, Krishnamurthi R, Chugh S et al. Global burden of stroke and risk factors in 188 countries, during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet Neurol. 2016;15(9):913–24.
2. Global Burden of Disease compare data visualization. Seattle: Institute for Health Metrics and Evaluation, University of Washington; 2016. Available from https://vizhub.Healthdata.Org/gbd-compare/, accessed 29 September 2019.
3. Vanacker P, Lambrou D, Eskandari A, Mosimann PJ, Maghraoui A, Michel P. Eligibility and Predictors for Acute Revascularization Procedures in a Stroke Center. Stroke. 2016;47(7):1844–9.
4. Aguiar de Sousa D, von Martial R, Abilleira S, Gattringer T, Kobayashi A, Gallofré M et al. Access to and delivery of acute ischaemic stroke treatments: A survey of national scientific societies and stroke experts in 44 European countries. Eur Stroke J. 2019;4(1):13-28.
5. Schwamm LH, Ali SF, Reeves MJ, Smith EE, Saver JL, Messe S et al. Temporal trends in patient characteristics and treatment with intravenous thrombolysis among acute ischemic stroke patients at Get With The Guidelines-Stroke hospitals. Circ Cardiovasc Qual Outcomes. 2013; 6(5):543–9.
6. Urimubenshi G, Cadilhac DA, Kagwiza JN, Wu O, Langhorne P. Stroke care in Africa: A systematic review of the literature. Int J Stroke. 2018;13(8):797–805.
7. Pandian JD, William AG, Kate MP, Norrving B, Mensah GA, Davis S et al. Strategies to Improve Stroke Care Services in Low- and Middle-Income Countries: A Systematic Review. Neuroepidemiology. 2017;49(1-2):4561.
8. Wardlaw JM, Murray V, Berge E, del Zoppo GJ. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev. 2014(7):CD000213.
9. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet. 2014;384(9958):1929–35.
10. Engelter ST, Fluri F, Buitrago-Tellez C, Marsch S, Steck AJ, Ruegg S et al. Life-threatening orolingual angioedema during thrombolysis in acute ischemic stroke. J Neurol. 2005;252(10):1167–70.
11. Hill MD, Lye T, Moss H, Barber PA, Demchuk AM, Newcommon NJ et al. Hemi-orolingual angioedema and ACE inhibition after alteplase treatment of stroke. Neurology. 2003;60(9): 1525–7.

12. Preparation for the third High-level Meeting of the General Assembly on the Prevention and Control of Non-communicable Diseases, to be held in 2018 - Report by the Director-General. Geneva: World Health Organization; 2018. Available from http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_27-en.pdf, 29 September 2019.
13. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2018;49(3):e46–e110.
14. Boulanger JM, Lindsay MP, Gubitz G, Smith EE, Stotts G, Foley N et al. Canadian Stroke Best Practice Recommendations for Acute Stroke Management: Prehospital, Emergency Department, and Acute Inpatient Stroke Care, 6th Edition, Update 2018. Int J Stroke. 2018;13(9):949–84.
15. Bryer A, Connor M, Haug P, Cheyip B, Staub H, Tipping B et al. South African guideline for management of ischaemic stroke and transient ischaemic attack 2010: a guideline from the South African Stroke Society (SASS) and the SASS Writing Committee. S Afr Med J. 2010;100(11 Pt 2):747–78.
16. Dong Q, Dong Y, Liu L, Xu A, Zhang Y, Zheng H et al. The Chinese Stroke Association scientific statement: intravenous thrombolysis in acute ischaemic stroke. Stroke Vasc Neurol. 2017;2(3): 147–59.
17. Michel P, Engelter S, Arnold M, Hungerbühler HJ, Nedeltchev K, Georgiadis D et al. Thrombolyse de l'attaque cérébrale ischémique : Recommandations actualisées. Swiss Medical Forum. 2009;9(49):982–4.
18. Cho KH, Ko SB, Kim DH, Park HK, Cho AH, Hong KS et al. Focused Update of Korean Clinical Practice Guidelines for the Thrombolysis in Acute Stroke Management. Korean J Stroke. 2012;14:95–105.
19. Holmes M, Davis S, Simpson E. Alteplase for the treatment of acute ischaemic stroke: a NICE single technology appraisal; an evidence review group perspective. Pharmacoeconomics. 2015;33(3):225–33.
20. Kleindorfer D, Broderick J, Demaerschalk B, Saver J. Cost of Alteplase Has More Than Doubled Over the Past Decade. Stroke. 2017;48(7):2000–2.
21. Dirks M, Baeten SA, Dippel DW, van Exel NJ, van Wijngaarden JD, Huijsman R et al. Real-life costs and effects of an implementation program to increase thrombolysis in stroke. Neurology. 2012;79(6):508–14.
22. Penaloza-Ramos MC, Sheppard JP, Jowett S, Barton P, Mant J, Quinn T et al. Cost-effectiveness of optimizing acute stroke care services for thrombolysis. Stroke. 2014;45(2):553–62.
23. Pan Y, Chen Q, Zhao X, Liao X, Wang C, Du W et al. Cost-effectiveness of thrombolysis within 4.5 hours of acute ischemic stroke in China. PLoS One. 2014;9(10):e110525.
24. Araujo DV, Teich V, Passos RB, Martins SC. Analysis of the cost-effectiveness of thrombolysis with alteplase in stroke. Arq Bras Cardiol. 2010;95(1):12–20.
25. Joo H, Wang G, George MG. A literature review of cost-effectiveness of intravenous recombinant tissue plasminogen activator for treating acute ischemic stroke. Stroke Vasc Neurol. 2017;2(2): 73–83.

# Section 17: GASTROINTESTINAL MEDICINES

## 17.2 Antiemetic medicines

*Aprepitant – addition – EML and EMLc*

**Aprepitant** **ATC Code: A04AD12**

**Proposal**

The application requested the inclusion of aprepitant on the EML and EMLc as an antiemetic medicine for the supportive care of cancer patients receiving moderately to highly emetogenic chemotherapy.

**Applicants**

European Society for Medical Oncology (ESMO)

**WHO Technical Department**

Comments on the application were received from the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it supported the inclusion of aprepitant on the Model Lists as supportive care for chemotherapy-induced nausea in patients receiving moderately to highly emetogenic antineoplastic chemotherapy.

**EML/EMLc**

EML and EMLc

**Section**

17.2 Antiemetic medicines

**Dose form(s) & strengths(s)**

Capsule: 40 mg, 80 mg, 125 mg, 165 mg
Powder for oral suspension: 125 mg

**Core/Complementary**

Complementary

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Aprepitant has not previously been considered for inclusion on the Model Lists.

**Public health relevance** (burden of disease)

Chemotherapy-induced nausea and vomiting (CINV) is one of the most represented and significant side-effects related to chemotherapy. According to European Society of Medical Oncology (ESMO) and to the Multinational Association of Supportive Care in Cancer (MASCC), vomiting and, especially, nausea, continue to be two of the most distressing side-effects of cancer chemotherapy (*1*). Inadequately controlled CINV and radiotherapy-induced nausea and vomiting (RINV) can precipitate a number of medical complications, resulting in life-threatening conditions, including severe dehydration and electrolyte imbalance with electrocardiogram (ECG) changes or myocardial dysfunctions and Mallory-Weiss tears of the oesophagus. These complications can impact on the burden of care, increasing the efforts and costs of hospitalization and reducing the overall quality of life for patients, including a poorer outcome (*2*). The distress resulting from these symptoms may potentially lead to the patient's refusal to continue with the most effective antitumour therapy (*3*). According to a temporal criterion, the chemotherapy-associated emetic symptoms are categorized as acute or delayed: acute CINV occurs in the first 24 hours after chemotherapy, and delayed CINV at more than 24 hours. Aprepitant is indicated for prevention of both acute and delayed CINV.

A four-level classification of chemotherapy agents has been accepted by registration authorities and groups producing recommendations on antiemetics, according to the emetogenic potential: high (emetic risk >90%); moderate (30%–90%); low (10%–30%); and minimal (<10%). To provide an example, anthracycline-taxane containing regimens and cisplatin > 50 mg/m² are considered highly emetogenic; carboplatin, bendamustine and doxorubicin monotherapy are classified as moderately emetogenic; docetaxel monotherapy, gemcitabine, 5-FU and bortezomib are considered low emetogenic medicines (*4*).

**Summary of evidence: benefits** (from the application)

The application presented the findings of multiple clinical trials of aprepitant, using the MASCC/ESMO 2016 consensus guidelines for the prevention of chemotherapy and radiotherapy-induced nausea and vomiting (*1*) as a reference source. For the prevention of highly emetogenic chemotherapy CINV, a three-drug regimen including single doses of an anti-5-HT3, dexamethasone and anti-NK1 given before chemotherapy is recommended (MASCC level of confidence: high; MASCC level of consensus: high; ESMO level of evidence I; ESMO grade of recommendation: A) in the MASCC/ESMO guidelines.

***Adults:***

In a multicentre, double-blind, placebo-controlled trial in 421 Chinese cancer patients (*5*), addition of aprepitant to standard therapy with granisetron and

dexamethasone resulted in an increased absolute rate of patients achieving a complete response (no emesis and no use of rescue therapy) during the overall phase (+12.9%, p=0.007). The benefit was mainly attributable to better control of delayed CINV with an increase of 14.6% of patients in absolute terms. Complete response rates for treatment groups were almost identical for acute CINV.

In a multicentre, double-blind, placebo-controlled trial in 324 Japanese cancer patients (*6*), addition of aprepitant to therapy with a 5-HT3 receptor antagonist and dexamethasone prior to chemotherapy resulted in a higher percentage of patients with "no vomiting" in the overall phase (78.2 vs 54.8; p<0.0001), delayed phase (80.1 vs 56.9; p<0.0001), and acute phase 96.0 vs 91.1, respectively; p=0.0495). The percentage of patients with "no significant nausea" was higher in the aprepitant group than in the placebo group in the overall phase (85.4 vs 74.7; p=0.0143) and in the delayed phase (85.4 vs 76.0; p=0.0274), but there was no difference between groups in the acute phase.

Similar results have been observed in patients receiving moderately to highly emetogenic chemotherapy in other disease-oriented clinical trials using moderately to highly emetogenic regimens, including treatments for lung cancer and germ-cell tumours trials in Asian and non-Asian populations (*7–12*).

In a clinical trial of 264 patients preparing to undergo a stem cell transplant, patients were randomized to receive oral aprepitant or placebo in combination with oral ondansetron and dexamethasone during and for three days after the completion of the preparative high-dose cyclophosphamide regimens before the transplant (*13*). Patients who received aprepitant had higher complete response rates (81.9% vs 65.8%; p<0.001) compared to the standard treatment. 48.9% of patients in the aprepitant arm were able to maintain an intake of food >50% of normal versus only 14.6% of patients in the placebo arm, supporting the value of aprepitant in the overall supportive care of cancer patients.

***Children:***

In a randomized, double-blind, placebo-controlled trial, chemotherapy naive children aged 5 to 18 years receiving highly emetogenic chemotherapy were randomized to intravenous ondansetron (0.15 mg/kg) and dexamethasone (0.15 mg/kg) prior to chemotherapy followed by oral ondansetron and dexamethasone and either oral aprepitant (15-40 kg = days 1–3, 80 mg; 41-65 kg = day 1, 125 mg and days 2–3, 80 mg) one hour before chemotherapy or placebo (n=96) (*14*). The patients enrolled presented with both haematological and solid tumours: 25% received the treatment for Hodgkin lymphoma and the remaining 75% for sarcoma (osteosarcoma, Ewing sarcoma, rhabdomyosarcoma) or adenoid cystic carcinoma. Overall, 84% of patients in the placebo arm had moderate to severe vomiting compared to 56% in the aprepitant arm (p=0.004). There was less moderate and severe vomiting reported in the group receiving aprepitant

compared to the placebo group (38% vs 72, p = 0.001) in the acute phase and a non-significant difference between the two groups in the delayed phase (42% vs 56%, p = 0.18). Complete response was higher in aprepitant arm, registered in the acute phase for 48% of patients compared to 12% in the placebo arm (p<0.001). The use of aprepitant resulted in better food intake (normal in 48% and 28% of the children receiving aprepitant versus placebo, p=0.04) and fluid intake (normal in 62% and 40%, p=0.03).

In another Phase III trial, aprepitant for CINV prevention was assessed in patients aged six months to 17 years scheduled to receive either moderately or highly emetogenic chemotherapy (*15*). 307 patients were randomized to receive aprepitant plus ondansetron on day 1, followed by aprepitant on days 2 and 3, or placebo plus ondansetron on day 1 followed by placebo on days 2 and 3; dexamethasone was incorporated in nearly one third of the patients, with no difference between the study and control group. Patients presented with haematological and solid tumours. 77/152 (51%) patients in the aprepitant group and 39/150 (26%) in the control group achieved a complete response in the delayed phase (p<0.0001), reporting an increase of 25% in absolute terms; similar results were found in the acute phase (complete response in the acute phase for aprepitant: 66% vs 52%, p=0.0135) and overall control (40% vs 20%, p=0.0002).

***Meta-analyses:***

Clinical data of aprepitant as antiemetic agent for moderately to highly emetogenic chemotherapy have been analysed systematically, addressing the role and benefit in cancer treatments.

A meta-analysis performed in China, of ten studies of aprepitant for prevention of CINV, involving 4376 patients (*16*) found that for acute CINV, aprepitant improved the complete response by 14.21% in the acute phase, when combined with ondansetron and dexamethasone (83.33% vs 72.96%; p<0.001); patients receiving cisplatin seemed to derive a greater benefit than those who received an anthracycline plus cyclophosphamide regimen. For delayed CINV, aprepitant could improve vomiting by 14.98% compared with ondansetron (p=0.004).

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**Summary of evidence: harms** (from the application)

The safety of aprepitant has been evaluated in the clinical trials.

Hu et al (*5*) reported similar occurrences of drug-related adverse events (AEs) in 11.7% (24/205) of patients in the aprepitant group and 13.3% (28/210) of patients in the placebo-controlled therapy group. One or more AEs were reported in 40.0% (8/205) of patients in the aprepitant group and in 44.3% (93/210) of patients in the standard therapy group, representing similar occurrences. AEs included fatigue (5.9% and 1.9% in the aprepitant and placebo-controlled group, respectively), dizziness (2.4% and 0%), anaemia (2% and 0%),

insomnia (2% and 5.7%), upper abdominal pain (0% and 2.9%), and non-cardiac chest pain (0% and 1%). Overall, no severe drug-related serious AEs or laboratory anomalies were reported during cycle 1, and there were no discontinuations due to medication-related AEs.

In the trial of patients preparing for stem-cell transplantation (*13*), incorporation of aprepitant had no effect on the engraftment and the survival, supporting the oncological safety in terms of the cancer outcome and excluding significant interference with the antineoplastic agents used.

Pharmacokinetic studies have shown that drug–drug interactions with aprepitant may exist, but are not considered clinically meaningful (*17*).

In children, the safety profile of aprepitant appears consistent with the reports in adult populations (*15*).

**Additional evidence** (not in the application)

N/A

**WHO Guidelines**

None available.

**Costs/cost-effectiveness**

The application presented two studies that evaluated the cost-effectiveness of aprepitant regimens for CINV.

In a decision–analytic model study in Germany, an aprepitant regimen (aprepitant/ondansetron/dexamethasone) was compared with a control (ondansetron/dexamethasone) regimen, addressing clinical results and resource utilization (*18*). Incremental drug cost per patient and cycle for antiemetic prophylaxis was € 73.38. Expected health care utilization cost was € 154.99 in the aprepitant group and € 178.77 in the control group. Hence, it was estimated that 42% of the aprepitant drug cost was offset by lower resource use in the aprepitant group. Cost offsets arose mainly from lower doses of dexamethasone (€ 12.54), reduced use of rescue medication (€ 7.38), and avoided hospitalizations (€ 15.86). For the cost-effectiveness analysis (CEA), the range was € 26,135–31,646 per QALY gained with aprepitant and was judged cost-effective.

The same conclusion was reached in a CEA performed in UK, considering patients receiving chemotherapy for breast cancer (*19*). An average of £ 37.11 (78%) of the cost of aprepitant was offset by the reduction in health care resource utilization costs; use of the aprepitant was associated with an additional cost of £ 28 for each emesis-free day gained and £ 22 for each CINV-free day gained. The ICER with aprepitant, was £ 10 847/QALY.

**Availability**

Aprepitant is available globally. Generic brands are available.

### Other considerations

Aprepitant should be used in combination with dexamethasone and a 5-HT3 receptor antagonist.

### Committee recommendations

The Committee recognized the importance of adequate control of nausea and vomiting in patients undergoing cancer chemotherapy, in terms quality of life and clinical outcomes of treatment.

The Expert Committee recommended the addition of aprepitant to the complementary list of the EML and EMLc as an antiemetic medicine for the supportive care of cancer patients receiving moderately to highly emetogenic chemotherapy on the basis of a favourable benefit to risk profile.

The Committee noted that aprepitant, in combination with dexamethasone and a 5-HT3 receptor antagonist (e.g. ondansetron), is more effective than standard antiemetic therapy at reducing both acute and delayed onset nausea and vomiting associated with chemotherapy.

## References

1. Roila F, Molassiotis A, Herrstedt J, Aapro M, Gralla RJ, Bruera E et al. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann Oncol. 2016;27(suppl 5):v119–v33.
2. Schnell FM. Chemotherapy-induced nausea and vomiting: the importance of acute antiemetic control. Oncologist. 2003;8(2):187–98.
3. Doherty KM. Closing the gap in prophylactic antiemetic therapy: patient factors in calculating the emetogenic potential of chemotherapy. Clin J Oncol Nurs. 1999;3(3):113–9.
4. Grunberg SM, Osoba D, Hesketh PJ, Gralla RJ, Borjeson S, Rapoport BL et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity--an update. Support Care Cancer. 2005;13(2):80–4.
5. Hu Z, Cheng Y, Zhang H, Zhou C, Han B, Zhang Y et al. Aprepitant triple therapy for the prevention of chemotherapy-induced nausea and vomiting following high-dose cisplatin in Chinese patients: a randomized, double-blind, placebo-controlled phase III trial. Support Care Cancer. 2014;22(4):979–87.
6. Yahata H, Kobayashi H, Sonoda K, Shimokawa M, Ohgami T, Saito T et al. Efficacy of aprepitant for the prevention of chemotherapy-induced nausea and vomiting with a moderately emetogenic chemotherapy regimen: a multicenter, placebo-controlled, double-blind, randomized study in patients with gynecologic cancer receiving paclitaxel and carboplatin. Int J Clin Oncol. 2016;21(3):491–7.
7. Ito Y, Karayama M, Inui N, Kuroishi S, Nakano H, Nakamura Y et al. Aprepitant in patients with advanced non-small-cell lung cancer receiving carboplatin-based chemotherapy. Lung Cancer. 2014;84(3):259–64.

8. Nishimura J, Satoh T, Fukunaga M, Takemoto H, Nakata K, Ide Y et al. Combination antiemetic therapy with aprepitant/fosaprepitant in patients with colorectal cancer receiving oxaliplatin-based chemotherapy (SENRI trial): a multicentre, randomised, controlled phase 3 trial. Eur J Cancer. 2015;51(10):1274–82.
9. Albany C, Brames MJ, Fausel C, Johnson CS, Picus J, Einhorn LH. Randomized, double-blind, placebo-controlled, phase III cross-over study evaluating the oral neurokinin-1 antagonist aprepitant in combination with a 5HT3 receptor antagonist and dexamethasone in patients with germ cell tumors receiving 5-day cisplatin combination chemotherapy regimens: a hoosier oncology group study. J Clin Oncol. 2012;30(32):3998–4003.
10. Olver IN, Grimison P, Chatfield M, Stockler MR, Toner GC, Gebski V et al. Results of a 7-day aprepitant schedule for the prevention of nausea and vomiting in 5-day cisplatin-based germ cell tumor chemotherapy. Support Care Cancer. 2013;21(6):1561–8.
11. Hamada S, Hinotsu S, Kawai K, Yamada S, Narita S, Kamba T et al. Antiemetic efficacy and safety of a combination of palonosetron, aprepitant, and dexamethasone in patients with testicular germ cell tumor receiving 5-day cisplatin-based combination chemotherapy. Support Care Cancer. 2014;22(8):2161–6.
12. Bechtel T, McBride A, Crawford B, Bullington S, Hofmeister CC, Benson DM, Jr. et al. Aprepitant for the control of delayed nausea and vomiting associated with the use of high-dose melphalan for autologous peripheral blood stem cell transplants in patients with multiple myeloma: a phase II study. Support Care Cancer. 2014;22(11):2911–6.
13. Stiff PJ, Fox-Geiman MP, Kiley K, Rychlik K, Parthasarathy M, Fletcher-Gonzalez D et al. Prevention of nausea and vomiting associated with stem cell transplant: results of a prospective, randomized trial of aprepitant used with highly emetogenic preparative regimens. Biol Blood Marrow Transplant. 2013;19(1):49–55.e1.
14. Bakhshi S, Batra A, Biswas B, Dhawan D, Paul R, Sreenivas V. Aprepitant as an add-on therapy in children receiving highly emetogenic chemotherapy: a randomized, double-blind, placebo-controlled trial. Support Care Cancer. 2015;23(11):3229–37.
15. Kang HJ, Loftus S, Taylor A, DiCristina C, Green S, Zwaan CM. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting in children: a randomised, double-blind, phase 3 trial. Lancet Oncol. 2015;16(4):385–94.
16. Fang ZW, Zhai SD. [A meta-analysis of aprepitant for prevention of chemotherapy-induced nausea and vomiting]. Beijing da xue xue bao Yi xue ban/Journal of Peking University Health sciences. 2010;42(6):756–63.
17. Aapro M, Carides A, Rapoport BL, Schmoll HJ, Zhang L, Warr D. Aprepitant and fosaprepitant: a 10-year review of efficacy and safety. Oncologist. 2015;20(4):450–8.
18. Lordick F, Ehlken B, Ihbe-Heffinger A, Berger K, Krobot KJ, Pellissier J et al. Health outcomes and cost-effectiveness of aprepitant in outpatients receiving antiemetic prophylaxis for highly emetogenic chemotherapy in Germany. Eur J Cancer. 2007;43(2):299–307.
19. Humphreys S, Pellissier J, Jones A. Cost-effectiveness of an aprepitant regimen for prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer in the UK. Cancer Manag Res. 2013;5:215–24.

*Ondansetron – square box – EML and EMLc*

## Ondansetron — ATC Code: A04AA01

**Proposal**

The application requested the addition of a square box to the listing of ondansetron on the EML and EMLc, to correct an omission from the original recommendation to list.

**Applicants**

EML Secretariat

**WHO Technical Department**

Comments on the application were received from the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it supported the addition of a square box to the listings of ondansetron as representative of the pharmacological class of 5-HT3 receptor antagonists, stating that this class of medicines are essential medicines for the optimal management of common treatment-related adverse events associated with emetogenic chemotherapy.

**EML/EMLc**

EML and EMLc

**Section**

2.3 Medicines for other common symptoms in palliative care
17.2 Antiemetic medicines

**Dose form(s) & strengths(s)**

Injection: 2 mg base/mL in 2- mL ampoule (as hydrochloride)
Oral liquid: 4 mg base/5 mL
Solid oral dosage form: Eq 4 mg base; Eq 8 mg base: Eq 24 mg base

**Core/Complementary**

Core

**Individual/Square box listing**

Square box

**Background** (if relevant, eg. resubmission, previous EC consideration)

Ondansetron was first included on the EML and EMLc following a review of antiemetic medicines considered by the 2009 Expert Committee (*1*). Listing was recommended with a square box symbol, designating ondansetron as representative of the pharmacological class of 5-HT3 receptor antagonists. However, the square box was inadvertently omitted when the lists were published.

Alternative 5-HT3 receptor antagonists within the pharmacological class are shown below:

| ATC Code | Medicine | DDD | Units | RoA |
|---|---|---|---|---|
| A04AA01 | Ondansetron | 16 | mg | O, P, R |
| A04AA02 | Granisetron | 2 / 3 / 3.1 | mg | O/ P / TD |
| A04AA03 | Tropisetron | 5 | mg | O / P |
| A04AA04 | Dolasetron | 0.2 / 0.1 | g | O / P |
| A04AA05 | Palonosetron | 0.5 / 0.25 | mg | O / P |

**Public health relevance** (burden of disease)

N/A

**Summary of evidence: benefits** (from the application)

N/A

**Summary of evidence: harms** (from the application)

N/A

**Additional evidence** (not in the application)

A 2016 systematic review of 299 studies (58 412 patients) identified during the application review process investigated the comparative safety and effectiveness of 5-HT3 receptor antagonists in patients undergoing chemotherapy. The review concluded that most 5-HT3 receptor antagonists used alone, or in combination with corticosteroids, were effective at decreasing the occurrence of nausea and/or vomiting, and were similarly safe when compared to each other (*2*).

**WHO Guidelines**

None available.

**Costs/cost-effectiveness**

The square box indicating therapeutic equivalence between alternative 5-HT3 receptor antagonists will allow tendering among available options or competition in pooled procurement mechanisms at country/local level or benchmarking for lowering prices.

### Availability

The 5-HT3 receptor antagonists have wide market availability and are available in generic forms.

### Other considerations

N/A

### Committee recommendations

The Committee recommended the addition of a square box to the listing of ondansetron on the EML and EMLc, noting that the original recommendation to list ondansetron in 2009 had included a square box.

## References

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2009 (including the 16th WHO Model List of Essential Medicines and the 2nd WHO Model List of Essential Medicines for Children) (WHO Technical Report Series, No. 958). Geneva: World Health Organization; 2009. Available from https://apps.who.int/iris/bitstream/handle/10665/44287/WHO_TRS_958_eng.pdf, accessed 30 October 2019.
2. Tricco AC, Blondal E, Veroniki AA, Soobiah C, Vafaei A, Ivory J et al. Comparative safety and effectiveness of serotonin receptor antagonists in patients undergoing chemotherapy: a systematic review and network meta-analysis. BMC Med. 2016;14(1):216.

## 17.5 Medicines used in diarrhoea

*Oral rehydration salts (ORS) and zinc (co-packaged) – new formulation – EMLc*

| Oral rehydration salts and zinc sulfate | ATC Code: A07CA, A12CB01 |
|---|---|

**Proposal**

The application requested inclusion of co-packaged oral rehydration salts (ORS) and zinc sulfate tablets on the core list of the EMLc.

**Applicants**

Diarrhea Innovations Group

**WHO Technical Department**

Maternal, Newborn, Child and Adolescent Health

**EML/EMLc**

EMLc

**Section**

17.5 Medicines used in diarrhoea

**Dose form(s) & strengths(s)**

Powder for dilution (refer section 17.5.1) – solid oral dosage form (refer section 17.5.2) co-packaged for the treatment of acute diarrhoea.

**Core/Complementary**

Core

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Oral rehydration salts and zinc sulfate 20 mg solid oral dosage form are currently both listed individually on the EML and EMLc for use in the treatment of diarrhoea.

**Public health relevance** (burden of disease)

Diarrhoea is present globally, in all regions and among all populations. However, an inequitable proportion of diarrhoea morbidity and mortality occurs in

low-income countries, which in turn have fewer resources and less robust infrastructure to manage the burden (*1*). *The Global Burden of Disease Study 2016* (GBD) estimated diarrhoea as the eighth leading cause of death, responsible for well more than 1.6 million deaths and the fifth leading cause of death among children younger than 5 years (446 000 deaths). Approximately 90% (89.37%) of diarrhoeal deaths occurred in South Asia and sub-Saharan Africa (*2*).

**Summary of evidence: benefits** (from the application)

The benefits associated with ORS and zinc have been previously considered and accepted at the time of the original listings.

The current application identified a number of studies (*3*–*8*) that provide supporting evidence for the benefits of co-packaged ORS and zinc, including:

- Increased uptake and coverage of ORS and zinc (as a combination therapy, and as individual components), reducing the risk of severe health consequences of chronic diarrhoea and stunting, acute diarrhoea, and zinc deficiency among children.
- Improved adherence to the combined therapy of ORS and zinc.
- Improved adherence to/preparation of individual components (e.g. correct concentration of prepared ORS and completion of a full course of zinc).
- Improved dispensing practices by health care workers.
- Reduced hospitalizations due to diarrhoea.
- Reductions in inappropriate antibiotic prescription and use.
- Enhanced satisfaction levels by caregivers with ORS and zinc relative to status quo products.
- Enhanced opportunities for developing private sector models and leveraging value chains to improve availability and access closer to the household level.

**Summary of evidence: harms** (from the application)

Overall, ORS is safe, with few reports of adverse events. Additional adverse events that occur with ORS administration include oedematous (puffy) eyelids, which are a sign of over hydration, and vomiting. Zinc supplementation has been utilized extensively with demonstrated safety in the treatment of diarrhoea. To date, there have been no reports of severe adverse reactions from any form of zinc treatment for diarrhoea, alone or in combination with ORS.

**Additional evidence** (not in the application)

N/A

**WHO Guidelines**

The current WHO recommendations for ORS and zinc use in the management of diarrhoea in children with no signs of dehydration (Plan A) are:

Low-osmolarity ORS (containing 75 mEq/L of sodium and 75 mmol/L of glucose) after each loose motion:

- In a child younger than 2 years of age, provide 50 mL to 100 mL of ORS solution.
- In a child 2 to 10 years of age, provide 100 mL to 200 mL of ORS solution.
- In a child older than 10 years of age, provide ORS ad libitum (i.e. to drink freely).

Zinc sulfate from the start of the diarrhoea:

- In a child younger than six months, provide one half of a 20 mg tablet (i.e. 10 mg) once a day for 10 to 14 days.
- In a child older than six months, provide one whole 20 mg tablet once a day for 10 to 14 days.

The current WHO recommendations for ORS and zinc use in the management of diarrhoea in children with some dehydration (Plan B) are:

Low-osmolarity ORS (containing 75 mEq/L of sodium and 75 mmol/L of glucose):

- ORS in the first four hours is administered according to the weight of the child (or the child's age if the weight is not known).

Zinc sulfate from the start of the diarrhoea:

- As per Plan A

**Costs/cost-effectiveness**

The application presented the comparative costs of co-packaged and individually packaged ORS and zinc from five African countries. In each case, the co-packaged product was less expensive than the combined cost of the individual products.

**Availability**

Co-packaged ORS and zinc is available from multiple suppliers.

**Other considerations**

The Committee noted the multiple letters of support received in relation to this application.

### Committee recommendations

The Committee recommended the inclusion of co-packaged oral rehydration salts (ORS) and zinc sulfate tablets on the core list of the EMLc. The Committee considered that since these products are recommended to be administered together in the management of diarrhoea, the availability of the co-packaged product will be practical and support better adherence to treatment. Countries may also realize cost savings with the co-packaged product.

## References

1. Mills A. Health care systems in low- and middle-income countries. N Engl J Med. 2014;370(6): 552–7.
2. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100): 1151–210.
3. Borapich D, Warsh M. Improving Child Health in Cambodia: Social Marketing of Diarrhea Treatment Kit, Results of a Pilot Project. Cases in Public Health Communication & Marketing. 2010;4:4–22.
4. Gebremedhin S, Mamo G, Gezahign H, Kung'u J, Adish A. The effectiveness bundling of zinc with Oral Rehydration Salts (ORS) for improving adherence to acute watery diarrhea treatment in Ethiopia: cluster randomised controlled trial. BMC Public Health. 2016;16:457.
5. Roche M, Meza RG, Vossenaar M. An Intervention to Co-package Zinc and Oral Rehydration Salts (ORS) Improves Health Provider Prescription and Maternal Adherence to WHO-recommended Diarrhea Treatment in Western Guatemala. The FASEB Journal. 2015;29(1_supplement):902.23.
6. Habib MA, Soofi S, Sadiq K, Samejo T, Hussain M, Mirani M et al. A study to evaluate the acceptability, feasibility and impact of packaged interventions ("Diarrhea Pack") for prevention and treatment of childhood diarrhea in rural Pakistan. BMC Public Health. 2013;13:922.
7. Ramchandani R. Emulating Commercial, Private-Sector Value-Chains to Improve Access to ORS and Zinc in Rural Zambia: Evaluation of the Colalife Trial. Dissertation submitted to The Johns Hopkins University in conformity with the requirements for the degree of Doctor of Public Health. Available from https://jscholarship.library.jhu.edu/handle/1774.2/39229, accessed 29 September 2019.
8. Goh N, Pollak K. Progress over a Decade of Zinc and ORS Scale-up: Best Practices and Lessons Learned. Boston MA, USA: Clinton Health Access Initiative; 2016. Available from https://clintonhealthaccess.org/content/uploads/2016/02/Progress-over-a-Decade-of-Zinc-and-ORS-Scale-Up.pdf, accessed 29 September 2019.

## Section 18: MEDICINES FOR ENDOCRINE DISORDERS

## 18.5 Insulin and other medicines used for diabetes

*Long-acting insulin analogues (including biosimilars) – addition – EML*

| Long-acting insulin analogues (including biosimilars) | |
|---|---|
| Insulin detemir | ATC Code: A10AE05 |
| Insulin glargine | ATC Code: A10AE04 |
| Insulin degludec | ATC Code: A10AE06 |

**Proposal**

The application proposed the inclusion of long-acting insulin analogues on the core list of the EML for treatment of patients with type 1 diabetes.

**Applicant**

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Knowledge Translation Program, St Michael's Hospital, Toronto, Canada.

**WHO Technical Department**

Comments on the application were received from the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it did not support the application to add long-acting insulin analogues (including biosimilars) to the EML, nor was the application developed in consultation with the technical department.

**EML/EMLc**

EML

**Section**

Core

**Dose form(s) & strengths(s)**

Insulin detemir: injection 100 units/mL
Insulin glargine: injection 100 units/mL
Insulin degludec: injection 100 units/mL

**Core/Complementary**

Core

**Individual/Square box listing**

Square box

**Background** (if relevant, eg. resubmission, previous EC consideration)

Human insulin has been included on the EML since the first list in 1977 (*1*). In 1985, the WHO Expert Committee on the Selection and Use of Essential Medicines approved the inclusion of isophane neutral protamine Hagedorn (NPH) insulin (*2*).

Since 1996, different insulin analogues, altered forms of human insulins, have been introduced on markets worldwide. In recent years, additional comparative evidence on biosimilars and reference medications in terms of efficacy and safety became available.

In 2017, at the 21st meeting of the Expert Committee of the WHO EML, an application for the inclusion of long-acting analogues to the EML was rejected due to the limited magnitude of the benefits of analogues over human insulin in terms of reduced glycated haemoglobin and reduced hypoglycaemia as compared to the large difference in price between analogues and human insulin (*3*).

Since that time, additional evidence has become available encompassing both effectiveness and increasing affordability of analogues.

**Public health relevance** (burden of disease)

Diabetes mellitus has an increasing worldwide prevalence. If current trends continue, it is estimated that 642 adults will be living with diabetes by 2040 (*4*). The incidence of type 1 diabetes mellitus (T1DM) accounts for a small proportion of all diabetes (range: 5–10%) (*5*).

All people living with type 1 diabetes have an absolute need for insulin for survival. Insulin is also required by a subset of patients with type 2 diabetes (*6*). Lack of access to affordable insulin is a problem globally and contributes to the complications of untreated or sub-optimally treated diabetes and premature deaths (*7*).

**Summary of evidence: benefits** (from the application)

The application presented the findings of a network meta-analysis (NMA) to evaluate the comparative effectiveness and safety of long- or intermediate-acting insulin versus biosimilar insulins in patients with T1DM, updating the results of a previous systematic review.

The review compared basal regimens and categorizes treatments as per class of basal insulin (i.e. intermediate acting, long-acting and ultra-long-acting), and specific type of basal insulin, including insulin origin and insulin frequency. The analyses were adjusted for bolus regimen.

Sixty-eight primary studies (*8–75*) (and 12 companion reports) involving 15 150 patients with average age ranging from 23 to 54 years were included.

Sixty-two (91%) studies were randomized controlled trials (RCTs) and the majority had an unclear/high risk of bias on random sequence generation, allocation concealment, selective reporting, and 'other' bias (e.g. funding bias). Details of the included studies are available in Appendix File 1 of the application at: https://www.who.int/selection_medicines/committees/expert/22/applications/s18.5_insulin-analogues.pdf?ua=1.

Primary efficacy outcomes of the network meta-analysis were A1c and fasting plasma glucose. Secondary efficacy outcomes were mortality, any (total) vascular complication, microvascular complications, macrovascular complications and quality of life.

**A1c**

A basal insulin class NMA was conducted including 26 RCTs and 9241 patients and three treatment nodes (long-acting, intermediate-acting and ultra-long-acting biosimilar). Long-acting insulin was statistically superior to intermediate-acting insulin (mean difference MD −0.14, 95%CI −0.21 to −0.07).

A specific type of insulin NMA was conducted on the A1c outcome including 34 RCTs and 11 894 patients and nine treatment nodes. Across the 36 treatment comparisons, the following 11 showed statistically significant results:

- Intermediate-acting (human) insulin administered four times a day was *inferior* to intermediate-acting (animal and human) insulin administered twice a day (mean difference MD 0.31, 95% CI 0.05 to 0.57).
- Intermediate-acting (human) insulin administered qid was *inferior* to intermediate-acting (human) insulin administered bid (MD 0.43, 95%CI 0.23 to 0.63).
- Intermediate-acting (human) insulin administered qid was *inferior* to intermediate-acting (human) insulin administered once daily (od) (MD 0.32, 95%CI 0.10 to 0.53).
- Long-acting (biosimilar) insulin administered od was *superior* to intermediate-acting (human) insulin administered qid (MD −0.46, 95%CI −0.67 to −0.24).
- Long-acting (human) insulin administered bid was *superior* to intermediate-acting (human) insulin administered qid (MD −0.49, 95%CI −0.70 to −0.29).
- Long-acting (human) insulin administered bid was *superior* to intermediate-acting (human) insulin administered od (MD −0.18, 95%CI −0.30 to −0.06).

- Long-acting (human) insulin administered od was *superior* to intermediate-acting (animal and human) insulin administered bid (MD −0.19, 95%CI −0.37 to −0.01).
- Long-acting (human) insulin administered od was *superior* to intermediate-acting (animal) insulin administered bid (MD −1.27, 95%CI −2.54 to −0.01).
- Long-acting (human) insulin administered od was *superior* to intermediate-acting (human) insulin administered qid (MD −0.50, 95%CI −0.69 to −0.31).
- Long-acting (human) insulin administered od was *superior* to intermediate-acting (human) insulin administered od (MD −0.18, 95%CI −0.29 to −0.08).
- Ultra-long-acting (biosimilar) insulin administered od was *superior* to intermediate-acting (human) insulin administered qid (MD −0.44, 95%CI −0.64 to −0.23).

A sensitivity analysis to examine the impact of imputing missing standard deviations on the results resulted in the exclusion of seven trials. The pairwise treatment comparisons above were no longer statistically significant when the seven trials were excluded.

When meta-regression analyses were conducted for follow-up duration, A1c level (mild: <8%, severe: ≥8%); proportion of women; duration of diabetes; and risk of bias associated with random sequence generation and allocation concealment, none of the results remained statistically significant.

Statistically significant results were shown for meta-regression analyses on:

- bolus type (rapid vs short): long-acting (human) insulin administered od was *superior* to intermediate-acting (animal) insulin administered bid (MD −1.27, 95%CI −2.54 to −0.001);
- study design (parallel or crossover trials): long-acting (human) insulin administered bid was *superior* to intermediate-acting (animal) insulin administered bid (MD −1.27, 95%CI −2.53 to −0.0007);
- baseline A1c: intermediate-acting (animal and human) insulin administered bid was *superior* to intermediate-acting (animal) insulin administered bid (MD −1.32, 95%CI −2.63 to −0.02);
- age: long-acting (human) insulin administered bid, was *superior* to intermediate-acting (animal) insulin administered bid (MD −1.31, 95%CI −2.58 to −0.04) and long-acting (human) insulin administered od was superior to intermediate-acting (animal) insulin administered bid (MD −1.28, 95%CI −2.54 to −0.007).

### Fasting plasma glucose

A basal insulin class NMA was conducted on the fasting plasma glucose outcome including 21 RCTs, 7685 patients, and three treatment nodes. Long-acting insulin was statistically superior to intermediate-acting insulin (MD −1.03, 95%CI −1.33 to −0.73) and ultra-long-acting insulin was superior to intermediate-acting insulin (MD −1.45, 95%CI −2.12 to −0.79).

A specific type of insulin NMA was conducted on the fasting plasma glucose outcome including 28 RCTs, 9773 patients, and eight treatment nodes. Across the 28 treatment comparisons, the following nine showed statistically significant results:

- Long-acting (biosimilar) insulin administered od was *superior* to intermediate-acting (human) insulin administered bid (MD −1.07, 95%CI −1.98 to −0.15).
- Long-acting (human) insulin administered bid was *superior* to intermediate-acting (human) insulin administered bid (MD −0.82, 95%CI −1.21 to −0.43).
- Long-acting (human) insulin administered od was *superior* to intermediate-acting (human) insulin administered bid (MD −1.26, 95%CI −1.66 to −0.85).
- Long-acting (human) insulin administered od was *superior* to intermediate-acting (human) insulin administered od (MD −1.15, 95%CI −1.82 to −0.49).
- Long-acting (human) insulin administered od was *superior* to long-acting (human) bid (MD −0.43, 95%CI −0.82 to −0.05).
- Ultra-long-acting (biosimilar) insulin administered od was *superior* to intermediate-acting (human) insulin administered qid (MD −1.20, 95%CI −2.31 to −0.09).
- Ultra-long-acting (biosimilar) insulin administered od was *superior* to intermediate-acting (human) bid (MD −1.55, 95%CI −2.24 to −0.87).
- Ultra-long-acting (biosimilar) insulin administered od was *superior* to intermediate-acting (human) insulin administered od (MD −1.45, 95%CI −2.34 to −0.56).
- Ultra-long-acting (biosimilar) insulin administered od was *superior* to long-acting (human) insulin administered bid (MD −0.73, 95%CI −1.38 to −0.08).

### Mortality

A NMA was not possible for all-cause mortality for basal insulin classes. Two pairwise meta-analyses were possible for long-acting versus intermediate-acting

insulin (four RCTs, 1682 patients), as well as ultra-long-acting versus long-acting insulin (two RCTs, 1540 patients). None of the results were statistically significant.

A NMA was not possible for all-cause mortality for specific types of insulin. Three pairwise meta-analyses were possible comparing long-acting (human) insulin administered bid versus intermediate-acting (human) insulin administered bid (two RCTs, 653 patients), long-acting (human) insulin administered od versus long-acting (biosimilar) insulin administered od (two RCTs, 1093 patients) and long-acting (human) insulin administered od versus ultra-long-acting (biosimilar) insulin administered od (two RCTs, 1540 patients). None of the results were statistically significant.

#### Any (total) vascular complication

A basal insulin class NMA was conducted on any vascular complication, including 11 RCTs and 4709 patients. Across the three treatment comparisons, none were statistically significant.

A specific type of insulin NMA was conducted on any vascular complication including 13 RCTs and 5589 patients. Across the 10 treatment comparisons, none were statistically significant.

#### Microvascular complications

A basal insulin class NMA was conducted to compare long-acting, intermediate-acting and ultra-long acting insulins on microvascular complications including eight RCTs and 3131 patients. The transitivity assumption was upheld but inconsistency could not be assessed since there were no closed loops in the network meta-analysis diagram. Across the three treatment comparisons, none were statistically significant.

A specific type of insulin NMA was conducted on microvascular complications including 10 RCTs and 4011 patients. Across the 10 treatment comparisons, none were statistically significant.

#### Macrovascular complications

For basal insulin classes, a NMA was not possible for macrovascular complications. Two pairwise meta-analyses were possible; long-acting insulin versus intermediate-acting insulin (three RCTs, 998 patients) and ultra-long-acting biosimilar insulin versus long-acting insulin (three RCTs, 2098 patients). The results of pairwise treatment comparisons were not statistically significant.

For specific types of insulin, a NMA was not possible for macrovascular complications. Two pairwise meta-analyses were possible for long-acting (human) insulin administered bid versus intermediate-acting (human) insulin administered bid (four RCTs, 1258 patients) and long-acting (human) insulin administered od versus ultra-long-acting (biosimilar) od (two RCTs, 1540 patients). The results were not statistically significant.

**Quality of life**

A NMA or pairwise meta-analyses were not possible for health-related quality of life for basal insulin classes or specific types of insulin. One study including 517 patients reported total quality of life and long-acting (human) insulin administered od was not statistically significant compared with intermediate-acting (human) insulin administered bid. The same study reported general quality of life and long-acting (human) insulin administered od was not statistically significant compared with intermediate-acting (human) insulin administered bid. With respect to basal insulin classes, similar results were observed when long-acting insulin was compared to intermediate-acting insulin.

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**Summary of evidence: harms** (from the application)

**Weight change**

A basal insulin class NMA was conducted including 16 RCTs, 6822 patients, and three treatment nodes. Long-acting insulin was statistically superior to intermediate-acting insulin (MD −0.70, 95%CI −1.07 to −0.33).

A specific type of insulin NMA was conducted including 20 RCTs, 8335 patients, and seven treatment nodes. Across the 21 treatment comparisons, the following four showed statistically significant results:

- Long-acting (human) insulin administered bid was *superior* to intermediate-acting (human) insulin administered bid (MD −0.85, 95%CI −1.24 to −0.46).
- Long-acting (human) insulin administered bid was *superior* to intermediate-acting (human) insulin administered od (MD −1.18, 95%CI −2.13 to −0.24).
- Long-acting (human) insulin administered bid was *superior* to long-acting (biosimilar) insulin administered od (MD −0.96, 95%CI −1.91 to −0.01).
- Long-acting (human) insulin administered bid was superior to ultra-long-acting (biosimilar) insulin administered od (MD −0.69, 95%CI −1.32 to −0.06).

**All-cause hypoglycaemia** (defined differently across RCTs)

A basal insulin class NMA was conducted including 17 RCTs and 5949 patients. Across the three treatment comparisons, none were statistically significant.

A specific type of insulin NMA was conducted including 22 RCTs and 6917 patients. Across the 21 treatment comparisons, none were statistically significant.

**Major or serious hypoglycaemia** (defined differently across RCTs)

A basal insulin class NMA was conducted including 19 RCTs, 7324 patients, and three treatment nodes. Long-acting insulin was statistically superior to intermediate-acting insulin (odds ratio OR 0.63, 95%CI 0.51 to 0.76).

A specific type of insulin NMA was conducted including 25 RCTs and 9300 patients. Across the 21 treatment comparisons, the following four showed statistically significant results:

- Long-acting (biosimilar) insulin administered od was *superior* to intermediate-acting (human) insulin administered bid (OR 0.48, 95%CI 0.24 to 0.97).
- Long-acting (human) insulin administered bid was *superior* to intermediate-acting (human) insulin administered bid (OR 0.69, 95%CI 0.54 to 0.88).
- Long-acting (human) insulin administered od was *superior* to intermediate-acting (human) insulin administered bid (OR 0.53, 95%CI 0.39 to 0.72).
- Long-acting (human) insulin administered od was *superior* to intermediate-acting (human) insulin administered od (OR 0.60, 95%CI 0.42 to 0.86).

**Minor or mild hypoglycaemia**

For basal insulin classes, a NMA was not possible. One pairwise meta-analysis was possible for long-acting versus intermediate-acting insulin (eight RCTs, 2949 patients) and the results were not statistically significant.

A specific type of insulin NMA was conducted including 11 RCTs and 3926 patients. Across the 15 treatment comparisons, none were statistically significant.

**Nocturnal hypoglycaemia** (defined differently across RCTs)

A basal insulin class NMA was conducted including 16 RCTs, 6669 patients, and three treatment nodes. Long-acting insulin was statistically superior to intermediate-acting insulin (OR 0.71, 95%CI 0.57 to 0.89) and ultra-long-acting biosimilar insulin was statistically superior to intermediate-acting insulin (OR 0.60, 95%CI 0.42 to 0.86).

A specific type of insulin NMA was conducted including 19 RCTs and 7564 patients. Across the 15 treatment comparisons, the following two showed statistically significant results:

- Intermediate-acting (human) insulin administered bid was *inferior* to ultra-long-acting (biosimilar) insulin administered od (OR 1.58, 95%CI 1.11 to 2.25).

– Long-acting (human) insulin administered bid was superior to intermediate-acting (human) insulin administered bid (OR 0.59, 95%CI 0.44 to 0.79).

#### Incident cancers

For basal insulin classes, a NMA was not possible. One pairwise meta-analysis was possible for long-acting versus intermediate-acting insulin (three RCTs, 1651 patients) and the results were not statistically significant.

For specific types of insulin, a NMA was not possible. One pairwise meta-analysis was possible (two RCTs and 1204 patients), which compared long-acting (human) insulin administered od versus intermediate-acting (human) insulin administered bid. The results were not statistically significant.

#### Any (total) adverse events, serious adverse events, and dropouts due to adverse events

For basal insulin classes, NMAs were conducted on any adverse events including 16 RCTs and 5367 patients, on serious adverse events including 20 RCTs and 6840 patients, and on withdrawals due to adverse events including 14 RCTs and 5440 patients. Across the three treatment comparisons in each NMA, none were statistically significant.

For specific types of insulin, NMAs were conducted on any adverse events including 22 RCTs and 6830 patients, on serious adverse events including 26 RCTs and 8989 patients, and on withdrawals due to adverse events including 21 RCTs and 7795 patients. Across the 15 treatment comparisons in each NMA, none were statistically significant.

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**Additional evidence** (not in the application)

The current application does not include data on long-acting insulin analogue use in children. Long-acting insulin analogues have been investigated extensively in the paediatric age-group in low- and high-resource settings and were found to be safe and effective (*76–80*). They are approved in children from age two years (glargine and detemir) or one year (degludec) (*81*). Long-acting analogues have also been successfully used in infants and have shown positive effects on glucose control and on hypoglycaemia. However, the evidence is based on case reports (*82*, *83*).

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#### WHO Guidelines

The WHO 2018 *Guidelines on second- and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes mellitus* (*84*) make the following recommendations regarding the use of insulin:

– Use human insulin (short-acting regular human insulin and intermediate-acting human insulin (NPH insulin)) to manage

blood glucose in adults with type 1 diabetes and in adults with type 2 diabetes for whom insulin is indicated (strong recommendation, low quality evidence).

– Consider long-acting insulin analogues to manage blood glucose in adults with type 1 or type 2 diabetes who have frequent severe hypoglycaemia with human insulin (weak recommendation, moderate quality evidence for severe hypoglycaemia).

Recommendations from the 2018 WHO guidelines targeting type 1 diabetes were based on evidence from systematic reviews of randomized controlled trials (*85*–*87*).

For patients with type 1 diabetes, the mean difference in HbA1c level between short-acting insulin analogues and regular human insulin was −0.15% (95%CI −0.20% to −0.10%) (low quality evidence). The difference in HbA1c level in patients treated with short-acting insulin analogues compared with those treated with regular human insulin was not considered clinically meaningful by the guidelines development group. Long-acting insulin analogues and human NPH insulin had similar effects on HbA1c level (moderate quality evidence). Long-acting insulin analogues reduced risk for severe hypoglycaemia, but only the reduction with detemir was statistically significant (moderate quality evidence). The guideline panel concluded that the relatively modest overall benefit from insulin analogues was outweighed by the large price difference between human insulin and insulin analogues. Thus, the panel considered use of long-acting detemir and glargine insulin analogues as alternatives to human insulin only in specific circumstances, such as unexplained and frequent severe hypoglycaemic events.

**Costs/cost-effectiveness**

Ten cost-effectiveness analyses reported in three studies compared long-acting insulin detemir once a day with intermediate-acting insulin NPH once a day (*72*, *73*, *75*). Two studies (*72*, *75*) found that detemir was less costly and more effective, while the third (*73*) showed that detemir was more costly but also more effective than NPH. Two cost-effectiveness analyses reported in a single study compared long-acting insulin detemir once a day with long-acting insulin glargine once a day (*74*). This study demonstrated that detemir is more cost-effective than glargine. Finally, a single cost-effectiveness analysis in a single study compared ultra-long-acting biosimilar insulin degludec once a day with long-acting insulin glargine once a day (*71*). Degludec was shown to be the more cost-effective treatment in comparison to glargine.

### Availability

Three pharmaceutical companies are solely responsible for the supply of almost all insulin on markets worldwide. Despite being available for almost 100 years, achieving reliable, equitable and affordable access to insulin, human or analogue, remains a public health challenge in many countries (*88*). The Committee recognized the need for a wider understanding of the complexities of access to insulin and the current insulin market and recommended WHO to prioritize the coordination of a series of actions to address the issues of insulin access and affordability.

### Other considerations

The review found long-acting insulin analogues to be superior to intermediate acting insulin with regard to major or serious hypoglycaemia, which may represent an advantage particularly in settings where food security is not reliable. Glucagon, used in the management of severe hypoglycaemia, has very limited availability in many low-resource settings (*89*). Thus, the lower incidence of major or serious hypoglycaemia associated with the use of (ultra) long-acting insulin analogues may offer further advantages in such settings.

The Committee acknowledged and noted the comments received in relation to this application from organizations and individuals expressing concern about the potential inclusion of insulin analogues on the Model List and associated consequences.

### Committee recommendations

The Committee acknowledged that insulin is a life-saving essential medicine for which a compelling public health need exists. Yet despite being available for almost 100 years, achieving reliable, equitable and affordable access to insulin remains a public health challenge in many countries.

The Committee did not recommend the addition of insulin analogues to the EML, reiterating the conclusion of the 2017 Committee, that although the available evidence for long-acting insulin analogues shows some efficacy advantages and reduced hypoglycaemia compared to human insulin, the price differential that exists between analogue and human insulin remains disproportionately high in most settings.

The Committee remained concerned about the ongoing problems of access and affordability of insulin worldwide, despite human insulin not being patented. The Committee noted the long-standing domination of the insulin market by three manufacturers, limiting broader competition and slowing the entry of biosimilars to the market.

Recognizing the complexities of these problems and the need for a wider understanding of the insulin market and access to insulin, the Committee

recommended WHO coordinate a series of actions to address the issues of insulin access and affordability. In the absence of other coordinated actions, the Committee considered that the inclusion of insulin analogues for adults on the EML would be inadequate to address the underlying issues of poor access and affordability of insulins more generally.

The Committee recommended that a WHO-led approach should be multi-factorial and multi-disciplinary and should include:

- establishment of an independent WHO technical working group on access to insulin;
- consultation with Member States and other stakeholders to identify/clarify barriers to access at country level;
- strategies to address current regulatory barriers for biosimilar insulins, such as the expansion of the WHO Prequalification Programme;
- development of a comprehensive approach to address insulin prices, including mechanisms for pooled procurement;
- identification of evidence and research gaps regarding insulin use and supply, including setting-specific differences in clinical practice and health systems (e.g. food insecurity, displaced populations, emergencies).

The Committee would welcome a report that comprehensively describes the actions that are undertaken by WHO over the next biennium and an application that reviews in-depth the current challenges for optimal global access and the role of insulin analogues in children.

## References

1. The selection of essential drugs. Report of a WHO Expert Committee, 1977 (WHO Technical Report Series No. 615). Geneva: World Health Organization; 1977. Available from https://apps.who.int/iris/bitstream/handle/10665/41272/WHO_TRS_615.pdf, accessed 30 October 2019.
2. The use of essential drugs. Second report of the WHO Expert Committee (WHO Technical Report Series No. 722). Geneva: World Health Organization; 1985. Available from https://apps.who.int/iris/bitstream/handle/10665/38831/WHO_TRS_722.pdf, accessed 30 October 2019.
3. The selection and use of essential medicines. Report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children) (WHO Technical Report Series, No. 1006). Geneva: World Health Organization; 2017. Available from https://apps.who.int/iris/bitstream/handle/10665/259481/9789241210157-eng.pdf, accessed 30 October 2019.
4. Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract. 2017;128:40–50.

5. You WP, Henneberg M. Type 1 diabetes prevalence increasing globally and regionally: the role of natural selection and life expectancy at birth. BMJ Open Diabetes Res Care. 2016;4(1):e000161.
6. Basu S, Yudkin JS, Kehlenbrink S, Davies JI, Wild SH, Lipska KJ et al. Estimation of global insulin use for type 2 diabetes, 2018-30: a microsimulation analysis. Lancet Diabetes Endocrinol. 2019;7(1):25–33.
7. Global Report on Diabetes. Geneva, Switzerland: World Health Organization, 2016.
8. Ashwell SG, Gebbie J, Home PD. Twice-daily compared with once-daily insulin glargine in people with Type 1 diabetes using meal-time insulin aspart. Diabet Med. 2006;23(8):879–86.
9. Bartley PC, Bogoev M, Larsen J, Philotheou A. Long-term efficacy and safety of insulin detemir compared to Neutral Protamine Hagedorn insulin in patients with Type 1 diabetes using a treat-to-target basal-bolus regimen with insulin aspart at meals: a 2-year, randomized, controlled trial. Diabet Med. 2008;25(4):442–9.
10. Birkeland KI, Home PD, Wendisch U, Ratner RE, Johansen T, Endahl LA et al. Insulin degludec in type 1 diabetes: a randomized controlled trial of a new-generation ultra-long-acting insulin compared with insulin glargine. Diabetes Care. 2011;34(3):661–5.
11. Birtwell AJ, Owens DR, Jones IR, Hayes TM, Beale DJ, el-Shaboury AH et al. Comparison of highly purified semi-synthetic insulin and highly purified porcine insulin in the treatment of type I diabetes: interim report of a multi-centre randomised single blind study. Diabete Metab. 1984;10(5):295–8.
12. Blevins TC, Dahl D, Rosenstock J, Ilag LL, Huster WJ, Zielonka JS et al. Efficacy and safety of LY2963016 insulin glargine compared with insulin glargine (Lantus(R)) in patients with type 1 diabetes in a randomized controlled trial: the ELEMENT 1 study. Diabetes Obes Metab. 2015;17(8):726–33.
13. Bode BW, Buse JB, Fisher M, Garg SK, Marre M, Merker L et al. Insulin degludec improves glycaemic control with lower nocturnal hypoglycaemia risk than insulin glargine in basal-bolus treatment with mealtime insulin aspart in Type 1 diabetes (BEGIN((R)) Basal-Bolus Type 1): 2-year results of a randomized clinical trial. Diabet Med. 2013;30(11):1293–7.
14. Bolli GB, Songini M, Trovati M, Del Prato S, Ghirlanda G, Cordera R et al. Lower fasting blood glucose, glucose variability and nocturnal hypoglycaemia with glargine vs NPH basal insulin in subjects with Type 1 diabetes. Nutr Metab Cardiovasc Dis. 2009;19(8):571–9.
15. Chatterjee S, Jarvis-Kay J, Rengarajan T, Lawrence IG, McNally PG, Davies MJ. Glargine versus NPH insulin: efficacy in comparison with insulin aspart in a basal bolus regimen in type 1 diabetes--the glargine and aspart study (GLASS) a randomised cross-over study. Diabetes Res Clin Pract. 2007;77(2):215–22.
16. Crutchlow MF, Palcza JS, Mostoller KM, Mahon CD, Barbour AM, Marcos MC et al. Single-dose euglycaemic clamp studies demonstrating pharmacokinetic and pharmacodynamic similarity between MK-1293 insulin glargine and originator insulin glargine (Lantus) in subjects with type 1 diabetes and healthy subjects. Diabetes Obes Metab. 2018;20(2):400–8.
17. Danne T, Lupke K, Walte K, Von Schuetz W, Gall MA. Insulin detemir is characterized by a consistent pharmacokinetic profile across age-groups in children, adolescents, and adults with type 1 diabetes. Diabetes Care. 2003;26(11):3087–92.
18. Davies M, Sasaki T, Gross JL, Bantwal G, Ono Y, Nishida T et al. Comparison of insulin degludec with insulin detemir in type 1 diabetes: a 1-year treat-to-target trial. Diabetes Obes Metab. 2016;18(1):96–9.

19. De Leeuw I, Vague P, Selam JL, Skeie S, Lang H, Draeger E et al. Insulin detemir used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycaemia and less weight gain over 12 months in comparison to NPH insulin. Diabetes Obes Metab. 2005;7(1):73–82.
20. Derosa G, Franzetti I, Querci F, Romano D, D'Angelo A, Maffioli P. Glucose-lowering effect and glycaemic variability of insulin glargine, insulin detemir and insulin lispro protamine in people with type 1 diabetes. Diabetes Obes Metab. 2015;17(6):554–9.
21. Eichner HL, Lauritano AA, Woertz LL, Selam JL, Gupta S, Charles MA. Cellular immune alterations associated with human insulin therapy. Diabetes Res. 1988;8(3):111–5.
22. Fulcher GR, Gilbert RE, Yue DK. Glargine is superior to neutral protamine Hagedorn for improving glycated haemoglobin and fasting blood glucose levels during intensive insulin therapy. Intern Med J. 2005;35(9):536–42.
23. Hamann A, Matthaei S, Rosak C, Silvestre L. A randomized clinical trial comparing breakfast, dinner, or bedtime administration of insulin glargine in patients with type 1 diabetes. Diabetes Care. 2003;26(6):1738–44.
24. Heise T, Nosek L, Ronn BB, Endahl L, Heinemann L, Kapitza C et al. Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. Diabetes. 2004;53(6):1614–20.
25. Heise T, Hovelmann U, Nosek L, Hermanski L, Bottcher SG, Haahr H. Comparison of the pharmacokinetic and pharmacodynamic profiles of insulin degludec and insulin glargine. Expert Opin Drug Metab Toxicol. 2015;11(8):1193–201.
26. Heise T, Bain SC, Bracken RM, Zijlstra E, Nosek L, Stender-Petersen K et al. Similar risk of exercise-related hypoglycaemia for insulin degludec to that for insulin glargine in patients with type 1 diabetes: a randomized cross-over trial. Diabetes Obes Metab. 2016;18(2):196–9.
27. Heise T, Norskov M, Nosek L, Kaplan K, Famulla S, Haahr HL. Insulin degludec: Lower day-to-day and within-day variability in pharmacodynamic response compared with insulin glargine 300 U/mL in type 1 diabetes. Diabetes Obes Metab. 2017;19(7):1032–9.
28. Heller S, Koenen C, Bode B. Comparison of insulin detemir and insulin glargine in a basal-bolus regimen, with insulin aspart as the mealtime insulin, in patients with type 1 diabetes: a 52-week, multinational, randomized, open-label, parallel-group, treat-to-target noninferiority trial. Clin Ther. 2009;31(10):2086–97.
29. Hermansen K, Madsbad S, Perrild H, Kristensen A, Axelsen M. Comparison of the soluble basal insulin analog insulin detemir with NPH insulin: a randomized open crossover trial in type 1 diabetic subjects on basal-bolus therapy. Diabetes Care. 2001;24(2):296–301.
30. Home P, Bartley P, Russell-Jones D, Hanaire-Broutin H, Heeg JE, Abrams P et al. Insulin detemir offers improved glycemic control compared with NPH insulin in people with type 1 diabetes: a randomized clinical trial. Diabetes Care. 2004;27(5):1081–7.
31. Home PD, Rosskamp R, Forjanic-Klapproth J, Dressler A. A randomized multicentre trial of insulin glargine compared with NPH insulin in people with type 1 diabetes. Diabetes Metab Res Rev. 2005;21(6):545–53.
32. Iga R, Uchino H, Kanazawa K, Usui S, Miyagi M, Kumashiro N et al. Glycemic Variability in Type 1 Diabetes Compared with Degludec and Glargine on the Morning Injection: An Open-label Randomized Controlled Trial. Diabetes Ther. 2017;8(4):783–92.
33. Ikushima I, Kaku K, Hirao K, Bardtrum L, Haahr H. Pharmacokinetic and pharmacodynamic properties of insulin degludec in Japanese patients with type 1 diabetes mellitus reflect similarities with Caucasian patients. J Diabetes Investig. 2016;7(2):270–5.

34. Kobayashi M, Iwamoto Y, Kaku K, Kawamori R, Tajima N. 48-week Randomized Multicenter Open-label Parallel Group Phase 3 Trial to Compare Insulin Detemir and NPH Insulin Efficacy and Safety in Subjects with Insulin Requiring Diabetes Mellitus in a Basal-bolus Regimen. Journal of the Japan Diabetes Society. 2007;50(9):649–63.
35. Koehler G, Heller S, Korsatko S, Roepstorff C, Rasmussen S, Haahr H et al. Insulin degludec is not associated with a delayed or diminished response to hypoglycaemia compared with insulin glargine in type 1 diabetes: a double-blind randomised crossover study. Diabetologia. 2014;57(1):40–9.
36. Kolendorf K, Ross GP, Pavlic-Renar I, Perriello G, Philotheou A, Jendle J et al. Insulin detemir lowers the risk of hypoglycaemia and provides more consistent plasma glucose levels compared with NPH insulin in Type 1 diabetes. Diabet Med. 2006;23(7):729–35.
37. Korsatko S, Deller S, Koehler G, Mader JK, Neubauer K, Adrian CL et al. A comparison of the steady-state pharmacokinetic and pharmacodynamic profiles of 100 and 200 U/mL formulations of ultra-long-acting insulin degludec. Clin Drug Investig. 2013;33(7):515–21.
38. Lane W, Bailey TS, Gerety G, Gumprecht J, Philis-Tsimikas A, Hansen CT et al. Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 1 Diabetes: The SWITCH 1 Randomized Clinical Trial. JAMA. 2017;318(1):33–44.
39. Larsen ML, Bjerrum P, Egstrup K. A comparison of semisynthetic human insulin and porcine insulin in the treatment of established diabetes. Dan Med Bull. 1984;31(3):243–4.
40. Le Floch JP, Levy M, Mosnier-Pudar H, Nobels F, Laroche S, Gonbert S et al. Comparison of once- versus twice-daily administration of insulin detemir, used with mealtime insulin aspart, in basal-bolus therapy for type 1 diabetes: assessment of detemir administration in a progressive treat-to-target trial (ADAPT). Diabetes Care. 2009;32(1):32–7.
41. Linnebjerg H, Lam EC, Zhang X, Seger ME, Coutant D, Chua L et al. Duration of action of two insulin glargine products, LY2963016 insulin glargine and Lantus insulin glargine, in subjects with type 1 diabetes mellitus. Diabetes Obes Metab. 2017;19(1):33–9.
42. Mathiesen ER, Hod M, Ivanisevic M, Duran Garcia S, Brondsted L, Jovanovic L et al. Maternal efficacy and safety outcomes in a randomized, controlled trial comparing insulin detemir with NPH insulin in 310 pregnant women with type 1 diabetes. Diabetes Care. 2012;35(10):2012–7.
43. Mathieu C, Hollander P, Miranda-Palma B, Cooper J, Franek E, Russell-Jones D et al. Efficacy and safety of insulin degludec in a flexible dosing regimen vs insulin glargine in patients with type 1 diabetes (BEGIN: Flex T1): a 26-week randomized, treat-to-target trial with a 26-week extension. J Clin Endocrinol Metab. 2013;98(3):1154–62.
44. Heise T, Hermanski L, Nosek L, Feldman A, Rasmussen S, Haahr H. Insulin degludec: four times lower pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes. Diabetes Obes Metab. 2012;14(9):859–64.
45. Oswald GA, Yudkin JS. A within patient cross over trial of 4 insulin regimens in antibody-negative, C-peptide negative patients. Diabetes Res. 1987;4(2):85–9.
46. Pedersen C, Hoegholm A. A comparison of semisynthetic human NPH insulin and porcine NPH insulin in the treatment of insulin-dependent diabetes mellitus. Diabet Med. 1987;4(4):304–6.
47. Pesic M, Zivic S, Radenkovic S, Velojic M, Dimic D, Antic S. Comparison between basal insulin glargine and NPH insulin in patients with diabetes type 1 on conventional intensive insulin therapy. Vojnosanit Pregl. 2007;64(4):247–52.
48. Efficacy and safety of insulin detemir in type 1 diabetes. 2007. (ClinicalTrials.gov Identifier NCT00595374). Bethesda: U.S. National Library of Medicines; 2016. Available from www.clinicaltrials.gov/ct2/show/study/NCT00595374, accessed 29 September 2019.

49. Pieber TR, Eugene-Jolchine I, Derobert E. Efficacy and safety of HOE 901 versus NPH insulin in patients with type 1 diabetes. The European Study Group of HOE 901 in type 1 diabetes. Diabetes Care. 2000;23(2):157–62.
50. Pieber TR, Draeger E, Kristensen A, Grill V. Comparison of three multiple injection regimens for Type 1 diabetes: morning plus dinner or bedtime administration of insulin detemir vs. morning plus bedtime NPH insulin. Diabet Med. 2005;22(7):850–7.
51. Pieber TR, Treichel HC, Hompesch B, Philotheou A, Mordhorst L, Gall MA et al. Comparison of insulin detemir and insulin glargine in subjects with Type 1 diabetes using intensive insulin therapy. Diabet Med. 2007;24(6):635–42.
52. Porcellati F, Rossetti P, Pampanelli S, Fanelli CG, Torlone E, Scionti L et al. Better long-term glycaemic control with the basal insulin glargine as compared with NPH in patients with Type 1 diabetes mellitus given meal-time lispro insulin. Diabet Med. 2004;21(11):1213–20.
53. Segovia Portoles R, Ferrer-Garcia JC, Merino-Torres JF, Penalba MT, Albalat Galera R, Pinon-Selles F. [Optimal timing of insulin detemir injection in patients with type 1 diabetes and poor metabolic control]. Endocrinol Nutr. 2010;57(4):140–6.
54. Radman M, Jurisic D, Ljutic D, Jerkovic R, Kovacic N, Hozo IS. Assessing glycemia in type 1 diabetic patients using a microdialysis system for continuous glucose monitoring. Ann Saudi Med. 2007;27(3):166–70.
55. Raskin P, Klaff L, Bergenstal R, Halle JP, Donley D, Mecca T. A 16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin lispro in patients with type 1 diabetes. Diabetes Care. 2000;23(11):1666–71.
56. Ratner RE, Hirsch IB, Neifing JL, Garg SK, Mecca TE, Wilson CA. Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. U.S. Study Group of Insulin Glargine in Type 1 Diabetes. Diabetes Care. 2000;23(5):639–43.
57. Renard E, Dubois-Laforgue D, Guerci B, Variability Study G. Non-inferiority of insulin glargine versus insulin detemir on blood glucose variability in type 1 diabetes patients: a multicenter, randomized, crossover study. Diabetes Technol Ther. 2011;13(12):1213–8.
58. Richard JL, Rodier M, Cavalie G, Mirouze J, Monnier L. Human (recombinant DNA) and porcine NPH insulins are unequally effective in diabetic patients. A comparative study using continuous blood glucose monitoring. Acta Diabetol Lat. 1984;21(3):211–7.
59. Rosenstock J, Park G, Zimmerman J, Group. USIGHTDI. Basal insulin glargine (HOE 901) versus NPH insulin in patients with type 1 diabetes on multiple daily insulin regimens. Diabetes Care. 2000;23:1137–42.
60. Rossetti P, Pampanelli S, Fanelli C, Porcellati F, Costa E, Torlone E et al. Intensive replacement of basal insulin in patients with type 1 diabetes given rapid-acting insulin analog at mealtime: a 3-month comparison between administration of NPH insulin four times daily and glargine insulin at dinner or bedtime. Diabetes Care. 2003;26(5):1490–6.
61. Russell-Jones D, Simpson R, Hylleberg B, Draeger E, Bolinder J. Effects of QD insulin detemir or neutral protamine Hagedorn on blood glucose control in patients with type I diabetes mellitus using a basal-bolus regimen. Clin Ther. 2004;26(5):724–36.
62. Stades AM, Hoekstra JB, van den Tweel I, Erkelens DW, Holleman F. Additional lunchtime basal insulin during insulin lispro intensive therapy in a randomized, multicenter, crossover study in adults : a real-life design. Diabetes Care. 2002;25(4):712–7.
63. Standl E, Lang H, Roberts A. The 12-month efficacy and safety of insulin detemir and NPH insulin in basal-bolus therapy for the treatment of type 1 diabetes. Diabetes Technol Ther. 2004;6(5):579–88.

64. Tunbridge FK, Newens A, Home PD, Davis SN, Murphy M, Burrin JM et al. Double-blind crossover trial of isophane (NPH)- and lente-based insulin regimens. Diabetes Care. 1989;12(2):115–9.

65. Vague P, Selam JL, Skeie S, De Leeuw I, Elte JW, Haahr H et al. Insulin detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with premeal insulin aspart. Diabetes Care. 2003;26(3):590–6.

66. van Golen LW, Veltman DJ, RG IJ, Deijen JB, Heijboer AC, Barkhof F et al. Effects of insulin detemir and NPH insulin on body weight and appetite-regulating brain regions in human type 1 diabetes: a randomized controlled trial. PLoS One. 2014;9(4):e94483.

67. Vaughan K. An Open-Label, Randomized, Multi-center, Parallel-Group Clinical Trial Comparing the Efficacy and Safety of Mylan's Insulin Glargine with Lantus in Type 1 Diabetes Mellitus Patients. Amsterdam: European Medicines Agency/EU Clinical Trials Register; 2017. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-000747-32/results, accessed 29 September 2019.

68. Verma M, Hazra P, Iyer H, Arun A, Akundi S, Dixit MN et al. Basalog® is similar to Lantus® in producing glycemic control in patients with type 1 diabetes mellitus on multiple daily insulin regimens. Int J Diabetes Dev Ctries. 2011;31(1):26–31.

69. Witthaus E, Stewart J, Bradley C. Treatment satisfaction and psychological well-being with insulin glargine compared with NPH in patients with Type 1 diabetes. Diabet Med. 2001;18(8):619–25.

70. Zachariah S, Sheldon B, Shojaee-Moradie F, Jackson NC, Backhouse K, Johnsen S et al. Insulin detemir reduces weight gain as a result of reduced food intake in patients with type 1 diabetes. Diabetes Care. 2011;34(7):1487–91.

71. Evans M, Wolden M, Gundgaard J, Chubb B, Christensen T. Cost-effectiveness of insulin degludec compared with insulin glargine in a basal-bolus regimen in patients with type 1 diabetes mellitus in the UK. J Med Econ. 2015;18(1):56–68.

72. Gschwend MH, Aagren M, Valentine WJ. Cost-effectiveness of insulin detemir compared with neutral protamine Hagedorn insulin in patients with type 1 diabetes using a basal-bolus regimen in five European countries. J Med Econ. 2009;12(2):114–23.

73. Tunis SL, Minshall ME, Conner C, McCormick JI, Kapor J, Yale JF et al. Cost-effectiveness of insulin detemir compared to NPH insulin for type 1 and type 2 diabetes mellitus in the Canadian payer setting: modeling analysis. Curr Med Res Opin. 2009;25(5):1273–84.

74. Valentine WJ, Palmer AJ, Erny-Albrecht KM, Ray JA, Cobden D, Foos V et al. Cost-effectiveness of basal insulin from a US health system perspective: comparative analyses of detemir, glargine, and NPH. Adv Ther. 2006;23(2):191–207.

75. Valentine WJ, Aagren M, Haglund M, Ericsson A, Gschwend MH. Evaluation of the long-term cost-effectiveness of insulin detemir compared with neutral protamine hagedorn insulin in patients with type 1 diabetes using a basal-bolus regimen in Sweden. Scand J Public Health. 2011;39(1):79–87.

76. Karges B, Kapellen T, Neu A, Hofer SE, Rohrer T, Rosenbauer J et al. Long-acting insulin analogs and the risk of diabetic ketoacidosis in children and adolescents with type 1 diabetes: a prospective study of 10,682 patients from 271 institutions. Diabetes Care. 2010;33(5):1031–3.

77. Thalange N, Deeb L, Iotova V, Kawamura T, Klingensmith G, Philotheou A et al. Insulin degludec in combination with bolus insulin aspart is safe and effective in children and adolescents with type 1 diabetes. Pediatr Diabetes. 2015;16(3):164–76.

78. Mona HM, Maha AM, Hend SM, Hanan NM. Effect of insulin glargine on glycemic control in adolescents with type 1-diabetes. Egyptian Pediatric Association Gazette. 2015;63(2):35–8.

79. Sharef SW, Ullah I, Al-Shidhani A, Al-Farsi T, Al-Yaarubi S. Switching to multiple daily insulin injections in children and adolescents with type 1 diabetes: revisiting benefits from oman. Oman Med J. 2015;30(2):83–9.

80. Biester T, Blaesig S, Remus K, Aschemeier B, Kordonouri O, Granhall C et al. Insulin degludec's ultra-long pharmacokinetic properties observed in adults are retained in children and adolescents with type 1 diabetes. Pediatr Diabetes. 2014;15(1):27–33.

81. Danne T, Phillip M, Buckingham BA, Jarosz-Chobot P, Saboo B, Urakami T et al. ISPAD Clinical Practice Consensus Guidelines 2018: Insulin treatment in children and adolescents with diabetes. Pediatr Diabetes. 2018;19 Suppl 27:115–35.

82. Passanisi S, Timpanaro T, Lo Presti D, Mammi C, Caruso-Nicoletti M. Treatment of transient neonatal diabetes mellitus: insulin pump or insulin glargine? Our experience. Diabetes Technol Ther. 2014;16(12):880–4.

83. Park JH, Shin SY, Shim YJ, Choi JH, Kim HS. Multiple daily injection of insulin regimen for a 10-month-old infant with type 1 diabetes mellitus and diabetic ketoacidosis. Ann Pediatr Endocrinol Metab. 2016;21(2):96–8.

84. Guidelines on second- and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes mellitus. Geneva: World Health Organization; 2018. Available from https://apps.who.int/iris/bitstream/handle/10665/272433/9789241550284-eng.pdf?ua=1, accessed 29 September 2019.

85. Tricco AC, Ashoor HM, Antony J, Beyene J, Veroniki AA, Isaranuwatchai W et al. Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systematic review and network meta-analysis. BMJ. 2014;349:g5459.

86. Horvath K, Jeitler K, Berghold A, Ebrahim SH, Gratzer TW, Plank J et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2007(2):CD005613.

87. Fullerton B, Siebenhofer A, Jeitler K, Horvath K, Semlitsch T, Berghold A et al. Short-acting insulin analogues versus regular human insulin for adults with type 1 diabetes mellitus. Cochrane Database Syst Rev. 2016(6):CD012161.

88. Beran D, Ewen M, Laing R. Constraints and challenges in access to insulin: a global perspective. Lancet Diabetes Endocrinol. 2016;4(3):275–85.

89. Ogle GD, Middlehurst AC, Silink M. The IDF Life for a Child Program Index of diabetes care for children and youth. Pediatr Diabetes. 2016;17(5):374–84.

## 18.6 Medicines for hypoglycaemia

*Diazoxide – addition – EMLc*

**Diazoxide** **ATC Code: V03AH01**

**Proposal**

The application requested the inclusion of diazoxide on the EMLc for the management of hypoglycaemia secondary to prolonged hyperinsulinism (HI).

**Applicant**

Global Pediatric Endocrinology and Diabetes (GPED)
Caring and Living as Neighbours (CLAN)
Congenital Hyperinsulinism International (CHI)

**WHO Technical Department**

Comments on the applications were received from the WHO department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it supported the addition of diazoxide to the complementary list of the EMLc, stating that congenital hyperinsulinism is a rare but serious condition requiring specialist assessment and care, and that inclusion of diazoxide on the EMLc could facilitate access to this medicine in countries where it is currently unavailable.

**EML/EMLc**

EMLc

**Section**

18.6 Medicines for hypoglycaemia

**Dose form(s) & strengths(s)**

Oral liquid: 50 mg/mL
Tablet: 50 mg

**Core/Complementary**

Complementary

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Diazoxide had not previously been considered for inclusion on the EMLc for hypoglycaemia secondary to prolonged HI.

**Public health relevance** (burden of disease)

Congenital hyperinsulinism (HI) disorders are a group of disorders characterized by inappropriately persistent secretion of insulin in the context of low blood glucose. This condition can be transient or permanent. It is responsible for permanent neurological damage in the newborn and infant. Congenital HI has an estimated incidence ranging from 1 in 50 000 live births, with considerably higher incidence (up to 1 in 2500) seen in populations with high rates of consanguineous unions (*1*). Recurrent episodes of hypoglycaemia produced by HI increase risk for seizures, brain damage and intellectual disability. Management of hypoglycaemia is critical to prevent and reduce the risk of these serious consequences (*2*).

Neurological damage is present in up to 50% of children with early onset HI. Neurodevelopmental damage is observed in transient, permanent, mild and severe forms of HI, emphasizing the need for rapid diagnosis and prompt management (*3*–*6*).

Diazoxide is indicated for hypoglycaemia that is secondary to transient and prolonged inappropriate insulin secretion and as a first-line treatment in patients with permanent HI where a dietary approach alone does not appropriately prevent hypoglycaemia.

**Summary of evidence: benefits** (from the application)

No randomized controlled trials involving diazoxide were identified in the application.

Case series studies from China (*7*), Germany (*5*), Turkey (*8*, *9*), Thailand (*10*) and the United Kingdom (*11*) have reported the clinical response to diazoxide therapy ranging from 40% to 74% at dose ranges up to 20 mg/kg/day.

The effect of diazoxide depends on the genetic cause of hyperinsulinism. The majority of cases of neonatal onset persistent congenital HI are caused by defects in the KATP channel genes of the beta-cell of the pancreas, and diazoxide is ineffective in these patients (*12*).

**Summary of evidence: harms** (from the application)

The total number of patients who have received diazoxide to date has not been assessed. It is estimated that tens of thousands of patients have received diazoxide since 1964. The application summarized safety findings for diazoxide from cohort studies and case reports (*5*, *7*, *13*–*24*). The medicine is usually well tolerated. Adverse effects include water retention and hyponatraemia at onset of therapy, and hypertrichosis (in particular on back and limbs) that is reversible

after the treatment is discontinued. Less commonly reported adverse events include rash, thrombocytopenia, neutropenia, heart failure, extrapyramidal adverse events and paradoxical hypoglycaemia. Adverse events may be dose-related and are usually reversible with dose reduction or discontinuation of therapy. Heart failure secondary to water retention has been reported in premature babies and associated with reopening of the ductus arteriosus. Diazoxide is recommended to be used with caution in these patients (*13*).

Pulmonary hypertension has been reported to the United States Food and Drug Administration and Health Canada in neonates and infants treated with diazoxide.

The application noted that overall, the quality of the safety data is weak as it comes from small series of patients and case reports. No randomized controlled trials are available. Adverse events data was not systematically collected in the cohort studies. The likelihood that adverse events were associated with diazoxide was not assessed in any of the cohort studies or case reports.

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**Additional evidence** (not in the application)

A retrospective cohort study of 295 patients investigated the prevalence of adverse events in children with congenital HI treated with diazoxide (*25*). 2.4% of children developed pulmonary hypertension after initiation of diazoxide (most of them had additional risk factors such as prematurity, structural heart disease and respiratory failure). In addition, 15.6% developed neutropenia, 4.7% thrombocytopenia and 5% hyperuricaemia. The authors concluded that screening for neutropenia, thrombocytopenia and hyperuricaemia in diazoxide-treated patients may be of value given the relatively high prevalence of these events.

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**WHO Guidelines**

The 2013 *WHO Pocket book of Hospital Care for Children* (*26*) recognizes the importance of hypoglycaemia and the need to treat it as an emergency in order to prevent neurological sequelae. It focuses on the most common causes of hypoglycaemia and does not consider HI or make recommendations regarding diazoxide treatment.

Clinical practice guidelines for congenital HI developed by the Japanese Society for Pediatric Endocrinology and the Japanese Society of Pediatric Surgeons (*12*) make the following recommendations for first-line treatment of congenital HI:

- Maintain blood glucose above the target range by continuous glucose infusion. [Recommendation level 1, Evidence level A].
- When blood glucose is successfully maintained by continuous glucose infusion, nutritional support by frequent feeding, continuous feeding, cornstarch (after nine months), or formula for glycogen

storage diseases should be attempted. [Recommendation level 1, Evidence level A].

- When blood glucose is not maintained by continuous glucose infusion, or when it is difficult to withdraw glucose infusion for an extended period, a 5-day trial of oral diazoxide, in 2–3 divided doses, at 5–15 mg/kg/day should be attempted, unless contraindicated by cardiac failure or pulmonary hypertension. [Recommendation level 1, Evidence level A].
- When diazoxide is effective in stabilizing blood glucose levels, intravenous glucose infusion should be withdrawn and transfer to nutritional support (frequent feeding, continuous feeding, or cornstarch formula for glycogen storage diseases) should be attempted. [Recommendation level 1, Evidence level A].
- While on diazoxide, the patient should be on a glucose self-monitoring regimen to detect episodes of hypoglycaemia. Furthermore, complete blood count (CBC), blood chemistry, and physical examination should be performed to detect frequent adverse events, such as hypertrichosis, tachycardia, or oedema. [Recommendation level 1, Evidence level B].
- When euglycaemia is not achieved by the first-line treatment and continuous glucose infusion cannot be withdrawn, the second-line treatment should be initiated. [Recommendation level 1, Evidence level A].

**Costs/cost-effectiveness**

No information was provided in the application regarding the cost and cost-effectiveness of diazoxide.

Preliminary results of an international survey of paediatric endocrinologists conducted in 2018 by Congenital Hyperinsulinism International to assess the availability and need for diazoxide reported that 53% of respondents agreed that cost to the patient was an obstacle to accessing diazoxide.

**Availability**

Global availability, reliable supply and regulatory approval of diazoxide is variable.

**Other considerations**

N/A

**Committee recommendations**

The Committee recommended the addition of diazoxide to the complementary list of the EMLc for the management of hypoglycaemia secondary to prolonged

hyperinsulinism (HI), based on evidence of favourable efficacy and tolerability, and taking into account the serious consequences of this condition in children not treated.

The Committee noted the variable global availability and reliability of supply of diazoxide and considered inclusion of diazoxide on the EMLc could help to facilitate more reliable access.

## References


1. Arnoux JB, Verkarre V, Saint-Martin C, Montravers F, Brassier A, Valayannopoulos V et al. Congenital hyperinsulinism: current trends in diagnosis and therapy. Orphanet J Rare Dis. 2011;6:63.
2. Hussain K, Blankenstein O, De Lonlay P, Christesen HT. Hyperinsulinaemic hypoglycaemia: biochemical basis and the importance of maintaining normoglycaemia during management. Arch Dis Child. 2007;92(7):568–70.
3. Avatapalle HB, Banerjee I, Shah S, Pryce M, Nicholson J, Rigby L et al. Abnormal Neurodevelopmental Outcomes are Common in Children with Transient Congenital Hyperinsulinism. Front Endocrinol (Lausanne). 2013;4:60.
4. Ludwig A, Ziegenhorn K, Empting S, Meissner T, Marquard J, Holl R et al. Glucose metabolism and neurological outcome in congenital hyperinsulinism. Semin Pediatr Surg. 2011;20(1):45–9.
5. Meissner T, Wendel U, Burgard P, Schaetzle S, Mayatepek E. Long-term follow-up of 114 patients with congenital hyperinsulinism. Eur J Endocrinol. 2003;149(1):43–51.
6. Menni F, de Lonlay P, Sevin C, Touati G, Peigne C, Barbier V et al. Neurologic outcomes of 90 neonates and infants with persistent hyperinsulinemic hypoglycemia. Pediatrics. 2001;107(3):476–9.
7. Gong C, Huang S, Su C, Qi Z, Liu F, Wu D et al. Congenital hyperinsulinism in Chinese patients: 5-yr treatment outcome of 95 clinical cases with genetic analysis of 55 cases. Pediatr Diabetes. 2016;17(3):227–34.
8. Guven A, Cebeci AN, Ellard S, Flanagan SE. Clinical and Genetic Characteristics, Management and Long-Term Follow-Up of Turkish Patients with Congenital Hyperinsulinism. J Clin Res Pediatr Endocrinol. 2016;8(2):197–204.
9. Demirbilek H, Arya VB, Ozbek MN, Akinci A, Dogan M, Demirel F et al. Clinical characteristics and phenotype-genotype analysis in Turkish patients with congenital hyperinsulinism; predominance of recessive KATP channel mutations. Eur J Endocrinol. 2014;170(6):885–92.
10. Sawathiparnich P, Likitmaskul S, Angsusingha K, Nimkarn S, Chaichanwatanakul K, Laohapansang M et al. Persistent hyperinsulinemic hypoglycemia of infancy: experience at Siriraj Hospital. J Med Assoc Thai. 2002;85 Suppl 2:S506–12.
11. Banerjee I, Skae M, Flanagan SE, Rigby L, Patel L, Didi M et al. The contribution of rapid KATP channel gene mutation analysis to the clinical management of children with congenital hyperinsulinism. Eur J Endocrinol. 2011;164(5):733–40.
12. Yorifuji T, Horikawa R, Hasegawa T, Adachi M, Soneda S, Minagawa M et al. Clinical practice guidelines for congenital hyperinsulinism. Clin Paediatr Endocrinol. 2017;26(3):127–52.
13. Yoshida K, Kawai M, Marumo C, Kanazawa H, Matsukura T, Kusuda S et al. High prevalence of severe circulatory complications with diazoxide in premature infants. Neonatology. 2014;105(3):166–71.
14. Hu S, Xu Z, Yan J, Liu M, Sun B, Li W et al. The treatment effect of diazoxide on 44 patients with congenital hyperinsulinism. J Pediatr Endocrinol Metab. 2012;25(11–12):1119–22.

15. Touati G, Poggi-Travert F, Ogier de Baulny H, Rahier J, Brunelle F, Nihoul-Fekete C et al. Long-term treatment of persistent hyperinsulinaemic hypoglycaemia of infancy with diazoxide: a retrospective review of 77 cases and analysis of efficacy-predicting criteria. Eur J Pediatr. 1998;157(8):628–33.
16. Abu-Osba YK, Manasra KB, Mathew PM. Complications of diazoxide treatment in persistent neonatal hyperinsulinism. Arch Dis Child. 1989;64(10):1496–500.
17. Goode PN, Farndon JR, Anderson J, Johnston ID, Morte JA. Diazoxide in the management of patients with insulinoma. World J Surg. 1986;10(4):586–92.
18. Silvani P, Camporesi A, Mandelli A, Wolfler A, Salvo I. A case of severe diazoxide toxicity. Paediatr Anaesth. 2004;14(7):607–9.
19. Parker JJ, Allen DB. Hypertrophic cardiomyopathy after prolonged diazoxide therapy for hyperinsulinemic hypoglycemia. J Pediatr. 1991;118(6):906–9.
20. Combs JT, Grunt JA, Brandt IK. Hematologic reactions to diazoxide. Pediatrics. 1967;40(1):90-2.
21. McGraw ME, Price DA. Complications of diazoxide in the treatment of nesidioblastosis. Arch Dis Child. 1985;60(1):62–4.
22. Ponmani C, Gannon H, Hussain K, Senniappan S. Paradoxical hypoglycaemia associated with diazoxide therapy for hyperinsulinaemic hypoglycaemia. Horm Res Paediatr. 2013;80(2):129–33.
23. Darendeliler F, Bundak R, Bas F, Saka N, Gunoz H. Long-term diazoxide treatment in persistent hyperinsulinemic hypoglycemia of infancy: a patient report. J Pediatr Endocrinol Metab. 1997;10(1):79–81.
24. Tas E, Mahmood B, Garibaldi L, Sperling M. Liver injury may increase the risk of diazoxide toxicity: a case report. Eur J Pediatr. 2015;174(3):403–6.
25. Herrera A, Vajravelu ME, Givler S, Mitteer L, Avitabile CM, Lord K et al. Prevalence of Adverse Events in Children With Congenital Hyperinsulinism Treated With Diazoxide. J Clin Endocrinol Metab. 2018;103(12):4365–72.
26. Pocket book of hospital care for children: guidelines for the managment of common illnesses with limited resources. Geneva: World Health Organization; 2013. Available from https://www.who.int/maternal_child_adolescent/documents/9241546700/en/, accessed 30 October 2019.

## 18.7 Thyroid hormones and antithyroid medicines

*Medicines for first-line treatment of primary hyperthyroidism – review – EML and EMLc*

| | |
|---|---|
| **Methimazole** | **ATC Code: H03BB01** |
| **Propylthiouracil** | **ATC Code: H03BA02** |

**Proposal**

The application requested:

- inclusion on the core list of the EML and EMLc of methimazole (INN thiamazole) with a square box for the first-line management of Graves' hyperthyroidism in children and non-pregnant adults;
- transferring the current EML listing for propylthiouracil from the core to the complementary list, and removal of the square box.
- Inclusion of a note with the listing of propylthiouracil specifying use only when alternative first-line treatments are not appropriate or available, to reinforce its place as a second-line therapy.

**Applicant**

Global Pediatric Endocrinology and Diabetes (GPED)

**WHO Technical Department**

Comments on the application were received from the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it did not support the requests made in the application and considered the evidence presented in the application to be deficient.

**EML/EMLc**

EML and EMLc

**Section**

18.8 Thyroid hormones and antithyroid medicines

**Dose form(s) & strengths(s)**

Methimazole: tablet 5 mg, 10 mg, 20 mg
Propylthiouracil: tablet 50 mg

**Core/Complementary**

Methimazole: core
Propylthiouracil: complementary

**Individual/Square box listing**

Methimazole: Square box incorporating carbimazole as a therapeutically equivalent alternative.
Propylthiouracil: individual

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**Background** (if relevant, eg. resubmission, previous EC consideration)

Propylthiouracil (PTU) with a square box has been included on the core list of the EML since the first list in 1977. In 2007, it was added (without a square box) to the complementary list of the EMLc. The EMLc Subcommittee noted that PTU was licensed for use in children aged over 6 years, although in some settings carbimazole (CMZ) was the more commonly used drug. The EMLc Subcommittee decided to list PTU but recommended the role of CMZ in children be reviewed (*1*).

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**Public health relevance** (burden of disease)

Graves' disease is the most common cause of hyperthyroidism. Women are affected more frequently than men at a ratio of 8:1, most commonly in the third to fifth decade of life (*2*). A meta-analysis of European studies estimated a mean prevalence rate of 0.75% for males and females combined and an incidence rate of 51 cases per 100 000 per year with a significant influence of ethnicity and iodine nutrition (*3*).

Among children, Graves' disease represents more than 90% of the cases of hyperthyroidism with an incidence ranging from 0.1 per 100 000 children and 3.0 per 100 000 adolescents per year (*4*).

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**Summary of evidence: benefits** (from the application)

The application identified four randomized controlled trials (RCTs) that compared the effectiveness of PTU and MMI in adults and one retrospective study in children and adolescents.

The trials in adults found MMI to have similar or greater effectiveness than PTU at reducing or normalizing thyroid hormone concentrations (*5*–*8*). The paediatric study found no significant difference in the mean duration for normalization of serum T4 concentration between MMI (1.7 ± 1.0 months) and PTU (2.3 ± 2.4) treated patients (*9*).

Two RCTs evaluated the effect of MMI (10) and CMZ (11) taken once, twice or three times daily. The results indicated that once daily dosing is as effective as multiple daily dosing.

The application acknowledged that in general, less information was available for CMZ but because CMZ is metabolized to MMI after absorption, it was assumed that data that apply to MMI also apply to CMZ.

**Summary of evidence: harms** (from the application)

Overall, both PTU and MMI/CMZ all present with minor and major adverse events in adults and in children. However, major adverse events were less commonly reported for patients receiving MMI/CMZ. Common minor side-effects for these medicines include pruritis, skin rash, urticaria and arthralgias. Major adverse events are uncommon but include agranulocytosis, hepatic failure, vasculitis and fetal malformations.

In the RCT by Nakamura et al (*5*), the overall incidence of adverse events was higher in the PTU group than the MMI 30 mg/d group (51.9% vs 30%). The percentage of patients who showed aspartate aminotransferase (AST) and alanine aminotransferase (ALT) higher than double the upper range of the normal standard was significantly higher for the PTU group compared to the MMI 30 mg/d group (26.9% vs 6.6%). Skin eruption or urticaria was similar between groups. Leukocytopenia (less than 1000/mm$^3$) was observed in five patients in the PTU group only.

A retrospective cohort study of 71 379 Taiwanese patients found MMI/CBZ to be associated in a dose-dependent manner with an increased risk for hepatitis compared to PTU. However, no significant difference in risk was observed between groups for acute liver failure or cholestasis (*12*).

In the paediatric retrospective study, minor adverse events were observed more frequently among PTU treated patients compared to MMI treated patient (31.9% vs 25.0%), although the difference was not significant. The incidence of liver dysfunction was significantly higher among PTU treated patients (18.9% vs 6.3%) (*9*). A 2000 RCT involving 40 children found no difference in side-effects between patients receiving PTU or MMI within the same age groups (*13*).

Agranulocytosis has been observed with both MMI/CMZ and PTU (*14*). There have been reports of PTU-related liver failure and death in adults and children (*15*), where the risk is five times higher in children than in adults. Between 1990 and 2008, a total of 23 PTU-related liver transplants were reported, and 30% of recipients were paediatric patients. No MMI-related liver transplants were reported in the same time period (*16*). Antineutrophil cytoplasmic antibodies (ANCA) vasculitis has been reported, more often related to PTU than MMI (*17*, *18*).

A high prevalence of birth defects in children exposed to anti-thyroid drugs in early pregnancy has been reported (*19*). It is not clear whether MMI and CMZ lead to a higher prevalence of fetal malformations compared to PTU. Some studies have shown similar rates of fetal defects with both drugs (*12*). However, this rate may not be higher than the rate of malformations in the control population (*20*). In contrast, a recent meta-analysis showed an increased risk of neonatal congenital malformations associated with MMI, but not PTU when compared to no antithyroid medicines exposure (*21*). However, the fetal

malformations associated with PTU may be less severe and easier to correct than those associated with MMI and CMZ.

**Additional evidence** (not in the application)

N/A

**WHO Guidelines**

There are no WHO guidelines currently available for the management of Graves' disease.

The 2018 European Thyroid Association guidelines for management of Graves' disease recommend MMI as preferred treatment for newly diagnosed patients (both adults and children). The guidelines further recommend that MMI-treated women should be switched to PTU when planning pregnancy and during the first trimester (*22*).

The 2016 American Thyroid Association Guidelines also recommend use of MMI in almost all patients. PTU is recommended for patients during the first trimester of pregnancy, in the treatment of thyroid storm, and in patients with minor reactions to MMI who refuse radioactive iodine therapy or surgery (*23*).

**Costs/cost-effectiveness**

Costs of PTU, MMI and CMZ vary considerably between countries. The application compared the calculated costs for one month of treatment with PTU, MMI or CMZ. For the induction treatment period, costs ranged from US$ 7 to US$ 37 per month for MMI, US$ 18 to US$ 27 per month for CMZ and from US$ 3.50 to US$ 68 per month for PTU. For the core treatment period, costs ranged from US$ 3.50 to US$ 18.50 per month for MMI, and from US$ 9 to 13.50 per month for CMZ and US$ 1.80 US$ 34 per month for PTU.

**Availability**

Usually, only one of CMZ or MMI is available in a given country reflecting differences in regulatory approval in different jurisdictions.

PTU is available globally.

**Other considerations**

N/A

**Committee recommendations**

The Committee recommended the addition of methimazole with a square box to the core list of the EML and to the complementary list of the EMLc for use as first-line therapy for hyperthyroidism. The square box listing should specify carbimazole as a therapeutically equivalent alternative.

The Committee recommended that propylthiouracil should remain on the core list of the EML for use in patients during the first trimester of pregnancy, and for other patients in whom alternative first-line treatment is not appropriate or available. The square box should be removed from the listing. The Committee also recommended that propylthiouracil should remain on the complementary list of the EMLc for use in patients for whom alternative first-line treatment is not appropriate or available.

The Committee considered that the available evidence indicated that efficacy of methimazole is at least equivalent to propylthiouracil. Compared to propylthiouracil however, methimazole demonstrated a more favourable safety profile with fewer reported major adverse events. The Committee noted that propylthiouracil remains the treatment of choice in some patients and therefore should remain available.

## References


1. The selection and use of essential medicines. Report of the WHO Expert Committee, October 2007 (including the Model List of Essential Medicines for Children) (WHO Technical Report Series, No. 950). Geneva: World Health Organization; 2008. Available from https://apps.who.int/iris/bitstream/handle/10665/43745/WHO_TRS_946_eng.pdf, accessed 30 October 2019.
2. De Leo S, Lee SY, Braverman LE. Hyperthyroidism. Lancet. 2016;388(10047):906–18.
3. Garmendia Madariaga A, Santos Palacios S, Guillen-Grima F, Galofre JC. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. J Clin Endocrinol Metab. 2014;99(3):923–31.
4. Lee HS, Hwang JS. The treatment of Graves' disease in children and adolescents. Ann Pediatr Endocrinol Metab. 2014;19(3):122–6.
5. Nakamura H, Noh JY, Itoh K, Fukata S, Miyauchi A, Hamada N. Comparison of methimazole and propylthiouracil in patients with hyperthyroidism caused by Graves' disease. J Clin Endocrinol Metab. 2007;92(6):2157–62.
6. He CT, Hsieh AT, Pei D, Hung YJ, Wu LY, Yang TC et al. Comparison of single daily dose of methimazole and propylthiouracil in the treatment of Graves' hyperthyroidism. Clin Endocrinol (Oxf). 2004;60(6):676–81.
7. Homsanit M, Sriussadaporn S, Vannasaeng S, Peerapatdit T, Nitiyanant W, Vichayanrat A. Efficacy of single daily dosage of methimazole vs. propylthiouracil in the induction of euthyroidism. Clin Endocrinol (Oxf). 2001;54(3):385–90.
8. Nicholas WC, Fischer RG, Stevenson RA, Bass JD. Single daily dose of methimazole compared to every 8 hours propylthiouracil in the treatment of hyperthyroidism. South Med J. 1995;88(9):973–6.
9. Sato H, Minagawa M, Sasaki N, Sugihara S, Kazukawa I, Minamitani K et al. Comparison of methimazole and propylthiouracil in the management of children and adolescents with Graves' disease: efficacy and adverse reactions during initial treatment and long-term outcome. J Pediatr Endocrinol Metab. 2011;24(5-6):257–63.

10. Sriussadaporn S, Pumchumpol W, Lertwattanarak R, Kunavisarut T. Efficacy of Once Daily versus Divided Daily Administration of Low Daily Dosage (15 mg/Day) of Methimazole in the Induction of Euthyroidism in Graves' Hyperthyroidism: A Randomized Controlled Study. Int J Endocrinol. 2017;2017:2619695.
11. Mafauzy M, Wan Mohamad WB, Zahary MK, Mustafa BE. Comparison of the efficacy of single and multiple regimens of carbimazole in the treatment of thyrotoxicosis. Med J Malaysia. 1993;48(1):71–5.
12. Wang MT, Lee WJ, Huang TY, Chu CL, Hsieh CH. Antithyroid drug-related hepatotoxicity in hyperthyroidism patients: a population-based cohort study. Br J Clin Pharmacol. 2014;78(3): 619–29.
13. Lazar L, Kalter-Leibovici O, Pertzelan A, Weintrob N, Josefsberg Z, Phillip M. Thyrotoxicosis in prepubertal children compared with pubertal and postpubertal patients. J Clin Endocrinol Metab. 2000;85(10):3678–82.
14. Marino M, Vitti P, Chiovato L. Graves' Disease. In: Jameson JL, editor. Endinocrinology: Adult and Pediatric. Philadelphia: Elsevier Saunders; 2016. p. 1437–64.
15. Akmal A, Kung J. Propylthiouracil, and methimazole, and carbimazole-related hepatotoxicity. Expert Opin Drug Saf. 2014;13(10):1397–406.
16. Rivkees SA, Mattison DR. Propylthiouracil (PTU) Hepatoxicity in Children and Recommendations for Discontinuation of Use. Int J Pediatr Endocrinol. 2009;2009:132041.
17. Gao Y, Zhao MH, Guo XH, Xin G, Gao Y, Wang HY. The prevalence and target antigens of antithyroid drugs induced antineutrophil cytoplasmic antibodies (ANCA) in Chinese patients with hyperthyroidism. Endocr Res. 2004;30(2):205–13.
18. Huang CN, Hsu TC, Chou HH, Tsay GJ. Prevalence of perinuclear antineutrophil cytoplasmic antibody in patients with Graves' disease treated with propylthiouracil or methimazole in Taiwan. J Formos Med Assoc. 2004;103(4):274–9.
19. Andersen SL, Olsen J, Wu CS, Laurberg P. Birth defects after early pregnancy use of antithyroid drugs: a Danish nationwide study. J Clin Endocrinol Metab. 2013;98(11):4373–81.
20. Koenig D, Spreux A, Hieronimus S, Chichmanian RM, Bastiani F, Fenichel P et al. Birth defects observed with maternal carbimazole treatment: Six cases reported to Nice's Pharmacovigilance Center. Ann Endocrinol (Paris). 2010;71(6):535–42.
21. Song R, Lin H, Chen Y, Zhang X, Feng W. Effects of methimazole and propylthiouracil exposure during pregnancy on the risk of neonatal congenital malformations: A meta-analysis. PLoS One. 2017;12(7):e0180108.
22. Kahaly GJ, Bartalena L, Hegedus L, Leenhardt L, Poppe K, Pearce SH. 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. Eur Thyroid J. 2018;7(4):167–86.
23. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid. 2016;26(10):1343–421.

# Section 22: MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE

## 22.3 Uterotonics

*Carbetocin (heat-stable) – addition – EML*

**Carbetocin** **ATC Code: H01BB03**

**Proposal**

The application requested the inclusion of heat-stable carbetocin on the EML for the prevention of postpartum haemorrhage (PPH).

**Applicant**

WHO Department of Reproductive Health and Research

**WHO Technical Department**

Reproductive Health and Research

**EML/EMLc**

EML

**Section**

22.3 Uterotonics

**Dose form(s) & strengths(s)**

Injection (heat stable): 100 micrograms/mL

**Core/Complementary**

Core

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Carbetocin has not previously been considered for inclusion on the EML for prevention of PPH. Oxytocin, misoprostol and ergometrine are currently included on the EML for the prevention of PPH.

**Public health relevance** (burden of disease)

Obstetric haemorrhage, especially PPH, is responsible for more than a quarter of all maternal deaths worldwide (*1*). In most low-income countries, PPH is the leading cause of maternal deaths.

PPH is commonly defined as a blood loss of 500 mL or more within 24 hours after birth, and affects about 5% of all women giving birth around the world (*2*, *3*). Uterine atony is the most common cause of PPH and a leading cause of PPH-related maternal mortality worldwide (*1*).

PPH can be prevented if prophylactic uterotonics are administered during the third stage of labour, and by timely and appropriate management (*4*). Oxytocin is the first choice uterotonic drug recommended by WHO. However, oxytocin is sensitive to heat exposure and must be transported and store at 2–8 °C continuously. This represents a problem in low-resource settings where the cold chain is difficult to maintain. Carbetocin, in its heat stable formulation, does not require cold chain transport and storage and can stay at room temperature for a long period of time (30 °C for three years, 40 °C for six months, 50 °C for three months and 60 °C for one month) (*5*). Based on the WHO CHAMPION trial results and on the updated WHO recommendations on uterotonics for the prevention of PPH, carbetocin is recommended for PPH prevention, especially in those settings where the cold storage of oxytocin is not possible.

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**Summary of evidence: benefits** (from the application)

The application presented the findings of a Cochrane systematic review and network meta-analysis of seven uterotonic options (*6*), and GRADE tables extracted from the WHO recommendations on uterotonics for prevention of PPH (*4*).

Carbetocin compared with placebo or no treatment was investigated in two randomized controlled trials (RCTs) involving 169 women in the network meta-analysis. There was moderate certainty evidence that carbetocin was associated with a substantial reduction in PPH ≥500 mL (relative risk (RR) 0.42, 95%CI 0.31 to 0.57), PPH ≥1000 mL (RR 0.52, 95%CI 0.38 to 0.72), blood transfusion (RR 0.48, 95%CI 0.26 to 0.89), and use of additional uterotonics (RR 0.19, 95%CI 0.13 to 0.27) when compared with placebo or no treatment. Evidence on whether the prophylactic use of carbetocin during the third stage of labour reduces maternal death when compared to placebo was of very low certainty. It was uncertain whether carbetocin reduced maternal intensive care unit (ICU) admissions due to the very low number of events. There was moderate certainty evidence that the use of prophylactic carbetocin probably reduces average blood loss compared with women receiving placebo or no treatment (mean difference: 138.37 mL, 95%CI 193.24 mL lower to 83.50 mL lower).

There is moderate certainty evidence that carbetocin has similar effects to oxytocin for the outcomes of maternal death, blood transfusion and ICU admissions. Carbetocin may be superior to oxytocin for the outcomes of PPH ≥500 mL (41 few events per 1000 women – moderate certainty evidence), use of additional uterotonics (74 fewer per 1000 women – low certainty evidence) and blood loss after birth (82 mL less, on average – low certainty evidence). There

was very low certainty evidence of a difference in effect between carbetocin and oxytocin for the outcome of PPH ≥1000 mL.

**Summary of evidence: harms** (from the application)

The application presented the findings of a Cochrane systematic review and network meta-analysis of seven uterotonic options (*6*), and GRADE tables extracted from the WHO recommendations on uterotonics for prevention of PPH (*4*).

Compared to placebo or no treatment, carbetocin was associated with little or no difference to the risk of experiencing adverse effects (i.e. nausea, vomiting, headache, abdominal pain, hypertension, shivering, fever and diarrhoea). Compared to oxytocin, there was no clear difference in terms of adverse effects. The certainty of the evidence ranged from very low to moderate.

**Additional evidence** (not in the application)

N/A

**WHO Guidelines**

The 2018 WHO recommendations for uterotonics for the prevention of PPH (*4*) recommend use of an effective uterotonic during the third stage of labour for all births. Recommended uterotonics are oxytocin, carbetocin, misoprostol, ergometrine/methylergometrine and oxytocin + ergometrine in fixed-dose combination.

The Guidelines Development Group made a context-specific recommendation for carbetocin and recommended its use in contexts where its cost is comparable to other effective uterotonics, noting that the current cost of using carbetocin for PPH prevention was greater than the cost of using other effective uterotonics.

**Costs/cost-effectiveness**

Ex-factory prices of carbetocin vary globally and range from € 8 to € 40 per unit (100 micrograms).

In 2013, WHO was approached by Merck for Mothers (a philanthropic initiative of Merck, known outside the United States as Merck Sharpe & Dohme (MSD)) and Ferring Pharmaceuticals to explore the potential value of heat-stable carbetocin for reducing the incidence of maternal death. WHO convened an international panel of stakeholders who identified the need for demonstration of non-inferiority of heat-stable carbetocin before a change in guidance and practice could be considered. If non-inferior to oxytocin, the heat-stable formulation of carbetocin would be made available in public sector health care facilities in high-burden countries at an affordable and sustainable "access price" (comparable to

the United Nations Population Fund (UNFPA) price of oxytocin), according to a memorandum of understanding signed by representatives of WHO, Ferring Pharmaceuticals and Merck (7). This price is a subsidized price of US$ 0.31 +/- 10% per ampoule of 100 µg heat-stable carbetocin (the UNFPA current price of Oxytocin is US$ 0.27 per unit (10 I.U.)).

It was noted that the cost-effectiveness of carbetocin varies across settings (*6*, *8*–*12*). The WHO recommendations for uterotonics state that "*carbetocin would probably be cost-effective if the unit cost is comparable to other effective uterotonics and in settings where the cost of PPH care is substantial*" (*4*).

### Availability

Carbetocin is approved in more than 80 countries worldwide, not including the United States and Japan. In most countries carbetocin is approved for prevention of uterine atony following delivery of the infant by caesarean section. In a few countries, primarily in Latin America and recently in Australia, it is also approved for prevention of uterine atony following vaginal delivery.

The currently approved product is manufactured in Germany.

The product Ferring will make available in low- and middle-income countries (LMICs) at access price will be manufactured in China and India. Ferring began the registration process in September 2018, where the first application was submitted to Swissmedic, via their procedure for Marketing Authorisation for Global Health Products (MAGHP). The approval by Swissmedic is anticipated in 2020, whereafter Ferring will pursue registrations in LMICs and seek WHO prequalification.

### Other considerations

The heat-stable formulation of carbetocin does not need to be transported under cold chain conditions, nor does it require refrigerated storage. This may make carbetocin a preferred choice in settings where cold chain transport and storage of oxytocin is not possible.

### Committee recommendations

The Committee recommended the addition of heat-stable carbetocin injection to the core list of the EML for the prevention of postpartum haemorrhage on the basis of similar effects compared to oxytocin for efficacy and safety outcomes. The Committee agreed that heat-stable carbetocin may offer advantages over oxytocin in some settings as it does not require cold chain transport or refrigerated storage.

The Committee noted the current higher cost of carbetocin compared to other uterotonics and agreed with the context-specific recommendation in WHO guidelines for the prevention of PPH, that carbetocin be used where its cost is comparable to other effective uterotonics.

The Committee also recommended that WHO facilitate increased access and affordability of carbetocin through inclusion in the WHO prequalification programme.

## References


1. Say L, Chou D, Gemmill A, Tuncalp O, Moller AB, Daniels J et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2(6):e323–33.
2. Souza JP, Gulmezoglu AM, Vogel J, Carroli G, Lumbiganon P, Qureshi Z et al. Moving beyond essential interventions for reduction of maternal mortality (the WHO Multicountry Survey on Maternal and Newborn Health): a cross-sectional study. Lancet. 2013;381(9879):1747–55.
3. Carroli G, Cuesta C, Abalos E, Gulmezoglu AM. Epidemiology of postpartum haemorrhage: a systematic review. Best Pract Res Clin Obstet Gynaecol. 2008;22(6):999–1012.
4. WHO recommendations: uterotonics for the prevention of postpartum haemorrhage. Geneva: World Health Organization; 2018. Available from https://apps.who.int/iris/bitstream/handle/10665/277276/9789241550420-eng.pdf?ua=1&ua=1, accessed 29 September 2019.
5. Malm M, Madsen I, Kjellstrom J. Development and stability of a heat-stable formulation of carbetocin for the prevention of postpartum haemorrhage for use in low and middle-income countries. J Pept Sci. 2018;24(6):e3082.
6. Gallos ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis. Cochrane Database Syst Rev. 2018;12:CD011689.
7. Widmer M, Piaggio G, Nguyen TMH, Osoti A, Owa OO, Misra S et al. Heat-Stable Carbetocin versus Oxytocin to Prevent Hemorrhage after Vaginal Birth. N Engl J Med. 2018;379(8):743–52.
8. Henriquez-Trujillo AR, Lucio-Romero RA, Bermudez-Gallegos K. Analysis of the cost-effectiveness of carbetocin for the prevention of hemorrhage following cesarean delivery in Ecuador. J Comp Eff Res. 2017;6(6):529–36.
9. Voon HY, Shafie AA, Bujang MA, Suharjono HN. Cost effectiveness analysis of carbetocin during cesarean section in a high volume maternity unit. J Obstet Gynaecol Res. 2018;44(1):109–16.
10. van der Nelson HA, Draycott T, Siassakos D, Yau CWH, Hatswell AJ. Carbetocin versus oxytocin for prevention of post-partum haemorrhage at caesarean section in the United Kingdom: An economic impact analysis. Eur J Obstet Gynecol Reprod Biol. 2017;210:286–91.
11. Luni Y, Borakati A, Matah A, Skeats K, Eedarapalli P. A prospective cohort study evaluating the cost-effectiveness of carbetocin for prevention of postpartum haemorrhage in caesarean sections. J Obstet Gynaecol. 2017;37(5):601–4.
12. Caceda SI, Ramos RR, Saborido CM. Pharmacoeconomic study comparing carbetocin with oxytocin for the prevention of hemorrhage following cesarean delivery in Lima, Peru. J Comp Eff Res. 2018;7(1):49–55.

*Mifepristone-misoprostol – change to listing – EML*

| **Mifepristone-misoprostol** | **ATC Code: G03XB01, G02AD06** |
|---|---|

**Proposal**

The application requested the following changes to the current listing on the EML of mifepristone-misoprostol:

- transfer from the complementary to the core list;
- removal of the note stating "Requires close medical supervision";
- removal of the boxed text stating "Where permitted under national law and where culturally acceptable";
- addition of a co-packaged presentation of mifepristone and misoprostol.

**Applicant**

WHO Department of Reproductive Health and Research

**WHO Technical Department**

Reproductive Health and Research

**EML/EMLc**

EML

**Section**

22.3 Uterotonics

**Dose form(s) & strengths(s)**

Tablet 200 mg – tablet 200 micrograms

Co-packaged mifepristone 200 mg tablet [1] and misoprostol 200 microgram tablet [4]

**Core/Complementary**

Core

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Mifepristone-misoprostol has been included on the EML for use in medical abortion since 2005. The Committee recommended listing on the complementary list with the note regarding the requirement for close medical supervision.

In reviewing the recommendation by the Committee, the Director-General sought clarification from the Committee regarding the risks and benefits of mifepristone-misoprostol. The Director-General subsequently made the decision to approve listing mifepristone-misoprostol on the EML with an additional note: "Where permitted under national law and where culturally acceptable."

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**Public health relevance** (burden of disease)

Despite the major advances in management of abortion over the past two decades, of the 55.7 million abortions that occurred worldwide each year between 2010–2014, 30.6 million (54.9%) were considered safe, 17.1 million (30.7%) are classified as less safe and 8.0 million (14.4%) were considered least safe according to new safety classifications. 24.3 million (97%) of unsafe abortions occur in low- and middle-income countries (LMICs) (*1*). In LMICs, around 7 million women are admitted to hospitals annually as a result of unsafe abortion (*2*). Globally, between 4.7% and 13% of maternal deaths have been attributed to unsafe abortion (*3*).

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**Summary of evidence: benefits** (from the application)

Evidence for the clinical effectiveness of mifepristone-misoprostol was evaluated at the time of original listing in 2005 (*4*). Updated evidence was considered as part of the development process for the 2018 WHO guidelines for medical management of abortion and continues to support the effectiveness, safety and acceptability of mifepristone-misoprostol (*5*).

Support for less medicalized service delivery of mifepristone-misoprostol exists in a number of WHO guidelines, clinical guidance and systematic reviews (*5–11*). Specifically, the WHO 2015 *Health worker roles in providing safe abortion care and post-abortion contraception* (*7*) and the 2018 *Medical management of abortion guidance* (*5*), state that administration of mifepristone-misoprostol does not require direct medical supervision or specialized care. WHO recommends that pregnant persons should be provided information and access to health care providers if they are experiencing signs of ongoing pregnancy or for any other medical reasons (*5*, *7*, *8*, *12*). One health worker can provide the entire package, but it is equally possible for sub-tasks to be performed by different health workers and at different locations.

The application states that specialized diagnostics or treatment are not needed (*6*). Provision of care generally requires access to quality mifepristone and

misoprostol in the correct dosages, instructions on how to use them (including dating of gestational age) and information about how to recognize complications (e.g. in the event of very heavy and/or prolonged bleeding) and where to seek help. Ultrasound scanning is not routinely required (*5–8*), and routine use of antibiotics and testing for sexually transmitted infections is not recommended. In the event of undiagnosed ectopic pregnancy, heavy, ongoing bleeding and/or retained products of conception that may not evacuate on its own, the pregnant person may require referral to a higher level care (*6–8*).

Evidence supports safe and effective provision of medical abortion for pregnancies less than 12 weeks uterine size by the following health care cadres: auxiliary nurses, auxiliary nurse midwives, nurses, midwives, associate and advanced associate clinicians, non-specialist and specialist doctors (*5–9*, *13–17*). It is recommended that every primary care health service delivery point have staff (regardless of their cadre) trained and competent to take a medical history, perform a bimanual and abdominal examination and establish a referral network with higher level facilities and/or providers who are available to manage complications in the rare event that they may arise.

The application stated that desired benefit of co-packaged mifepristone-misoprostol is to ensure availability of quality-assured products with consistent and clear dosing. A recent study of the provision of medical abortion and post-abortion contraception by mid-level health care providers in Kyrgyzstan involved training midwives and family nurses to provide medical abortion with co-packaged mifepristone-misoprostol (*18*). Results demonstrated that trained midwives and nurses can provide medical abortion safely and effectively. Although the study did not compare co-packaged mifepristone-misoprostol with individually packaged drugs, the authors recommended registration and market availability of high quality co-packaged mifepristone-misoprostol as a strategy to facilitate the scale up of safe abortion in Kyrgyzstan.

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**Summary of evidence: harms** (from the application)

Evidence for the safety of mifepristone-misoprostol was evaluated at the time of original listing in 2005 (*4*).

Recently published safety data from the United States reported an estimated mifepristone-associated mortality rate of 0.00063% (*19*). Studies including mifepristone-misoprostol medical abortions among more than 423 000 persons globally reported very low rates (0.01 to 0.7%) of non-fatal serious adverse events such as hospital admission, blood transfusion or serious infection after use of mifepristone (*19*). In addition, a pooled analysis of serious adverse reactions including data from 30 966 clinical study participants presenting for mifepristone-misoprostol medical abortion through 70 days gestation found no differences in rate or type of serious adverse reaction by geographical

location (*20*). Serious adverse reaction rates were reported in <0.5% of study participants and include atypical presentation of infection, sepsis and prolonged heavy bleeding/haemorrhage (*20*). These events were typically treatable without permanent sequelae.

The 2015 *WHO recommendations on health worker roles in providing safe abortion care and post-abortion contraception* highlight that the most commonly experienced non-life threatening side-effects can be managed in primary care and outpatient settings by various cadres of health care providers (*7*).

Evidence suggests that the provision of medical abortion by mid-level providers has no impact on the safety or efficacy of the abortion process (*21*). Self-management of medical abortion with mifepristone-misoprostol without the direct supervision of a health care provider is recommended in specific circumstances, in which pregnant persons have the appropriate information and access to health services should they be wanted or required (*5–7*, *22*).

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**Additional evidence** (not in the application)

N/A

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**WHO Guidelines**

***WHO Safe abortion: Technical and policy guidance*** (*6*) was first issued in 2003 and updated in 2012. It includes recommendations for clinical care, while also addressing policy, programmatic and health systems considerations in the provision of safe abortion.

***WHO Clinical practice handbook for safe abortion*** (*8*) was issued in 2014. It provides guidance to providers with requisite skills and training necessary to provide safe abortion and/or treat complications of unsafe abortion.

***WHO Health worker roles in providing safe abortion and post-abortion contraception*** (*7*) was issued in 2015 and contains recommendations on the roles of various health workers in the provision of abortion care, as well as self-management of medical abortion.

***WHO Medical management of abortion*** (*5*) guidelines issued in 2018 includes the following recommendations on medical abortion regimens for management of induced abortion:

For the medical management of induced abortion at less than 12 weeks gestation, the 2018 WHO guidelines recommend the use of 200 mg mifepristone administered orally, followed one to two days later by 800 micrograms misoprostol administered vaginally, sublingually or buccally. The minimum recommended interval between use of mifepristone and misoprostol is 24 hours (strong recommendation, moderate certainty evidence).

For the medical management of induced abortion at ≥ 12 weeks of gestation, the 2018 WHO guidelines suggest the use of 200 mg mifepristone administered orally, followed one to two days later by repeat doses of 400 micrograms misoprostol administered vaginally, sublingually or buccally every three hours. The minimum recommended interval between use of mifepristone and misoprostol is 24 hours (weak, conditional, discretionary or qualified recommendation, moderate certainty evidence).

**Costs/cost-effectiveness**

The price of individual and co-packaged mifepristone and misoprostol varies globally. The legal status of abortion, willing marketers and distributors and a perceived sustainable market all impact the cost to the buyer. Market flexibility is being regulated by the increasing number of new products in markets – both individual and co-packaged products. It is hoped that increasing access to quality co-packaged medicines for medical abortion will drive prices down.

The application stated that when purchased individually, the average cost of mifepristone and misoprostol for one medical abortion ranges from US$ 4.19 to US$ 10.03, while costs for the co-packaged product range from US$ 3.75 to US$ 11.75.

**Availability**

Mifepristone and misoprostol, both individually and co-packaged are available globally.

**Other considerations**

The Committee noted the large number of letters of support received in relation to this application.

**Committee recommendations**

The Expert Committee recommended moving mifepristone-misoprostol from the complementary to the core list of the EML, and removal of the note that states that close medical supervision is required, on the basis of the strong evidence presented that close medical supervision is not required for its safe and effective use.

The Committee also recommended the addition of a co-packaged presentation of mifepristone and misoprostol to the core list of the EML.

Recalling that their role and responsibility is to provide WHO with technical guidance in relation to the selection and use of essential medicines, the Expert Committee noted that its mandate does not extend to providing advice on the statement "Where permitted under national law and where culturally acceptable".

## References


1. Ganatra B, Gerdts C, Rossier C, Johnson BR, Jr., Tuncalp O, Assifi A et al. Global, regional, and subregional classification of abortions by safety, 2010-14: estimates from a Bayesian hierarchical model. Lancet. 2017;390(10110):2372–81.
2. Singh S, Maddow-Zimet I. Facility-based treatment for medical complications resulting from unsafe pregnancy termination in the developing world, 2012: a review of evidence from 26 countries. BJOG. 2016;123(9):1489–98.
3. Say L, Chou D, Gemmill A, Tuncalp O, Moller AB, Daniels J et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2(6):e323–33.
4. The selection and use of essential medicines. Report of the WHO Expert Committee, 2005 (including the 14th Model List of Essential Medicines) (WHO Technical Report Series, No. 933). Geneva: World Health Organization; 2005.
5. Medical management of abortion. Geneva: World Health Organization; 2018. Available from https://apps.who.int/iris/bitstream/handle/10665/278968/9789241550406-eng.pdf?ua=1, accessed 29 September 2019.
6. Safe abortion: technical and policy guidance for health systems. 2nd edition. Geneva, World Health Organization. 2012. Available from: https://apps.who.int/iris/bitstream/handle/10665/70914/9789241548434_eng.pdf?sequence=1, accessed 29 September 2019.
7. Health worker roles in providing safe abortion care and post-abortion contraception. Geneva, World Health Organization. 2015. Available from https://apps.who.int/iris/bitstream/handle/10665/181041/9789241549264_eng.pdf?sequence=1, accessed 29 September 2019.
8. Clinical practice handbook of safe abortion. Geneva, World Health Organization. 2014. Available from https://apps.who.int/iris/bitstream/handle/10665/97415/9789241548717_eng.pdf?sequence=1, accessed 29 September 2019.
9. Sjostrom S, Dragoman M, Fonhus MS, Ganatra B, Gemzell-Danielsson K. Effectiveness, safety, and acceptability of first-trimester medical termination of pregnancy performed by non-doctor providers: a systematic review. BJOG. 2017;124(13):1928–40.
10. Clinical updates in reproductive health. Chapel Hill: Ipas; 2019. Available from https://www.ipas.org/resources/clinical-updates-in-reproductive-health, accessed 29 September 2019.
11. Wildschut H, Both MI, Medema S, Thomee E, Wildhagen MF, Kapp N. Medical methods for mid-trimester termination of pregnancy. Cochrane Database Syst Rev. 2011(1):CD005216.
12. Abubeker FK, Kim CR, Lavelanet A. Medical termination of pregnancy in early first trimester (≤ 63 days): a systematic review. [Evidence synthesis for a WHO guideline]. 2018 (unpublished).
13. Ganatra B. Health worker roles in safe abortion care and post-abortion contraception. Lancet Glob Health. 2015;3(9):e512–3.
14. Glenton C, Sorhaindo AM, Ganatra B, Lewin S. Implementation considerations when expanding health worker roles to include safe abortion care: a five-country case study synthesis. BMC Public Health. 2017;17(1):730.
15. Gupta P, Iyengar SD, Ganatra B, Johnston HB, Iyengar K. Can community health workers play a greater role in increasing access to medical abortion services? A qualitative study. BMC Womens Health. 2017;17(1):37.
16. Barnard S, Kim C, Park MH, Ngo TD. Doctors or mid-level providers for abortion. Cochrane Database Syst Rev. 2015(7):CD011242.

17. Olavarrieta CD, Ganatra B, Sorhaindo A, Karver TS, Seuc A, Villalobos A et al. Nurse versus physician-provision of early medical abortion in Mexico: a randomized controlled non-inferiority trial. Bull World Health Organ. 2015;93(4):249–58.

18. Johnson BR, Jr., Maksutova E, Boobekova A, Davletova A, Kazakbaeva C, Kondrateva Y et al. Provision of medical abortion by midlevel healthcare providers in Kyrgyzstan: testing an intervention to expand safe abortion services to underserved rural and periurban areas. Contraception. 2018;97(2):160–6.

19. Raymond EG, Blanchard K, Blumenthal PD, Cleland K, Foster AM, Gold M et al. Sixteen Years of Overregulation: Time to Unburden Mifeprex. N Engl J Med. 2017;376(8):790–4.

20. Mifeprex product label, revised March 2016. Silver Spring: U.S. Food and Drug Administration; 2016. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf, accessed 29 September 2019.

21. Winikoff B, Sheldon W. Use of medicines changing the face of abortion. Int Perspect Sex Reprod Health. 2012;38(3):164–6.

22. Kapp N, Blanchard K, Coast E, Ganatra B, Harries J, Footman K et al. Developing a forward-looking agenda and methodologies for research of self-use of medical abortion. Contraception. 2018;97(2):184–8.

*Misoprostol – deletion of prevention of PPH indication – EML*

**Misoprostol** **ATC Code: G02AD06**

**Proposal**

The application requested the deletion of misoprostol from the EML for the indication of prevention of postpartum haemorrhage.

**Applicant**

Petra Sevcikova, Allyson Pollock

**WHO Technical Department**

The WHO Department of Reproductive Health and Research provided comments on the application and advised that it did not support the proposal to delete misoprostol from EML for PPH prevention indication.

In December 2018, WHO updated its recommendations on uterotonics based on a Cochrane systematic review and a network meta-analysis (NMA) that included 196 trials (and 135 559 women) (*1*). The updating of these recommendations followed WHO Guidelines Review Committee procedures as well as internationally accepted guideline development methods and standards that included not only the synthesis of evidence of effects of uterotonics but also incorporated evidence regarding values of key stakeholders, resource use, cost effectiveness, equity, acceptability and feasibility.

The technical department stated that the use of NMA for evidence of effects of available uterotonics offered additional advantages over pairwise meta-analyses used in conventional systematic reviews. It allowed a consistent and systematic assessment of eligibility, risk of bias and outcome reporting of all trials of uterotonic agents, including misoprostol. The evidence assessed and synthesized for misoprostol during this update included all eligible studies published as of May 2018. The NMA showed that when used for PPH prevention, misoprostol is associated with a substantial reduction in PPH (≥ 500 ml), severe PPH (≥ 1000 ml), blood transfusion and the use of additional uterotonics when compared with placebo or no uterotonic. It is noteworthy that the evidence of effects of misoprostol versus placebo or no uterotonics on the critical outcomes PPH ≥1000 mL (RR 0.71, 95%CI 0.59 to 0.85) and blood transfusion (RR 0.52, 95%CI 0.35 to 0.80) were of high certainty according to GRADE assessment (i.e. we are very confident that the true effect lies close to that of the estimate of the effect). Based on high certainty evidence of efficacy regarding priority PPH outcomes, which clearly outweighs the side-effects of misoprostol, and considerations of evidence across other important domains of GRADE evidence-to-decision framework, RHR advised that there was no scientific justification for the removal of misoprostol for its PPH indication from the EML.

The WHO 2018 PPH guideline panel reaffirmed the recommendation of misoprostol as an alternative option to oxytocin in settings where injectable uterotonics are not available having fully considered the most up-to-date body of scientific evidence, and implementation and regulatory issues raised in the proposal by Dr Sevcikova and Dr Pollock.

**EML/EMLc**

EML

**Section**

22.3 Uterotonics

**Dose form(s) & strengths(s)**

Tablet 200 micrograms

**Core/Complementary**

Core

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Misoprostol was added to the EML in 2011 for prevention of PPH in settings where parenteral uterotonics are not available or feasible. It was, and remains listed with a conditional note specifying that its use in PPH is limited to circumstances where oxytocin is not available or cannot be safely used.

This was the fourth application from Drs Sevcikova and Pollock requesting deletion of misoprostol from the EML for prevention of PPH. Most recently in 2017, the Expert Committee did not recommend deletion, noting that very few new clinical data were included in the application. The Committee considered that the evidence presented was insufficient to support deletion.

The Expert Committee once again acknowledged that misoprostol is less effective than oxytocin infusion and is associated with adverse events, particularly vomiting and shivering. The circumstances of use have not changed; misoprostol remains an alternative for the prevention of PPH in resource-poor, community and rural settings where intravenous oxytocin is not available or cannot be safely administered (*2*).

**Public health relevance** (burden of disease)

Obstetric haemorrhage, especially PPH, is responsible for more than a quarter of all maternal deaths worldwide (*3*). In most low-income countries, PPH is the leading cause of maternal deaths.

**Summary of evidence: benefits** (from the application)

The same evidence presented in the 2017 application was included in the current application. Only evidence not previously considered by the Committee is presented here.

To update the evidence base presented and considered in previous applications, the current application undertook a literature search for randomized controlled trials (RCTs) assessing misoprostol use in community and home birth settings in low- and middle-income countries (LMICs) published between November 2016 and November 2018. This search identified two systematic reviews (*1*, *4*), one of which was excluded as it included trials conducted in hospitals (*4*). No additional RCTs conducted in low-resource settings were identified.

The application presented results extracted from a sub-group analysis from the Cochrane systematic review by Gallos et al for the comparison of misoprostol versus placebo or no treatment from three trials conducted in the community setting (*5*–*7*).

| Efficacy outcomes | Effect size | Safety | Effect size |
|---|---|---|---|
| Death | RR 1.00 [95%CI 0.10 to 9.59] | Nausea | RR 1.12 [95%CI 0.74 to 1.70] |
| PPH >= 1000 ml | RR 0.59 [95%CI 0.39 to 0.88] | Vomiting | RR 1.27 [95%CI 0.80 to 2.01] |
| Blood transfusion | RR 0.14 [95%CI 0.02 to 1.15] | Headache | RR 0.94 [95%CI 0.32 to 2.77] |
| Severe maternal morbidity: | RR 1.00 [95%CI 0.14 to 7.05] | Shivering | RR 2.71 [95%CI 2.33 to 3.15] |
| PPH >= 500 ml | RR 0.73 [95%CI 0.56 to 0.96] | Fever | RR 2.87 [95%CI 0.90 to 9.18] |
| Additional uterotonics | RR 0.50 [95%CI 0.12 to 1.98] | Diarrhoea | RR 3.11 [95%CI 1.28 to 7.51] |
| Blood loss | MD −43.79 [95%CI −58.09 to −29.49] | | |
| Change in haemoglobin | MD −2.12 [95%CI −3.46 to −0.77] | | |

RR: risk ratio, MD: mean difference

Gallos et al reported no important differences were identified in the sub-group analysis by hospital or community setting (*1*).

Commenting on the quality of available evidence, the application noted that all community studies have important shortcomings either due to small numbers; use of alternative uterotonics in the control arm; confounding due to management practice and subjective assessment; and with one exception (*6*) (in which the numbers were very small), exclusion of high-risk women. PPH incidence fell in both the control and intervention groups in both the trials (*5*, *7*) that informed the 2011 decision to add misoprostol to the EML. This suggests factors other than misoprostol use are crucial in determining outcomes.

**Summary of evidence: harms** (from the application)

No new safety data (beyond that presented above) were included in the current application.

**Additional evidence** (not in the application)

N/A

**WHO Guidelines**

The 2018 WHO recommendations for uterotonics for the prevention of PPH (*8*) recommend use of an effective uterotonic during the third stage of labour for all births. Misoprostol 400 µg or 600 µg, orally is a recommended option for all births.

**Costs/cost-effectiveness**

The 2018 WHO recommendations state that as misoprostol is inexpensive and can also be used by lay health workers in community settings, it is associated with moderate savings and is probably cost-effective, especially when implemented in settings with a shortage of skilled health personnel (*8*).

**Availability**

N/A

**Other considerations**

N/A

**Committee recommendations**

The Committee did not recommend the deletion of the indication for prevention of PPH from the listing of misoprostol from EML. The Committee considered that the new evidence presented in this re-submission was insufficient to support any change to the current listing.

The Committee reiterated that misoprostol remains an effective alternative for prevention of PPH in resource-poor, community and rural

settings where oxytocin is unavailable or cannot be safely administered. The listing of misoprostol on the EML supports its appropriate use in such settings and is consistent with the 2018 WHO recommendations for uterotonics for the prevention of PPH.

## References


1. Gallos ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis. Cochrane Database Syst Rev. 2018;12:CD011689.
2. The selection and use of essential medicines. Report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children) (WHO Technical Report Series, No. 1006). Geneva: World Health Organization; 2017. Available from https://apps.who.int/iris/bitstream/handle/10665/259481/9789241210157-eng.pdf, accessed 30 October 2019.
3. Say L, Chou D, Gemmill A, Tuncalp O, Moller AB, Daniels J et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2(6):e323–33.
4. Abd El Aziz MA, Iraqi A, Abedi P, Jahanfar S. The effect of carbetocin compared to misoprostol in management of the third stage of labor and prevention of postpartum hemorrhage: a systematic review. Syst Rev. 2018;7(1):170.
5. Derman RJ, Kodkany BS, Goudar SS, Geller SE, Naik VA, Bellad MB et al. Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomised controlled trial. Lancet. 2006;368(9543):1248–53.
6. Hoj L, Cardoso P, Nielsen BB, Hvidman L, Nielsen J, Aaby P. Effect of sublingual misoprostol on severe postpartum haemorrhage in a primary health centre in Guinea-Bissau: randomised double blind clinical trial. BMJ. 2005;331(7519):723.
7. Mobeen N, Durocher J, Zuberi N, Jahan N, Blum J, Wasim S et al. Administration of misoprostol by trained traditional birth attendants to prevent postpartum haemorrhage in homebirths in Pakistan: a randomised placebo-controlled trial. BJOG. 2011;118(3):353–61.
8. WHO recommendations: uterotonics for the prevention of postpartum haemorrhage. Geneva: World Health Organization; 2018. Available from https://apps.who.int/iris/bitstream/handle/10665/277276/9789241550420-eng.pdf?ua=1&ua=1, accessed 29 September 2019.

*Tranexamic acid – new indication – EML*

| **Tranexamic acid** | **ATC Code: B02AA02** |
|---|---|

**Proposal**

The application requested inclusion of tranexamic acid (TXA) on the core list of the EML for the new indication of treatment of postpartum haemorrhage.

**Applicants**

WHO Department of Reproductive Health and Research

**WHO Technical Department**

Reproductive Health and Research

**EML/EMLc**

EML

**Section**

22.5 Other medicines administered to the mother

**Dose form(s) & strengths(s)**

Injection: 100 mg/mL

**Core/Complementary**

Core

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Tranexamic acid (TXA) had not previously been considered for inclusion on the EML for the treatment of postpartum haemorrhage.

In 2009, an application requesting EML listing of TXA to reduce blood loss during cardiac surgery was rejected as the indication was considered to be of uncertain public health relevance (*1*).

Tranexamic acid was recommended for inclusion on the EML in 2011 for treatment of adult patients with trauma and significant risk of ongoing haemorrhage (*2*).

**Public health relevance** (burden of disease)

Postpartum haemorrhage (PPH) is defined as blood loss of 500 mL or more within 24 hours after birth. Globally, nearly one quarter of all maternal deaths are associated with PPH, and in most low-income countries, it is the main cause of maternal mortality (*3*). Improving health care for women during childbirth to prevent and treat PPH is a necessary step towards achievement of the health targets of the Sustainable Development Goals.

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**Summary of evidence: benefits** (from the application)

The application presented the findings of a Cochrane systematic review on antifibrinolytic drugs for treating primary PPH (*4*) that included two trials: WOMAN and Ducloy-Bouthors (*5*, *6*), and GRADE tables extracted from the WHO recommendation on tranexamic acid for the treatment of PPH (*7*).

For the comparison of TXA (plus standard care) versus standard care alone, there was moderate certainty evidence that TXA was associated with slightly reduced all cause maternal mortality (RR 0.88, 95%CI 0.74 to 1.05, not statistically significant) and maternal mortality due to PPH (RR 0.81, 95%CI 0.65 to 1.00).

For maternal morbidity outcomes, moderate certainty evidence suggested little or no difference between treatment groups for any outcomes reported (respiratory failure: RR 0.87, 95%CI 0.67 to 1.12; seizure: two studies; RR 0.76, 95%CI 0.49 to 1.20; hepatic failure RR 0.96, 95%CI 0.58 to 1.60; cardiac failure: RR 0.95, 95%CI 0.73 to 1.23; renal failure: two studies; RR 1.09, 95%CI 0.85 to 1.39).

Moderate certainty evidence suggests little or no difference between treatment groups for transfusion of blood products, with more than half of the women in both arms of the WOMAN trial receiving a transfusion (two studies; RR 1.00, 95%CI 0.97 to 1.03).

Ducloy-Bouthors 2011 reported additional blood loss > 500 mL or > 1000 mL. Low quality evidence suggests TXA probably reduces blood loss > 500 mL (RR 0.50, 95%CI 0.27 to 0.93, 151 women). Although the direction of effect was the same for loss > 1000 ml, the study was insufficiently powered to demonstrate a difference between groups (4/77 women versus 8/74).

There was high certainty evidence of no difference between treatment groups in the use of additional uterotonics (99.3% vs 99.1%, two studies; RR 1.00, 95%CI 1.0 to 1.0).

High or moderate certainty evidence suggests there is probably little difference between treatment groups for most surgical interventions to control bleeding (hysterectomy (all): two studies; RR 1.01, 95%CI 0.88 to 1.17; ligature: RR 0.88, 95%CI 0.74 to 1.05; embolization: RR 0.82, 95%CI 0.42 to 1.62). High certainty evidence suggests laparotomy to control bleeding is reduced for women

in the TXA group (0.8% vs 1.3%) (RR 0.64, 95%CI 0.49 to 0.85) while brace sutures are increased (RR 1.19, 95%CI 1.01 to 1.41).

High certainty evidence suggests there is probably little or no difference in intrauterine tamponade (one study; RR 0.96, 95%CI 0.87 to 1.06) or manual removal of placenta: (one study; RR 0.95, 95%CI 0.87 to 1.04).

Sub-group analysis examining treatment effect by mode of birth (vaginal or caesarean) suggests no clear difference in effect on maternal death (all causes) and maternal death due to PPH for type of birth (moderate certainty evidence).

A sub-group analysis of the WOMAN trial investigated the effects of timing of TXA administration. There was a reduced risk of maternal mortality due to bleeding in women given TXA within three hours of delivery (RR 0.69, 95%CI 0.52 to 0.91; p=0.008) compared with women given TXA more than three hours after delivery (RR 1.07, 95%CI 0.76 to 1.51; p=0.70).

Compared to the control group, women who received TXA within one hour of delivery had a similar risk of death (any cause) (RR 0.98, 95%CI 0.72 to 1.33), as did women receiving TXA more than three hours after delivery (RR 1.00, 95%CI 0.75 to 1.33). However, women receiving TXA between one and three hours after delivery were at reduced risk of death from all causes (RR 0.69, 95%CI 0.49 to 0.96). There were similar findings for the composite outcome of death or hysterectomy: within one hour (RR 1.08, 95%CI 0.91 to 1.28), more than three hours (RR 1.01, 95%CI 0.82 to 1.25) and between one and three hours (RR 0.80, 95%CI 0.63 to 1.00).

Compared to the control group, women receiving TXA within one hour of delivery had reduced risk of laparotomy for bleeding (RR 0.48, 95%CI 0.29 to 0.79), as did women receiving TXA at one to three hours after birth (RR 0.54, 95%CI 0.31 to 0.95). Women receiving TXA more than three hours after birth were not at reduced risk of laparotomy for bleeding (RR 0.89, 95%CI 0.59 to 1.35).

In summary, there is evidence that TXA is associated with benefits in reducing maternal deaths due to bleeding and reducing the need for laparotomy to stop bleeding. Treatment within three hours of delivery appears to optimize benefits.

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**Summary of evidence: harms** (from the application)

The application presented the findings of a Cochrane systematic review on antifibrinolytic drugs for treating primary PPH (*4*) which included two trials – WOMAN and Ducloy-Bouthors (*5*, *6*), and GRADE tables extracted from the WHO recommendation on tranexamic acid for the treatment of PPH (*7*).

Moderate certainty evidence suggests there is probably little or no difference between treatment groups for thromboembolic events (any maternal thromboembolic event: RR 0.88, 95%CI 0.54 to 1.43; deep venous thrombosis: two studies; RR 0.62, 95%CI 0.20 to 1.88; pulmonary embolism RR 0.85, 95%CI

0.44 to 1.61; myocardial infarction: RR 0.66, 95%CI 0.11 to 3.97; stroke: RR 1.33, 95%CI 0.46 to 3.82).

Available neonatal outcome data were limited (data from WOMAN trial only). There were no neonatal thromboembolic events and no clear differences in deaths in breastfed neonates (eight deaths with TXA vs seven deaths with placebo) in the WOMAN trial.

Available data on longer-term outcomes was limited (data from the WOMAN trial only). Outcomes in the WOMAN trial were measured up to hospital discharge or 42 days if still in hospital. There was no information on longer-term outcomes in women or babies.

On balance, there does not appear to be evidence of maternal or newborn harms, or significant side-effects. While no difference in newborn thromboembolic events were seen, in the WOMAN trial most women and babies were followed until discharge from the health facility, thus this evidence is more likely representative of the first few days after birth.

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**Additional evidence** (not in the application)

N/A

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**WHO Guidelines**

In 2012, WHO published 32 recommendations for the prevention and treatment of PPH, including a weak recommendation on the use of TXA for treatment of PPH if oxytocin and other uterotonics fail to stop bleeding of if it is thought that bleeding may be partly due to trauma (*8*). In 2017, in response to important new evidence, the existing WHO recommendation on the use of TXA for PPH treatment was updated to recommend early use of intravenous TXA within three hours of birth in addition to standard care for women with clinically diagnosed PPH following vaginal birth or caesarean section (strong recommendation, moderate quality of evidence) (*7*).

In making this updated recommendation, the Guideline Development Group (GDG) also made the following remarks (*7*):

- *"Based on the dosing regimen used in the WOMAN trial, the GDG supports the administration of tranexamic acid (TXA) at a fixed dose of 1 g (100 mg/mL) intravenously (IV) at 1 mL per minute (i.e. administered over 10 minutes), with a second dose of 1 g IV if bleeding continues after 30 minutes, or if bleeding restarts within 24 hours of completing the first dose.*
- *The WOMAN trial defined "clinically diagnosed postpartum haemorrhage" as clinically estimated blood loss of more than 500 mL after a vaginal birth or 1000 mL after caesarean section, or any blood loss sufficient to compromise haemodynamic stability.*

- *Based on evidence from the WOMAN trial, the reference point for the start of the 3-hour window for starting TXA administration is time of birth. If time of birth is unknown, the best estimate of time of birth should be used as the reference point. As most deaths due to PPH occur within the first 2 to 3 hours after birth, it is critical that TXA is given as soon as possible to achieve clinical benefits.*
- *Analysis of the effects of timing of administration in the WOMAN trial, as well as an individual patient data (IPD) meta-analysis of 40 138 bleeding patients (including WOMAN trial participants), indicates that TXA administration beyond 3 hours does not confer any clinical benefit. Furthermore, the point estimates of effect of TXA use beyond 3 hours on death for trauma or after PPH were both in the direction of harm, albeit not statistically significant for women with PPH. In view of this evidence, the GDG does not support the use of TXA more than 3 hours after birth.*
- *Administration of TXA should be considered as part of the standard PPH treatment package. Standard care in the context of this recommendation includes routine care for PPH treatment, including fluid replacement, medical (uterotonics), monitoring of vital signs, nonsurgical (e.g. bimanual compression, intrauterine balloon tamponade, nonpneumatic antishock garment, aortic compression) and surgical interventions (e.t., brace sutures, arterial ligation, or hysterectomy) in accordance with WHO guidelines or adapted local PPH treatment protocols.*
- *TXA should be used in all cases of PPH, regardless of whether the bleeding is due to genital tract trauma or other causes.*
- *The use of TXA should be avoided in women with a clear contraindication to antifibrinolytic therapy (including TXA) (e.g. a known thromboembolic event during pregnancy).*
- *This recommendation applies only to IV use. The evaluation of benefits and potential harms of other routes of TXA administration is a research priority.*
- *Regardless of the level of health system resources, TXA should be recognized as a life-saving intervention and be made readily available for the management of PPH in settings where emergency obstetric care is provided."*

**Costs/cost-effectiveness:**

Research evidence on cost-effectiveness of TXA can be extrapolated from cost-effectiveness analysis of TXA for bleeding trauma patients (*9*). The study found

that administering TXA to bleeding trauma patients within three hours of injury saved an estimated 372, 315 and 755 life-years (LYs) per 1000 trauma patients in Tanzania, India and the United Kingdom respectively. The cost of giving TXA to 1000 patients was US$ 17 483 in Tanzania, US$ 19 550 in India and US$ 30 830 in the UK. The incremental cost of giving TXA versus not giving TXA was US$ 18 025 in Tanzania, US$ 20 670 in India and US$ 48 002 in the United Kingdom. The estimated incremental cost per LY gained of administering TXA is US$ 48, US$ 66 and US$ 64 in Tanzania, India and the United Kingdom respectively. Early administration of TXA to bleeding trauma patients is likely to be highly cost effective in low-, middle- and high-income settings. The cost of TXA varied between settings, with an approximated range of US$ 1.00 to US$ 5.70 per gram.

The use of TXA may also reduce subsequent costs related to surgical procedures for PPH treatment (such as laparotomy) as well as any complications associated with surgery.

Out-of-pocket costs to individual women might be higher when TXA is added to standard care for PPH in settings where women incur financial costs for birth.

**Availability**

Tranexamic acid 100 mg/mL injection is available from multiple generic manufacturers.

**Other considerations**

N/A

**Committee recommendations**

The Committee recommended listing of tranexamic acid (TXA) intravenous injection on the core list of the EML for the new indication of treatment of postpartum haemorrhage.

While the evidence presented in the application supporting the effectiveness of TXA for this indication was limited and came primarily from a single trial, the Committee considered there was benefit associated with the use of TXA in addition to standard care, when administered within three hours of childbirth. The Committee also considered that the use of different medicines with different pharmacological mechanisms of action may be useful in the management of PPH.

The Committee noted that there did not appear to be significant harms or adverse events associated with use of TXA in mothers or newborns, but that evidence was limited. The committee considered that further evidence of safety would be desirable.

## References


1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2009 (including the 16th WHO Model List of Essential Medicines and the 2nd WHO Model List of Essential Medicines for Children) (WHO Technical Report Series, No. 958). Geneva: World Health Organization; 2009. Available from https://apps.who.int/iris/bitstream/handle/10665/44287/WHO_TRS_958_eng.pdf, accessed 30 October 2019.
2. The selection and use of essential medicines. Report of the WHO Expert Committee, 2011 (including the 17th WHO Model List of Essential Medicines and the 3rd WHO Model List of Essential Medicines for Children) (WHO Technical Report Series, No. 965). Geneva: World Health Organization; 2012. Available from https://apps.who.int/iris/bitstream/handle/10665/44771/WHO_TRS_965_eng.pdf, accessed 30 October 2019.
3. Say L, Chou D, Gemmill A, Tuncalp O, Moller AB, Daniels J et al. Global causes of maternal death: a WHO systematic analysis. ancet Globl Health. 2014;2(6):e323–33.
4. Shakur H, Beaumont D, Pavord S, Gayet-Ageron A, Ker K, Mousa HA. Antifibrinolytic drugs for treating primary postpartum haemorrhage. Cochrane Database Syst Rev. 2018;2:CD012964.
5. WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet. 2017;389(10084): 2105–16.
6. Ducloy-Bouthors AS, Jude B, Duhamel A, Broisin F, Huissoud C, Keita-Meyer H et al. High-dose tranexamic acid reduces blood loss in postpartum haemorrhage. Crit Care. 2011;15(2):R117.
7. WHO recommendation on tranexamic acid for the treatment of postpartum haemorrhage. Geneva: World Health Organization; 2017. Available from https://www.who.int/reproductive health/publications/tranexamic-acid-pph-treatment/en/, accessed 30 October 2019.
8. WHO recommendations for the prevention and treatment of postpartum haemorrhage. Geneva: World Health Organization; 2012. Available from https://www.who.int/reproductivehealth/publications/maternal_perinatal_health/9789241548502/en/, accessed 30 October 2019.
9. Guerriero C, Cairns J, Perel P, Shakur H, Roberts I. Cost-effectiveness analysis of administering tranexamic acid to bleeding trauma patients using evidence from the CRASH-2 trial. PLoS One. 2011;6(5):e18987.

## Section 24: MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS

*Methylphenidate – addition – EML and EMLc*

**Methylphenidate** **ATC Code: N06BA04**

**Proposal**

The application requested the inclusion of methylphenidate on the complementary list of the EML and EMLc for the treatment of attention-deficit hyperactivity disorder (ADHD).

**Applicant**

Patricia Moscibrodzki and Craig L Katz

**WHO Technical Department**

Mental Health and Substance Abuse

**EML/EMLc**

EML and EMLc

**Section**

24 Medicines used in behavioural disorders

**Dose form(s) & strengths(s)**

Tablet (immediate-release): 10 mg, 20 mg

**Core/Complementary**

Complementary

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Methylphenidate had not previously been considered for inclusion on the Model List.

**Public health relevance** (burden of disease)

The mental disorders that methylphenidate is approved to treat have a high global disease burden. In 2010, mental neurological and substance use disorders accounted for 10.4% of global disability-adjusted life years (DALYs) and 28.5% of years of life lost due to disability, illness, or premature death (YLDs), making

them the leading cause of YLDs (*1*). The *Global Burden of Disease Study 2010* (GBD 2010) is the first to include conduct disorder (CD) and attention-deficit hyperactivity disorder (ADHD) for burden quantification (*2*). Globally, CD was responsible for 5.75 million YLDs/DALYs with ADHD responsible for a further 491 500 (*3*). Collectively, CD and ADHD accounted for 0.80% of total global YLDs and 0.25% of total global DALYs (*3*).

The prevalence of ADHD is a controversial issue with varying estimates across populations, using different diagnostic criteria and reporting. A 2015 systematic review and meta-analysis of 175 studies reporting point prevalence estimates of ADHD estimated the pooled prevalence to be 7.2% (95%CI 6.7% to 7.8%) (*4*).

A 2007 systematic review and meta-regression analysis of 102 studies (171 756 subjects) investigating the prevalence rates of ADHD/HD worldwide found large variability of ADHD/HD prevalence rates worldwide resulting mainly from methodological differences across studies. When adjusted for methodological differences, prevalence rate variability was only detected between studies conducted in North America and those conducted in Africa and the Middle East (*5*).

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**Summary of evidence: benefits** (from the application)

A literature review undertaken by the applicants included 28 studies and review articles as evidence for the comparative effectiveness of methylphenidate for the treatment of ADHD versus placebo or other stimulants (*6–15*), versus second-line non-stimulant therapies (*16–25*), and in patients with ADHD comorbid with other conditions (*26–31*) in children, adolescents and adults. The large majority of the trials and reviews were conducted in children and adolescents and were of short duration (three months). Summaries of the findings of the included trials were presented.

Based on this review, the applicants concluded that in the treatment of ADHD, methylphenidate has shown similar efficacy to amphetamine-based drugs with varying results on different psychometric scales. Some individual studies have demonstrated superiority of methylphenidate over amphetamine-based medicines, some have found superiority of amphetamine-based medicines over methylphenidate, and others have shown no difference between the two treatments. Given the currently available evidence, it has not been demonstrated that one stimulant is more efficacious than any other at a population level. In the comparison of methylphenidate with non-stimulant medications for treatment of ADHD, non-stimulant medications appear to have a lower efficacy though some studies show equivalent efficacy with atomoxetine. The application stated that methylphenidate is effective in reducing fatigue in palliative care patients when compared to placebo and that there is also evidence of methylphenidate

being effective in reducing symptoms in patients with ADHD comorbid with oppositional defiant disorder and aggression. No assessment was made in the application regarding the quality of the evidence or confidence in the estimates of benefit.

**Summary of evidence: harms** (from the application)

A literature review undertaken by the applicants included 29 studies and review articles as evidence for the comparative safety of methylphenidate for the treatment of ADHD versus placebo (*6*, *32–34*), versus other stimulants and non-stimulants (*9*, *11*, *12*, *14*, *16–19*, *21*, *35–38*), and in patients with ADHD comorbid with other conditions (*26*, *27*, *30*, *39–43*). The large majority of the trials and reviews were conducted in children and adolescents and were of short duration. Summaries of the findings of the included trials were presented.

Based on this review, the applicants concluded that there is considerable overlap in the adverse event profiles of methylphenidate- and amphetamine-based ADHD medications. Both have been associated with insomnia and appetite suppression as the most common adverse events. Overall, studies suggest that the frequency and severity of adverse events may be somewhat greater with amphetamine-based products. In comparison to other non-stimulant medications, methylphenidate was associated with less sleeping problems and higher tolerability. No assessment was made in the application regarding the quality of the evidence or confidence in the estimates of harm.

As methylphenidate is a controlled Schedule II substance under the 1971 *Convention on Psychotropic Substances*, the application addressed the issue of potential misuse. Methylphenidate-specific misuse data generally mimic results of studies looking at stimulant medication misuse in general. While there are limited data on malingering specifically for methylphenidate, studies of malingering for stimulants in general are likely generally applicable (*44*). Overall, the misuse of methylphenidate raises legitimate safety concerns for overdose and drug interactions with other medications or nonmedical use drugs, particularly since illicit users are generally unaware of these issues and often use methylphenidate with other recreational drugs. However, studies suggest that amphetamine-based drugs are being used more often than methylphenidate for non-medical use, particularly in immediate-release formulations (*45–48*).

**Additional evidence** (not in the application)

A 2014 Cochrane systematic review of immediate-release methylphenidate for treatment of adults with ADHD was withdrawn in 2016 following failure by the authors to satisfactorily address a number of criticisms of the methodology used and conclusions drawn (*49*, *50*). A commentary on the withdrawn review summarized the criticisms, which primarily focussed on the methodological flaws

and "misleading conclusions that gave a false sense of certainty of the benefits and the absence of harms, when this in fact could not be concluded" (*51*).

### WHO Guidelines

The 2016 *WHO mhGAP intervention guide for mental, neurological and substance use disorders in non-specialized health settings* (version 2.0) includes a recommendation to refer children (aged 6 years and above with a diagnosis of ADHD in whom other treatment approaches have failed) to a specialist for methylphenidate treatment (*52*).

### Costs/cost-effectiveness

The median buyer price of immediate release methylphenidate 10 mg, according to the *International Medical Products Price Guide* is US$ 0.067 per tablet/capsule (*53*).

A literature review undertaken by the applicants included 11 articles as evidence for the comparative cost-effectiveness of methylphenidate (*54–65*). Summaries of economic evaluations of methylphenidate for ADHD were presented, and the application concluded that the identified literature favoured methylphenidate as cost-effective or cost-neutral relative to stimulant and non-stimulant treatments.

The Committee considered that while methylphenidate appeared to be low cost and affordable, no conclusions could be drawn regarding the cost-effectiveness of the medicine given the considerable uncertainty in the estimates of benefit and harms.

### Availability

Methylphenidate immediate release tablets are available internationally in innovator and generic brands.

### Other considerations

Public comments on the application were received from Professor Ole Jakob Storebø and Dr Christian Gluud, authors of a 2015 Cochrane systematic review of methylphenidate use in children and adolescents (*6*) included in the application. They expressed concern in relation to limitations in the reporting and summary of the evidence in the application, with particular regard to the quality of the evidence, duration of trials, misplacement of evidence, and suspected selective biases. They stated that their assessment of the evidence supporting methylphenidate for ADHD (and other disorders) was more critical than that of the applicants, noting that the high risk of bias in the randomized trials likely overestimates positive intervention effects and underestimates risk of harms.

### Committee recommendations

The Committee did not recommend the addition of methylphenidate to the complementary list of the EML and EMLc for the treatment of attention-deficit hyperactivity disorder (ADHD) due to concerns regarding the quality and interpretation of the evidence for benefits and harms.

## References


1. Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet. 2013;382(9904):1575–86.
2. Erskine HE, Ferrari AJ, Nelson P, Polanczyk GV, Flaxman AD, Vos T et al. Epidemiological modelling of attention-deficit/hyperactivity disorder and conduct disorder for the Global Burden of Disease Study 2010. J Child Psychol Psychiatry. 2013;54(12):1263–74.
3. Erskine HE, Ferrari AJ, Polanczyk GV, Moffitt TE, Murray CJ, Vos T et al. The global burden of conduct disorder and attention-deficit/hyperactivity disorder in 2010. J Child Psychol Psychiatry. 2014;55(4):328–36.
4. Thomas R, Sanders S, Doust J, Beller E, Glasziou P. Prevalence of attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. Pediatrics. 2015;135(4):e994–1001.
5. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry. 2007;164(6):942–8.
6. Storebo OJ, Ramstad E, Krogh HB, Nilausen TD, Skoog M, Holmskov M et al. Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD). Cochrane Database Syst Rev. 2015(11):CD009885.
7. Bental B, Tirosh E. The effects of methylphenidate on word decoding accuracy in boys with attention-deficit/hyperactivity disorder. J Clin Psychopharmacol. 2008;28(1):89–92.
8. Flintoff MM, Barron RW, Swanson JM, Ledlow A, Kinsbourne M. Methylphenidate increases selectivity of visual scanning in children referred for hyperactivity. J Abnorm Child Psychol. 1982;10(2):145–61.
9. Arnold LE, Christopher J, Huestis R, Smeltzer DJ. Methylphenidate vs dextroamphetamine vs caffeine in minimal brain dysfunction: controlled comparison by placebo washout design with Bayes' analysis. Arch Gen Psychiatry. 1978;35(4):463–73.
10. Weiss G, Minde K, Douglas V, Werry J, Sykes D. Comparison of the effects of chlorpromazine, dextroamphetamine and methylphenidate on the behaviour and intellectual functioning of hyperactive children. Can Med Assoc J. 1971;104(1):20–5.
11. Luan R, Mu Z, Yue F, He S. Efficacy and Tolerability of Different Interventions in Children and Adolescents with Attention Deficit Hyperactivity Disorder. Front Psychiatry. 2017;8:229.
12. Li Y, Gao J, He S, Zhang Y, Wang Q. An Evaluation on the Efficacy and Safety of Treatments for Attention Deficit Hyperactivity Disorder in Children and Adolescents: a Comparison of Multiple Treatments. Mol Neurobiology. 2017;54(9):6655–69.
13. Hanwella R, Senanayake M, de Silva V. Comparative efficacy and acceptability of methylphenidate and atomoxetine in treatment of attention deficit hyperactivity disorder in children and adolescents: a meta-analysis. BMC Psychiatry. 2011;11:176.

14. Wang Y, Zheng Y, Du Y, Song DH, Shin YJ, Cho SC et al. Atomoxetine versus methylphenidate in paediatric outpatients with attention deficit hyperactivity disorder: a randomized, double-blind comparison trial. Aust N Z J Psychiatry. 2007;41(3):222–30.

15. Pelham WE, Gnagy EM, Chronis AM, Burrows-MacLean L, Fabiano GA, Onyango AN et al. A comparison of morning-only and morning/late afternoon Adderall to morning-only, twice-daily, and three times-daily methylphenidate in children with attention-deficit/hyperactivity disorder. Pediatrics. 1999;104(6):1300–11.

16. Padilha S, Virtuoso S, Tonin FS, Borba HHL, Pontarolo R. Efficacy and safety of drugs for attention deficit hyperactivity disorder in children and adolescents: a network meta-analysis. Eur Child Adolesc Psychiatry. 2018;27(10):1335–45.

17. Davari-Ashtiani R, Shahrbabaki ME, Razjouyan K, Amini H, Mazhabdar H. Buspirone versus methylphenidate in the treatment of attention deficit hyperactivity disorder: a double-blind and randomized trial. Child Psychiatry Hum Dev. 2010;41(6):641–8.

18. Salehi B, Imani R, Mohammadi MR, Fallah J, Mohammadi M, Ghanizadeh A et al. Ginkgo biloba for attention-deficit/hyperactivity disorder in children and adolescents: a double blind, randomized controlled trial. Prog Neuropsychopharmacol Biol Psychiatry. 2010;34(1):76–80.

19. Arabgol F, Panaghi L, Hebrani P. Reboxetine versus methylphenidate in treatment of children and adolescents with attention deficit-hyperactivity disorder. Eur Child Adolesc Psychiatry. 2009;18(1):53–9.

20. Mohammadi MR, Ghanizadeh A, Alaghband-Rad J, Tehranidoost M, Mesgarpour B, Soori H. Selegiline in comparison with methylphenidate in attention deficit hyperactivity disorder children and adolescents in a double-blind, randomized clinical trial. J Child Adolesc Psychopharmacol. 2004;14(3):418–25.

21. Buitelaar JK, van der Gaag RJ, Swaab-Barneveld H, Kuiper M. Pindolol and methylphenidate in children with attention-deficit hyperactivity disorder. Clinical efficacy and side-effects. J Child Psychol Psychiatry. 1996;37(5):587–95.

22. Conners CK, Taylor E. Pemoline, methylphenidate, and placebo in children with minimal brain dysfunction. Arch Gen Psychiatry. 1980;37(8):922–30.

23. Rapoport JL, Quinn PO, Bradbard G, Riddle KD, Brooks E. Imipramine and methylphenidate treatments of hyperactive boys. A double-blind comparison. Arch Gen Psychiatry. 1974;30(6): 789–93.

24. Peterson K, McDonagh MS, Fu R. Comparative benefits and harms of competing medications for adults with attention-deficit hyperactivity disorder: a systematic review and indirect comparison meta-analysis. Psychopharmacol. 2008;197(1):1–11.

25. Barnes JJ, O'Connell RG, Nandam LS, Dean AJ, Bellgrove MA. Monoaminergic modulation of behavioural and electrophysiological indices of error processing. Psychopharmacol. 2014;231(2):379–92.

26. Osland ST, Steeves TD, Pringsheim T. Pharmacological treatment for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders. Cochrane Database Syst Rev.. 2018;6:CD007990.

27. Correia Filho AG, Bodanese R, Silva TL, Alvares JP, Aman M, Rohde LA. Comparison of risperidone and methylphenidate for reducing ADHD symptoms in children and adolescents with moderate mental retardation. J Am Acad Child Adolesc Psychiatry. 2005;44(8):748–55.

28. Sturman N, Deckx L, van Driel ML. Methylphenidate for children and adolescents with autism spectrum disorder. Cochrane Database Syst Rev.. 2017;11:CD011144.

29. Golubchik P, Weizman A. The effect of methylphenidate treatment on suspiciousness in children with ADHD alone or comorbid with ODD. Int J Psychiatry Clin Pract. 2018;22(2):109–14.

30. Masi G, Manfredi A, Nieri G, Muratori P, Pfanner C, Milone A. A Naturalistic Comparison of Methylphenidate and Risperidone Monotherapy in Drug-Naive Youth With Attention-Deficit/Hyperactivity Disorder Comorbid With Oppositional Defiant Disorder and Aggression. J Clin Psychopharmacol. 2017;37(5):590–4.

31. Ruthirakuhan MT, Herrmann N, Abraham EH, Chan S, Lanctot KL. Pharmacological interventions for apathy in Alzheimer's disease. Cochrane Database Syst Rev.. 2018;5:CD012197.

32. Storebo OJ, Pedersen N, Ramstad E, Kielsholm ML, Nielsen SS, Krogh HB et al. Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents - assessment of adverse events in non-randomised studies. Cochrane Database Syst Rev. 2018;5:CD012069.

33. Pottegard A, Hallas J, Andersen JT, Lokkegaard EC, Dideriksen D, Aagaard L et al. First-trimester exposure to methylphenidate: a population-based cohort study. J Clin Psychiatry. 2014;75(1):e88–93.

34. Sobanski E, Schredl M, Kettler N, Alm B. Sleep in adults with attention deficit hyperactivity disorder (ADHD) before and during treatment with methylphenidate: a controlled polysomnographic study. Sleep. 2008;31(3):375–81.

35. Joseph A, Ayyagari R, Xie M, Cai S, Xie J, Huss M et al. Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison. Eur Child Adolesc Psychiatry. 2017;26(8):875–97.

36. Hennissen L, Bakker MJ, Banaschewski T, Carucci S, Coghill D, Danckaerts M et al. Cardiovascular Effects of Stimulant and Non-Stimulant Medication for Children and Adolescents with ADHD: A Systematic Review and Meta-Analysis of Trials of Methylphenidate, Amphetamines and Atomoxetine. CNS drugs. 2017;31(3):199–215.

37. Safer DJ. Relative cardiovascular safety of psychostimulants used to treat attention-deficit hyperactivity disorder. J Child Adolesc Psychopharmacol. 1992;2(4):279–90.

38. Liang EF, Lim SZ, Tam WW, Ho CS, Zhang MW, McIntyre RS et al. The Effect of Methylphenidate and Atomoxetine on Heart Rate and Systolic Blood Pressure in Young People and Adults with Attention-Deficit Hyperactivity Disorder (ADHD): Systematic Review, Meta-Analysis, and Meta-Regression. Int J Environ Res Public Health. 2018;15(8).

39. Jasper BW, Conklin HM, Lawford J, Morris EB, Howard SC, Wu S et al. Growth effects of methylphenidate among childhood cancer survivors: a 12-month case-matched open-label study. Pediatr Blood Cancer. 2009;52(1):39–43.

40. Wang LJ, Shyu YC, Yuan SS, Yang CJ, Yang KC, Lee TL et al. Attention-deficit hyperactivity disorder, its pharmacotherapy, and the risk of developing bipolar disorder: A nationwide population-based study in Taiwan. J Psychiatr Res. 2016;72:6–14.

41. Mannuzza S, Klein RG, Truong NL, Moulton JL, 3rd, Roizen ER, Howell KH et al. Age of methylphenidate treatment initiation in children with ADHD and later substance abuse: prospective follow-up into adulthood. Am J Psychiatry. 2008;165(5):604–9.

42. Steinhausen HC, Bisgaard C. Substance use disorders in association with attention-deficit/hyperactivity disorder, co-morbid mental disorders, and medication in a nationwide sample. Eur Neuropsychopharmacol. 2014;24(2):232–41.

43. Bushe CJ, Savill NC. Suicide related events and attention deficit hyperactivity disorder treatments in children and adolescents: a meta-analysis of atomoxetine and methylphenidate comparator clinical trials. Child Adolesc Psychiatry Ment Health. 2013;7:19.

44. Clemow DB. Misuse of Methylphenidate. In: Nielsen S, Bruno R, Schenk S, editors. Non-medical and illicit use of psychoactive drugs Current Topics in Behavioral Neurosciences. 34. Cham: Springer; 2015.
45. Mao AR, Babcock T, Brams M. ADHD in adults: current treatment trends with consideration of abuse potential of medications. J Psychiatr Pract. 2011;17(4):241–50.
46. Teter CJ, McCabe SE, LaGrange K, Cranford JA, Boyd CJ. Illicit use of specific prescription stimulants among college students: prevalence, motives, and routes of administration. Pharmacotherapy. 2006;26(10):1501–10.
47. Harstad E, Levy S. Attention-deficit/hyperactivity disorder and substance abuse. Pediatrics. 2014;134(1):e293–301.
48. Berman SM, Kuczenski R, McCracken JT, London ED. Potential adverse effects of amphetamine treatment on brain and behavior: a review. Mol Psychiatry. 2009;14(2):123–42.
49. Epstein T, Patsopoulos NA, Weiser M. Immediate-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults. Cochrane Database Syst Rev. 2014(9):CD005041.
50. Epstein T, Patsopoulos NA, Weiser M. WITHDRAWN: Immediate-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults. Cochrane Database Syst Rev. 2016(5):CD005041.
51. Boesen K, Saiz LC, Erviti J, Storebo OJ, Gluud C, Gotzsche PC et al. The Cochrane Collaboration withdraws a review on methylphenidate for adults with attention deficit hyperactivity disorder. Evid Based Med. 2017;22(4):143–7.
52. mhGAP intervention guide for mental, neurological and substance use disorders in non-specialized health settings (Version 2.0). Geneva: World Health Organization; 2016. Available from https://apps.who.int/iris/bitstream/handle/10665/250239/9789241549790-eng.pdf?sequence=1, accessed 29 September 2019.
53. International Medical Products Price Guide. Arlington: Management Sciences for Health; 2015. Available from http://mshpriceguide.org/en/single-drug-information/?DMFId=928&searchYear=2015, accessed 29 September 2019.
54. Maia CR, Stella SF, Wagner F, Pianca TG, Krieger FV, Cruz LN et al. Cost-utility analysis of methylphenidate treatment for children and adolescents with ADHD in Brazil. Revista brasileira de psiquiatria (Sao Paulo, Brazil : 1999). 2016;38(1):30–8.
55. Catala-Lopez F, Ridao M, Sanfelix-Gimeno G, Peiro S. Cost-effectiveness of pharmacological treatment of attention deficit hyperactivity disorder in children and adolescents: qualitative synthesis of scientific evidence. Revista de psiquiatria y salud mental. 2013;6(4):168–77.
56. Wu EQ, Hodgkins P, Ben-Hamadi R, Setyawan J, Xie J, Sikirica V et al. Cost effectiveness of pharmacotherapies for attention-deficit hyperactivity disorder: a systematic literature review. CNS drugs. 2012;26(7):581–600.
57. Miller A, Lee S, Raina P, Klassen A, Zupancic J, Olsen L. A review of therapies for attention-deficit/hyperactivity disorder. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 1998. Available from https://www.cadth.ca/review-therapies-attention-deficithyperactivity-disorder-0, accessed 29 September 2019.
58. Marchetti A, Magar R, Lau H, Murphy EL, Jensen PS, Conners CK et al. Pharmacotherapies for attention-deficit/hyperactivity disorder: expected-cost analysis. Clinical Ther. 2001;23(11): 1904–21.
59. Cottrell S, Tilden D, Robinson P, Bae J, Arellano J, Edgell E et al. A modeled economic evaluation comparing atomoxetine with stimulant therapy in the treatment of children with attention-deficit/hyperactivity disorder in the United Kingdom. Value Health. 2008;11(3):376–88.

60. King S, Griffin S, Hodges Z, Weatherly H, Asseburg C, Richardson G et al. A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents. Health Technol Assess. 2006;10(23):iii-iv, xiii–146.

61. Jensen PS, Garcia JA, Glied S, Crowe M, Foster M, Schlander M et al. Cost-effectiveness of ADHD treatments: findings from the multimodal treatment study of children with ADHD. Am J Psychiatry. 2005;162(9):1628-36.

62. Matza LS, Paramore C, Prasad M. A review of the economic burden of ADHD. Cost Eff Resour Alloc. 2005;3:5.

63. Narayan S, Hay J. Cost effectiveness of methylphenidate versus AMP/DEX mixed salts for the first-line treatment of ADHD. Expert Rev Pharmacoecon Outcomes Res. 2004;4(6):625–34.

64. Donnelly M, Haby MM, Carter R, Andrews G, Vos T. Cost-effectiveness of dexamphetamine and methylphenidate for the treatment of childhood attention deficit hyperactivity disorder. Aust N Z J Psychiatry. 2004;38(8):592–601.

65. Gilmore A, Milne R. Methylphenidate in children with hyperactivity: review and cost-utility analysis. Pharmacoepidemiology Drug Saf. 2001;10(2):85–94.

## 24.2 Medicines used in mood disorders

### 24.2.1 Medicines used in depressive disorders

*Escitalopram – addition – EML*

*Fluoxetine – addition of square box – EML*

| Selective serotonin reuptake inhibitors | |
|---|---|
| Escitalopram | ATC Code: N06AB10 |
| Fluoxetine | ATC Code: N06AB03 |

**Proposal**

Two applications regarding the listing of selective serotonin reuptake inhibitors (SSRIs) were received:

Application 1: requested the inclusion of escitalopram on the core list of the EML for the treatment of adults with major depressive disorder.

Application 2: requested the addition of a square box symbol to the current listing of fluoxetine on the core list of the EML for treatment of depressive disorders.

**Applicant**

Application 1: Dr Iona Machado, Dr Csilla Lippert, Dr Ricardo Lozano, Dr Michael J Ostacher

Application 2: Kavitha Kolappa, Corrado Barbui

**WHO Technical Department**

Mental Health and Substance Abuse

**EML/EMLc**

EML

**Section**

24.2.1 Medicines used in depressive disorders

**Dose form(s) & strengths(s)**

Application 1: Escitalopram: Tablet 10 mg
Application 2: Fluoxetine: Solid oral dosage form 20 mg

**Core/Complementary**

Core

**Individual/Square box listing**

Application 1: Individual
Application 2: Square box to include citalopram, escitalopram and sertraline.

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**Background** (if relevant, eg. resubmission, previous EC consideration)

Fluoxetine was added to the core list of the EML in 2007. The Committee considered that the available evidence supported the public health need, comparable effectiveness and generally more favourable tolerability of fluoxetine compared to amitriptyline. A square box was not recommended as the Committee felt there may be significant within-class differences among SSRIs in relation to safety (*1*).

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**Public health relevance** (burden of disease)

The public health relevance of depressive disorders is well established and has been previously accepted by the Committee. However, the global burden of disease due to depressive disorders is increasing over time. In 2017, depressive disorders were estimated to affect over 260 million people globally, including 160 million with major depressive disorder. According to the *Global Burden of Disease Study 2017*, depressive disorders were responsible for over 43 million disability-adjusted life years (DALYs) annually, accounting for 1.7% of total estimated DALYs due to any disease. Depressive disorders were also responsible for over 43 million years lived with disability (YLD), accounting for 5.0% of the total YLD globally (*2*).

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**Summary of evidence: benefits** (from the application)

Both applications presented the findings of a 2018 systematic review and network meta-analysis (NMA) of 522 randomized controlled trials (RCTs) involving 117 477 participants, which evaluated the comparative efficacy and tolerability of 21 antidepressant medicines compared to each other and to placebo for the treatment of depression in adults (*3*).

Compared to placebo, all SSRIs were associated with statistically significantly greater response rates. The greatest response rate seen was for paroxetine (odds ratio (OR) 1.75, 95%CI 1.61 to 1.90). With regard to acceptability, as measured by dropout rates, all SSRIs except for fluvoxamine showed an advantage over placebo, however this was only statistically significant for fluoxetine (OR 0.88, 95%CI 0.80 to 0.96).

In comparisons between SSRIs, there was moderate level GRADE evidence of statically significant superior efficacy of escitalopram compared to citalopram, fluoxetine, and fluvoxamine, and of paroxetine compared to fluoxetine. Other comparisons were not statistically significant.

The findings of a 2009 Cochrane systematic review of 22 RCTs comparing escitalopram to other antidepressants were largely consistent with

the 2018 NMA (*4*). In six studies (1823 participants) that compared response rates between escitalopram and citalopram, there was a statistically significant difference in favour of escitalopram (OR 0.67, 95%CI 0.50 to 0.89, p=0.006), also found in remission rates (OR 0.57, 95%CI 0.36 to 0.90, p=0.02). Three studies (783 participants) that directly compared escitalopram and fluoxetine did not find a statistically significant difference in response or remission rates but did find escitalopram to be more efficacious than fluoxetine in reduction of depressive symptoms from baseline (SMD −0.17, 95%CI −0.32 to −0.03, p=0.02) Two studies (784 participants) that compared escitalopram to paroxetine, and two studies (489 participants) that compared escitalopram to sertraline, did not find any statistically significant differences for any of the above parameters.

**Summary of evidence: harms** (from the application)

In the above-mentioned Cochrane review, 14 RCTs compared escitalopram to another SSRI (*4*). Escitalopram did not have significantly different rates of mild to severe adverse events than citalopram (n = 1802 in six RCTs), fluoxetine (n = 804 in four RCTs), or paroxetine (n = 784 in two RCTs). Also, there was no significant difference in serious adverse events for escitalopram compared to sertraline (n = 483 in 2 RCTs); however, escitalopram had a decreased incidence of diarrhoea. Overall, escitalopram and other SSRIs had similar rates of agitation, anxiety, constipation, diarrhoea, dry mouth, hypotension, insomnia, nausea, urinary complaints, drowsiness, vomiting, deaths, suicide, suicidality and other adverse events.

With respect to acceptability as measured by dropout rates, in the above-mentioned NMA, escitalopram was associated with moderate level GRADE evidence of superiority compared to fluvoxamine. There were no other statistically significant differences between SSRIs with regard to acceptability (*3*).

A 2006 meta-analysis using patient-level data from published and unpublished clinical trials based on mandatory reporting by pharmaceutical companies assessed the risk of suicidality (ideation or worse) amongst antidepressants (*5*, *6*). Half of the treatment indications were related to depression, with the remaining 50% for other psychiatric or non-psychiatric indications. Among SSRI, considering only data for adults with psychiatric diagnoses, suicidality risk was found to be lowest for sertraline and fluoxetine (low quality evidence). Suicidality risk was greatest for citalopram and escitalopram although the differences did not reach statistical significance (very low-quality evidence).

A 2014 meta-analysis examined the association between SSRI antidepressants and QTc (corrected QT) prolongation (*7*). Citalopram and escitalopram were associated with the greatest amount of QTc prolongation, while sertraline was associated with the least. Fluvoxamine was associated

with shortened QTc. Results for fluoxetine and paroxetine were not statistically significant.

With regard to sexual dysfunction, escitalopram and paroxetine have been associated with a higher risk of sexual dysfunction than fluoxetine. Pairwise comparisons of other SSRIs have not shown statistically significant differences (*8*).

The pharmacokinetic properties of individual SSRIs differ considerably. Considering potential for drug–drug interactions, many SSRIs are inhibitors of cytochrome P450 enzymes and may interact with other drugs that are metabolized by these enzymes. Fluoxetine and paroxetine are potent inhibitors of CYP2D6, fluvoxamine is a potent inhibitor of CYP1A2. Fluoxetine and fluvoxamine are also moderate inhibitors of CYP2C19. Citalopram, escitalopram and sertraline are considered to have the lowest potential for CYP enzyme-mediated interactions (*9*).

Fluoxetine has a half-life of one to four days and an active metabolite (norfluoxetine) with a half-life of seven to fifteen days. The half-lives of the other SSRIs are considerably shorter. Therefore, fluoxetine will take longer to reach steady-state concentrations and will remain in the body for longer following discontinuation of therapy. As a result, adverse reactions and drug-interactions with fluoxetine may persist for some time following cessation of treatment (*10*). Paroxetine has the shortest half-life among the SSRIs (one day) and has been found to have a higher potential for withdrawal symptoms following discontinuation (*11*).

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**Additional evidence** (not in the application)

N/A

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**WHO Guidelines**

The WHO Mental Health Gap Action Programme (mhGAP) Guidelines make the following recommendations in relation to antidepressants for treatment of adults with depression (*12*):

- Antidepressants should not be considered for the initial treatment of adults with mild depressive episode. (Strength of recommendation: Conditional; Quality of evidence: Low);
- Tricyclic antidepressants or fluoxetine should be considered in adults with moderate to severe depressive episode/disorder. (Strength of recommendation: Conditional; Quality of evidence: Low);
- If drug treatment is required in older people, tricyclic antidepressants should be avoided if possible. (Strength of recommendation: Conditional; Quality of evidence: Low)

– If drug treatment is required in women with depressive episode who are planning a pregnancy or are pregnant or breastfeeding, tricyclic antidepressants or fluoxetine should be considered. (Strength of recommendation: Conditional; Quality of evidence: Low).

SSRIs are also recommended as first-line treatment choices in numerous international guidelines (*13–17*). The choice of individual SSRI should be made after taking into consideration the differing safety and tolerability profiles, pharmacokinetic and pharmacodynamic factors, price and individual patient factors and patient preferences.

**Costs/cost-effectiveness**

SSRIs vary in price globally, but are generally inexpensive, with multiple generic brands available. Cost-effectiveness analyses in different settings have shown SSRIs to be cost-effective interventions (*18–27*).

**Availability**

SSRIs are widely available globally, with off-patent generic formulations available.

**Other considerations**

Letter of support for escitalopram application from the Ministry for Health and Welfare, National Centre for Mental Health, Republic of Korea: "More than one SSRI should be considered as essential drugs. It is an important point that patients may respond to specific SSRIs differently and it is difficult to predict which agent will be the most effective for each patient."

**Committee recommendations**

The Committee recommended the addition of a square box symbol to the current listing of fluoxetine on the core list of the EML for treatment of depressive disorders.

The Committee noted that medicines within the pharmacological class of selective serotonin reuptake inhibitors all have demonstrated efficacy, but can differ in terms of pharmacokinetics, adverse events and drug-interaction profiles. The availability of different SSRIs as essential medicines may be beneficial at country level to expand therapeutic alternatives for patients and support better procurement.

As a consequence of the recommendation for the square box with fluoxetine, the Committee did not recommend the separate addition of escitalopram to the core list of the EML. Escitalopram, and other SSRIs should be considered therapeutically equivalent alternatives to fluoxetine for selection at national level.

## References


1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2007 (including the 15th Model List of Essential Medicines) (WHO Technical Report Series No. 946). Geneva: World Health Organization; 2007. Available from https://apps.who.int/iris/bitstream/handle/10665/43745/WHO_TRS_946_eng.pdf, accessed 30 October 2019.
2. GBD Results Tool | GHDx. 2018. Seattle: Institute for Health Metrics and Evaluation, University of Washington; 2018. Available from http://ghdx.healthdata.org/gbd-results-tool, accessed 29 September 2019.
3. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet. 2018;391(10128):1357–66.
4. Cipriani A, Santilli C, Furukawa TA, Signoretti A, Nakagawa A, McGuire H et al. Escitalopram versus other antidepressive agents for depression. Cochrane Database Syst Rev. 2009(2):CD006532.
5. Stone M, Laughren T, Jones ML, Levenson M, Holland PC, Hughes A et al. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. BMJ. 2009;339:b2880.
6. Laughren TP. Memorandum: Department of Health and Human Services Public Health Service Food and Drug Administration Center for Drug Evaluation and Research. 2006. Available from http://dixitciencia.com/wp-content/uploads/2006-4272b1-01-FDA.pdf, accessed 29 September 2019.
7. Beach SR, Kostis WJ, Celano CM, Januzzi JL, Ruskin JN, Noseworthy PA et al. Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation. J Clin Psychiatry. 2014; 75(5):e441–9.
8. Reichenpfader U, Gartlehner G, Morgan LC, Greenblatt A, Nussbaumer B, Hansen RA et al. Sexual dysfunction associated with second-generation antidepressants in patients with major depressive disorder: results from a systematic review with network meta-analysis. Drug Saf. 2014;37(1):19–31.
9. Hirsch M, Birnbaum RJ. Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects Internet]. Waltham, MA: UpToDate; 2018. Available from https://www.uptodate.com/contents/selective-serotonin-reuptake-inhibitors-pharmacology-administration-and-side-effects, accessed 29 September 2019.
10. Hiemke C, Hartter S. Pharmacokinetics of selective serotonin reuptake inhibitors. Pharmacol Ther. 2000;85(1):11–28.
11. Fava GA, Gatti A, Belaise C, Guidi J, Offidani E. Withdrawal Symptoms after Selective Serotonin Reuptake Inhibitor Discontinuation: A Systematic Review. Psychother Psychosom. 2015;84(2):72–81.
12. Antidepressants (Tricyclic Antidepressants and Selective Serotonin Reuptake Inhibitors) in treatment of adults with depression. mhGAP Evidence Resource Center. Geneva: World Health Organization, 2012. Available from https://www.who.int/mental_health/mhgap/evidence/depression/q1/en/, accessed 29 September 2019.
13. Depression in adults: recognition and management. Clinical guideline [CG90]. October 2009. Last updated April 2018. London: National Institute for Health and Care Excellence; 2018. Available from http://www.nice.org.uk/guidance/CG90, accessed 29 September 2019.
14. Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. Can J Psychiatry. 2016;61(9):540–60.

15. Gelenberg AJ, Marlene Freeman CP, Markowitz JC et al. Practice guideline for the treatment of patients with major depressive disorder; Third Edition. Washington, DC: American Psychiatric Association; 2010. Available from http://www.psychiatryonline.com/pracGuide/pracGuideTopic_7.aspx, accessed 29 September 2019.
16. Malhi GS, Bassett D, Boyce P, Bryant R, Fitzgerald PB, Fritz K et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry. 2015;49(12):1087–206.
17. Emsley R, Flisher AJ, Grobler G, Seedat S, Szabo CP. The South African Society of Psychiatrists (SASOP) Treatment Guidlelines for Psychiatric Disorders. S Afr J Psychiatr. 2013;19(3).
18. Khoo AL, Zhou HJ, Teng M, Lin L, Zhao YJ, Soh LB et al. Network Meta-Analysis and Cost-Effectiveness Analysis of New Generation Antidepressants. CNS drugs. 2015;29(8):695–712.
19. Kaplan C, Zhang Y. Assessing the comparative-effectiveness of antidepressants commonly prescribed for depression in the US Medicare population. J Ment Health Policy Econ. 2012; 15(4):171–8.
20. Mencacci C, Aguglia E, Biggio G, Cappellari L, Di Sciascio G, Fagiolini A et al. C-QUALITY: cost and quality-of-life pharmacoeconomic analysis of antidepressants in major depressive disorder in Italy. Adv Ther. 2013;30(7):697–712.
21. Mencacci C, Di Sciascio G, Katz P, Ripellino C. Cost-effectiveness evaluation of escitalopram in major depressive disorder in Italy. ClinicoEconomics and outcomes research : CEOR. 2013;5:87–99.
22. Mencacci C, Aguglia E, Biggio G, Cappellari L, Di Sciascio G, Fagiolini A et al. C-QUALITY: cost and quality-of-life pharmacoeconomic analysis of antidepressants used in major depressive disorder in the regional Italian settings of Veneto and Sardinia. ClinicoEconomics and outcomes research : CEOR. 2013;5:611–21.
23. Nuijten MJ, Brignone M, Marteau F, den Boer JA, Hoencamp E. Cost-effectiveness of escitalopram in major depressive disorder in the Dutch health care setting. Clin Ther. 2012;34(6):1364–78.
24. Sorensen J, Stage KB, Damsbo N, Le Lay A, Hemels ME. A Danish cost-effectiveness model of escitalopram in comparison with citalopram and venlafaxine as first-line treatments for major depressive disorder in primary care. Nord J Psychiatry. 2007;61(2):100–8.
25. Armstrong EP, Skrepnek GH, Haim Erder M. Cost-utility comparison of escitalopram and sertraline in the treatment of major depressive disorder. Curr Med Res Opin. 2007;23(2):251–8.
26. Malone DC. A budget-impact and cost-effectiveness model for second-line treatment of major depression. J Manag Care Pharm. 2007;13(6 Suppl A):S8-18.
27. Kongsakon R, Bunchapattanasakda C. The treatment of major depressive disorders (MDD) in Thailand using escitalopram compared to fluoxetine and venlafaxine: a pharmacoeconomic evaluation. J Med Assoc Thai. 2008;91(7):1117–28.

# Section 25: MEDICINES ACTING ON THE RESPIRATORY TRACT

## 25.1 Antiasthmatic and medicines for chronic obstructive pulmonary disease

*Tiotropium – addition – EML*

**Tiotropium bromide** **ATC Code: R03BB04**

**Proposal**

The application requested the inclusion of tiotropium with a square box as representative of the pharmacological class of long-acting muscarinic agents (LAMA) to the EML for use in the treatment of chronic obstructive pulmonary disease (COPD).

**Applicant**

Forum of International Respiratory Societies

**WHO Technical Department**

Comments on the application were received from the Department of Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention. The technical unit supports the inclusion of tiotropium on the EML, stating that it is an effective formulation to control COPD symptoms and the frequency and severity of exacerbations. Its inclusion on the EML may improve equity by making it more accessible to patients who need prolonged bronchodilator effect.

**EML/EMLc**

EML

**Section**

25.1 Antiasthmatic and medicines for COPD

**Dose form(s) & strengths(s)**

Powder for inhalation in capsules 18 μg
Inhalation solution 1.25 μg per dose and 2.5 μg per dose

**Core/Complementary**

Core

**Individual/Square box listing**

Square box listing incorporating tiotropium bromide, glycopyrronium bromide, aclidinium bromide and umeclidinium bromide.

**Background** (if relevant, eg. resubmission, previous EC consideration)

Single agent LAMAs had not previously been considered for inclusion on the EML.

The short-acting muscarinic agent ipratropium has been included on the EML since 1998.

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**Public health relevance** (burden of disease)

COPD affects approximately 300 million people worldwide and was responsible for over 3 million deaths globally in 2017 (*1*). In 2017, it was the third leading cause of death worldwide, after ischaemic heart disease and stroke (*2*).

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**Summary of evidence: benefits** (from the application)

Data were presented from systematic reviews and network meta-analyses identified through a literature search conducted for the application.

A 2018 Cochrane systematic review and network meta-analysis of 99 studies (101 311 participants) compared the efficacy and safety of LAMA and long-acting beta agonist (LABA) monotherapy and LABA/LAMA and LABA/inhaled corticosteroid (ICS) dual combination therapy for COPD (*3*). The quality of the included studies was considered by the authors to be generally good. Results of the NMA suggested that the LABA/LAMA combination was the highest ranking treatment for reducing COPD exacerbations, followed by LAMA monotherapy in patients at both high- and low-risk for COPD exacerbations, although there was some uncertainty in the results. The authors also concluded that dual combination therapies appeared more effective than LABA or LAMA monotherapy for improving symptom and quality of life scores. For the comparison of LAMA versus LABA (six studies, 11 943 participants), LAMAs were associated with decreased moderate to severe exacerbations compared to LABA (odds ratio (OR) 0.86, 95%CI 0.79 to 0.93).

A 2014 Cochrane systematic review and NMA of 71 studies (73 062 participants) assessed the efficacy of long-acting therapies for COPD (beta-agonists, anticholinergics and corticosteroids) (*4*). The efficacy outcomes evaluated with St George's Respiratory Questionnaire (SGRQ) total score, and trough forced expiratory volume in 1 second (FEV1). Results from pairwise comparisons for the efficacy outcome of SGRQ total score indicated LABA/ICS as the highest ranked intervention, with a mean improvement over placebo of −3.89 units at six months (95% credible interval (CrI) −4.70 to −2.97) and −3.60 at 12 months (95%CrI −4.63 to −2.34). LAMAs and LABAs were ranked second and third at six months, with mean differences of −2.63 (95%CrI −3.53 to −1.97) and −2.29 (95%CrI −3.18 to −1.53), respectively. Inhaled corticosteroids were ranked fourth (MD −2.00, 95%CrI −3.06 to −0.87). Results from pairwise comparisons for the outcome of FEV1 also indicated LABA/ICS to be the highest ranking

intervention, followed by LAMAs and LABAs with essentially equivalent results, with ICS ranking fourth. The authors concluded that quality of life and lung function were improved most with LABA/ICS combination therapy. LAMA and LABA monotherapy demonstrated similar effects to each other.

A 2014 Cochrane systematic review of 12 randomized controlled trials (9547 participants) evaluated the efficacy and safety of the LAMA aclidinium bromide in patients with stable COPD (*5*). Compared to placebo, aclidinium was associated with improvements in quality of life as measured by SGRQ total score (mean difference −2.34, 95%CI −3.18 to −1.51). Aclidinium also reduced the number of hospitalizations due to severe exacerbations compared to placebo (OR 0.64; 95%CI 0.46 to 0.88; corresponding to 4 to 20 fewer per 1000 in absolute terms). However, the authors concluded that overall, aclidinium did not significantly reduce mortality, serious adverse events, or exacerbations requiring oral steroids and/or antibiotics. The available data were insufficient and of very low quality for efficacy comparisons of aclidinium versus tiotropium.

A 2018 Cochrane systematic review of seven randomized controlled trials (5921 participants) evaluated the efficacy and safety of combination therapy with aclidinium bromide and LABAs in patients with stable COPD (6). Compared to individual monotherapy or placebo, aclidinium/LABA combination therapy was associated with improved dyspnoea, lung function and quality of life. The authors found no evidence of a difference between combination therapy and monotherapy or placebo for exacerbations, hospital admissions, mortality, non-fatal serious adverse event (SAEs) or adverse events.

A 2015 Cochrane systematic review of 10 trials (10 894 participants) compared the relative effects of treatment with LABA plus tiotropium versus tiotropium or LABA monotherapy in patients with COPD (*7*). The authors concluded that LABA/tiotropium combination therapy was associated with a small mean improvement in health-related quality of life and FEV1 compared to either agent alone. There was no observed difference in hospital admissions or death between treatment groups.

The application also presented the results of systematic reviews and individual trials that compared monotherapy with aclidinium (*5*, *8*), glycopyrronium (*9–11*), tiotropium (*12–18*) and umeclidinium (*19*, *20*) versus placebo, other short- and long-acting LAMAs, and LABAs.

The findings of two network meta-analyses of LAMAs versus placebo indicated no significant differences among medicines within the class for most efficacy outcomes (*21*, *22*).

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**Summary of evidence: harms** (from the application)

Extensive use of LAMAs in a wide range of doses and clinical settings has shown them to be acceptably safe. Common adverse effects of LAMAs relate to their anticholinergic activity and include dry mouth, constipation and urinary

retention (*23*–*26*). However, inhaled anticholinergic medicines are poorly absorbed, which limits the systemic effects observed with atropine (*24*). Most safety data is available for tiotropium, but the rate of anticholinergic side-effects for the wider class of LAMAs appears to be low and generally similar (*27*).

In a large, long-term clinical trial in COPD patients, tiotropium added to other standard therapies had no effect on cardiovascular risk (*24*).

**Additional evidence** (not in the application)

N/A

**WHO Guidelines**

There are no current WHO guidelines for the management of COPD.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) released an updated report on its global strategy for the diagnosis, management and prevention of COPD in 2019 (*28*). LAMAs, alone or in combination with LABAs are recommended as initial pharmacological treatment for stable COPD in patients classified as Gold B, C and D using the "ABCD" assessment tool, which takes into account both symptom burden and exacerbation risk.

**Costs/cost-effectiveness**

A 2017 systematic review of 18 pharmacoeconomic analyses of COPD therapy included six analyses of LAMA monotherapy (tiotropium, glycopyrronium and aclidinium) (*29*). All studies were conducted in high-income settings and were funded by pharmaceutical companies. Based on these and previous studies, the authors considered that there was strong evidence that tiotropium monotherapy is cost-effective compared to usual care but considered evidence to be inconclusive for the relative cost-effectiveness of tiotropium, glycopyrronium and aclidinium versus each other.

The application presented wholesale monthly costs for tiotropium from Australia and the United States, between which, a substantial (10-fold) difference in cost exists. No information was presented in the application regarding the monthly treatment costs for other medicines in the class.

The United Kingdom's March 2019 NHS Prescription Services Drug Tariff reported similar prices (for one months' treatment) across the four LAMAs tiotropium, aclidinium, glycopyrronium and umeclidinium (*30*).

**Availability**

Tiotropium has wide international availability and is available in generic brands.

**Other considerations**

N/A

### Committee recommendations

The Committee recommended the inclusion of tiotropium with a square box as representative of the pharmacological class of long-acting muscarinic agents (LAMA) to the core list of the EML for use in the treatment of chronic obstructive pulmonary disease (COPD) based on the evidence presented for efficacy in reducing COPD exacerbations, safety and cost-effectiveness.

## References


1. GBD Results Tool | GHDx. 2018. Seattle: Institute for Health Metrics and Evaluation, University of Washington; 2018. Available from http://ghdx.healthdata.org/gbd-results-tool, accessed 29 September 2019.
2. Global Burden of Disease compare data visualization. Seattle: Institute for Health Metrics and Evaluation, University of Washington; 2016. Available from https://vizhub.Healthdata.Org/gbd-compare/, accessed 29 September 2019.
3. Oba Y, Keeney E, Ghatehorde N, Dias S. Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis. Cochrane Database Syst Rev. 2018;12:CD012620.
4. Kew KM, Dias S, Cates CJ. Long-acting inhaled therapy (beta-agonists, anticholinergics and steroids) for COPD: a network meta-analysis. Cochrane Database Syst Rev. 2014(3):CD010844.
5. Ni H, Soe Z, Moe S. Aclidinium bromide for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2014(9):CD010509.
6. Ni H, Moe S, Soe Z, Myint KT, Viswanathan KN. Combined aclidinium bromide and long-acting beta2-agonist for chronic obstructive pulmonary disease (COPD). Cochrane Database Syst Rev. 2018;12:CD011594.
7. Farne HA, Cates CJ. Long-acting beta2-agonist in addition to tiotropium versus either tiotropium or long-acting beta2-agonist alone for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2015(10):CD008989.
8. Wedzicha JA, Agusti A, Donaldson G, Chuecos F, Lamarca R, Garcia Gil E. Effect of Aclidinium Bromide on Exacerbations in Patients with Moderate-to-Severe COPD: A Pooled Analysis of Five Phase III, Randomized, Placebo-Controlled Studies. COPD. 2016;13(6):669–76.
9. D'Urzo A, Ferguson GT, van Noord JA, Hirata K, Martin C, Horton R et al. Efficacy and safety of once-daily NVA237 in patients with moderate-to-severe COPD: the GLOW1 trial. Respir Res. 2011;12:156.
10. Kerwin E, Hebert J, Gallagher N, Martin C, Overend T, Alagappan VK et al. Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: the GLOW2 study. Eur Respir J. 2012;40(5):1106–14.
11. Chapman KR, Beeh KM, Beier J, Bateman ED, D'Urzo A, Nutbrown R et al. A blinded evaluation of the efficacy and safety of glycopyrronium, a once-daily long-acting muscarinic antagonist, versus tiotropium, in patients with COPD: the GLOW5 study. BMC Pulm Med. 2014;14:4.
12. Karner C, Chong J, Poole P. Tiotropium versus placebo for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2014(7):CD009285.
13. Zhou Y, Zhong NS, Li X, Chen S, Zheng J, Zhao D et al. Tiotropium in Early-Stage Chronic Obstructive Pulmonary Disease. N Engl J Med. 2017;377(10):923–35.

14. Yohannes AM, Willgoss TG, Vestbo J. Tiotropium for treatment of stable COPD: a meta-analysis of clinically relevant outcomes. Respir Care. 2011;56(4):477–87.
15. Vogelmeier C, Hederer B, Glaab T, Schmidt H, Rutten-van Molken MP, Beeh KM et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. N Engl J Med. 2011;364(12): 1093–103.
16. Decramer ML, Chapman KR, Dahl R, Frith P, Devouassoux G, Fritscher C et al. Once-daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): a randomised, blinded, parallel-group study. Lancet Respir Med. 2013;1(7):524–33.
17. Chong J, Karner C, Poole P. Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2012(9):CD009157.
18. Cheyne L, Irvin-Sellers MJ, White J. Tiotropium versus ipratropium bromide for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2013(9):CD009552.
19. Trivedi R, Richard N, Mehta R, Church A. Umeclidinium in patients with COPD: a randomised, placebo-controlled study. Eur Respir J. 2014;43(1):72–81.
20. Feldman G, Maltais F, Khindri S, Vahdati-Bolouri M, Church A, Fahy WA et al. A randomized, blinded study to evaluate the efficacy and safety of umeclidinium 62.5 mug compared with tiotropium 18 mug in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2016;11:719–30.
21. Oba Y, Lone NA. Comparative efficacy of long-acting muscarinic antagonists in preventing COPD exacerbations: a network meta-analysis and meta-regression. Ther Adv Respir Dis. 2015;9(1):3–15.
22. Ismaila AS, Huisman EL, Punekar YS, Karabis A. Comparative efficacy of long-acting muscarinic antagonist monotherapies in COPD: a systematic review and network meta-analysis. Int J Chron Obstruct Pulmon Dis. 2015;10:2495–517.
23. Disse B, Speck GA, Rominger KL, Witek TJ, Jr., Hammer R. Tiotropium (Spiriva): mechanistical considerations and clinical profile in obstructive lung disease. Life Sci. 1999;64(6-7):457–64.
24. Tashkin DP. Long-acting anticholinergic use in chronic obstructive pulmonary disease: efficacy and safety. Curr Opin Pulm Med. 2010;16(2):97–105.
25. Kesten S, Jara M, Wentworth C, Lanes S. Pooled clinical trial analysis of tiotropium safety. Chest. 2006;130(6):1695–703.
26. Halpin DM, Dahl R, Hallmann C, Mueller A, Tashkin D. Tiotropium HandiHaler((R)) and Respimat((R)) in COPD: a pooled safety analysis. Int J Chron Obstruct Pulmon Dis. 2015;10:239-59.
27. Jones PW, Singh D, Bateman ED, Agusti A, Lamarca R, de Miquel G et al. Efficacy and safety of twice-daily aclidinium bromide in COPD patients: the ATTAIN study. Eur Respir J. 2012;40(4): 830–6.
28. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2019 Report). Fontana: Global Initiative for Chronic Obstructive Lung Disease; 2019. Available from https://goldcopd.org/, accessed 29 September 2019.
29. van der Schans S, Goossens LMA, Boland MRS, Kocks JWH, Postma MJ, van Boven JFM et al. Systematic Review and Quality Appraisal of Cost-Effectiveness Analyses of Pharmacologic Maintenance Treatment for Chronic Obstructive Pulmonary Disease: Methodological Considerations and Recommendations. Pharmacoeconomics. 2017;35(1):43–63.
30. NHS Business Services Authority Electronic Drug Tariff. March 2019. Available from http://www.drugtariff.nhsbsa.nhs.uk/#/00684922-DA/DA00684858/Home, accessed 26 March 2019.

## Section 27: VITAMINS AND MINERALS

*Iodine – change to listing – EML and EMLc*

**Iodine** **ATC Code: H03CA**

**Proposal**

The application requested a correction to the strength of iodine capsules listed on the EML and EMLc

**Applicant**

Guerbet

**WHO Technical Department**

N/A

**EML/EMLc**

EML and EMLc

**Section**

27. Vitamin and Minerals

**Dose form(s) & strengths(s)**

Capsule 190 mg

**Core/Complementary**

Core

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Iodine capsules 200 mg and iodized oil were added to the EML in 1990 for the prophylaxis of goitre in areas where severe iodine deficiency is endemic and where dietary intake of iodine, including iodized salt, is inadequate (*1*). The same formulations were included on the first EMLc in 2007 (*2*).

**Public health relevance** (burden of disease)

N/A

**Summary of evidence: benefits** (from the application)

N/A

**Summary of evidence: harms** (from the application)

N/A

**Additional evidence** (not in the application)

N/A

**WHO Guidelines**

N/A

**Costs/cost-effectiveness**

N/A

**Availability**

A discrepancy exists between the listed strength of iodine capsules on the EML and EMLc and the marketing authorization of the product.

The marketing authorization and Summary of Product Characteristics (SmPC) for the product marketed by Guebet report the qualitative and quantitative composition as 500 mg ethyl esters of iodised fatty acids from poppy seed oil, corresponding to 190 mg iodine (38% w/w).

**Other considerations**

N/A

**Committee recommendations**

The Committee recommended that the strength of iodine capsules in the EML and EMLc be corrected to 190 mg, to accurately reflect the quantitative composition as described in the marketing authorization and Summary of Product Characteristics (SmPC).

## References

1. The use of essential drugs. Report of the WHO Expert Committee, 1990 (WHO Technical Report Series, No. 796). Geneva: World Health Organization; 1990. Available from https://apps.who.int/iris/bitstream/handle/10665/39338/WHO_TRS_796.pdf, accessed 30 October 2019.
2. The selection and use of essential medicines. Report of the WHO Expert Committee, October 2007 (including the Model List of Essential Medicines for Children) (WHO Technical Report Series, No. 950). Geneva: World Health Organization; 2008. Available from https://apps.who.int/iris/bitstream/handle/10665/43745/WHO_TRS_946_eng.pdf, accessed 30 October 2019.

*Multiple micronutrient powders – addition – EMLc*

**Multiple micronutrient powders** **ATC Code: B03AE10**

**Proposal**

The application requested the inclusion of multiple micronutrient powders (MNP) for the prevention of anaemia in infants and children on the core list of the EMLc.

**Applicant**

Dr Stanley Zlotkin

**WHO Technical Department**

Nutrition for Health and Development

**EML/EMLc**

EMLc

**Section**

27. Vitamins and minerals

**Dose form(s) & strengths(s)**

Oral powder sachet 1 g containing:

- elemental iron 12.5 mg
- elemental zinc 5 mg
- vitamin A 300 mcg
- with or without other micronutrients at recommended daily values

**Core/Complementary**

Core

**Individual/Square box listing**

Individual

**Background** (if relevant, eg. resubmission, previous EC consideration)

Multiple micronutrient powders have not previously been considered for inclusion on the EMLc.

**Public health relevance** (burden of disease)

The global prevalence of anaemia worldwide for pre-school children in 2011 was 43% or an estimated 273 children, of which about 42% is attributable to

iron deficiency (*1*). Anaemia in early childhood reduces cognitive ability and causes developmental delays and disability (*1*). Currently, epidemiological and experimental data suggest that in order to minimize these risks, prevention of anaemia is preferred over treatment because the physiological impairments due to deficiency start at an early age and they may be irreversible, even after repletion of iron stores (2). There are no direct estimates for prevalence of zinc deficiency; however, it is believed to be as prevalent as iron deficiency affecting approximately 293 million children under five and is responsible for 13% of lower respiratory tract infections (primarily pneumonia and influenza) (*3*).

Amongst children under 5 years of age globally, an estimated 190 million have vitamin A deficiency. The prevalence of vitamin A deficiency is about 44% amongst children in Africa and about 50% in children in South-East Asia. Vitamin A deficiency associated with prevalence of night blindness is around 2% in African children, and about 0.5% in children in parts of South-East Asia (*3*).

Deficiencies of vitamins and minerals such as iron, zinc, vitamin A and others, often occur simultaneously in children due to factors such as poor nutritional status (*3*). The effects of these deficiencies in neonates can result in serious adverse events including mortality. Furthermore, the effects of these deficiencies in childhood may result in long-term, life-long irreversible physical and cognitive problems that lead to negative consequences for health and economic opportunities. Mineral and vitamin deficiencies particularly in iron, zinc and vitamin A, among other nutritional risk factors, are determined to be responsible for 3.9 million deaths (35% of total deaths) in children under the age of 5 years annually. These deficiencies are also responsible for 144 million disability-adjusted life years in the same population (*3*).

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**Summary of evidence: benefits** (from the application)

Evidence for the effectiveness of MNP comes from two systematic reviews that informed the development of the 2016 WHO Guidelines for use of multiple micronutrient powders for point-of-use fortification of foods consumed by infants and young children 6 to 23 months and children 2 to 12 years (*4*).

A 2011 Cochrane systematic review of 15 randomized and quasi-randomized trials (12 239 participants) evaluated the effects and safety of point-of-use fortification of foods with MNP for infants and young children from 6 to 23 months of age. The trials were conducted in low- and middle-income countries (LMICs) in Asia, Africa and the Americas. Six studies were conducted in malaria-endemic areas. Most trials were assessed as having a low risk of bias (*5*).

The Guideline Development Group reported that infants and young children from 6 to 23 months of age who consumed foods fortified at the point-of-use with multiple micronutrients powders had a lower risk for the critical outcome of anaemia, with a 26% reduction compared to placebo or

no intervention (risk ratio (RR) 0.74, 95%CI 0.66 to 0.83; 10 studies; 2802 participants, high quality evidence). They also had a lower risk for the critical outcome of iron deficiency, with a 52% reduction (RR: 0.48, 95%CI 0.36 to 0.62; five studies; 796 participants, moderate quality evidence). Compared to no treatment or placebo, children receiving multiple micronutrient powders had a 5.12 g/L higher haemoglobin concentration at follow-up (mean difference (MD) 5.12 g/L, 95%CI 2.70 to 7.54; 12 studies; 3565 participants, low quality evidence). With respect to iron status, compared to no treatment or placebo, children receiving multiple micronutrient powders had an average increase in serum ferritin concentration of 16.47 µg/L at follow up (MD: 16.47 µg/L, 95%CI 3.03 to 29.91; three studies; 694 participants, very low quality evidence). Regarding weight-for-age z-score, the mean difference was minimal (MD: 0.04 in z-score, 95%CI −0.13 to 0.21; four studies; 606 participants, low quality evidence) (*4*).

A second Cochrane systematic review of 12 randomized and quasi-randomized trials (5720 participants) assessed the effects and safety of point-of-use fortification of foods with MNP for children aged from 2 to 12 years. The trials were conducted in low- and middle-income countries in Asia, Africa and the Americas. Most trials were assessed as having a low risk of bias (*6*).

The Guideline Development Group reported that children aged 2 to 12 years receiving iron-containing multiple micronutrient powders for point-of-use fortification of foods were significantly less likely to have anaemia at follow-up than those children receiving no intervention or a placebo (prevalence ratio (PR) 0.66, 95%CI 0.49 to 0.88; 10 studies, 2448 participants, moderate quality evidence). These children also had a 3.37 g/L higher haemoglobin concentration at follow-up (MD 3.37 g/L, 95%CI 0.94 to 5.80; 11 studies; 2746 participants, low quality evidence). Also, children receiving iron-containing multiple micronutrient powders for point-of-use fortification of foods were significantly less likely to have iron deficiency at follow up than those children receiving no intervention or a placebo (PR 0.35, 95%CI 0.27 to 0.47; five studies; 1364 participants, moderate quality evidence). With respect to ferritin concentrations, children receiving iron-containing multiple micronutrient powders had, on average, 0.42 µg of ferritin more per litre at follow-up than those children receiving no intervention or a placebo (standardized mean difference (SMD): 0.42 µg/L, 95%CI −4.36 to 5.19; three studies; 1066 participants, very low quality evidence) (*4*).

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**Summary of evidence: harms** (from the application)

In the systematic review on MNP in infants and young children, data on morbidity, other indicators of vitamin and mineral status and side-effects were scarce due to a lack of standardization; however, none of the trials reported deaths attributable to the intervention and there was no difference regarding the patterns of morbidity between children receiving placebo or no intervention and

the ones receiving MNP. Only one of the studies conducted in malaria-endemic areas reported results related to malaria and found no difference in the presence of positive malaria smears between the groups (RR 0.24, 95%CI 0.05 to 1.12; 194 children). None of the trials reported on the outcome of all-cause mortality (*5*).

In the systematic review on MNP in older children, only one trial reported on the outcome of all-cause mortality and there were no deaths reported during this trial (MD 0, 95%CI –0.03 to 0.03; one study; 115 participants, low quality evidence). Finally, diarrhoea (three liquid stools or more per day) was reported by two trials and children receiving iron-containing MNP were as likely to have diarrhoea at follow-up as those children receiving no intervention or a placebo (RR 0.97, 95%CI 0.53 to 1.78; two studies; 366 participants, moderate quality evidence) (*6*).

A 2016 Cochrane systematic review evaluated the effects and safety of iron supplementation (including MNP), with or without folic acid, in children living in areas with hyperendemic or holoendemic malaria transmission. The review found that overall, iron does not cause an excess of clinical malaria (RR 0.93, 95%CI 0.87 to 1.00; 14 trials, 7168 children, high quality evidence). Iron probably does not cause an excess of clinical malaria in both populations where anaemia is common and those in which anaemia is uncommon. In areas where there are prevention and management services for malaria, iron (with or without folic acid) may reduce clinical malaria (RR 0.91, 95%CI 0.84 to 0.97; seven trials, 5586 participants, low quality evidence), while in areas where such services are unavailable, iron (with or without folic acid) may increase the incidence of malaria, although the lower CIs indicate no difference (RR 1.16, 95%CI 1.02 to 1.31; nine trials, 19 086 participants, low quality evidence). Iron supplementation does not cause an excess of severe malaria (RR 0.90, 95%CI 0.81 to 0.98; 6 trials, 3421 children, high quality evidence). Iron resulted in fewer anaemic children at follow up, and the end average change in haemoglobin from base line was higher with iron (*7*).

**Additional evidence** (not in the application)

N/A

**WHO Guidelines**

The 2016 WHO *Use of multiple micronutrient powders for point-of-use fortification of foods consumed by infants and young children 6–23 months and children 2–12 years* (*4*) make the following recommendations with regard to MNP:

- In populations where anaemia is a public health problem, point-of-use fortification of complementary foods with iron-containing micronutrient powders in infants and young children aged 6 to 23 months is recommended, to improve iron status and reduce

anaemia (strong recommendation, moderate quality evidence).

– In populations where anaemia is a public health problem, point-of-use fortification of foods with iron containing micronutrient powders in children aged 2 to 12 years is recommended, to improve iron status and reduce anaemia (strong recommendation, moderate quality evidence).

**Costs/cost-effectiveness**

The current listed price of the MNP provided by UNICEF Supply Catalogue website is US$ 0.62 to US$ 0.65 per pack (30 sachets) (*8*). The composition of the UNICEF supplied product differs from the composition of MNP proposed for inclusion on the EMLc with regard to the amount of iron, vitamin A and zinc, and the inclusion of 12 additional micronutrients.

The World Bank estimated the annual cost of MNP intervention at US$ 3.60 per child aged 12 to 23 months (*9*). A Copenhagen Consensus review found that micronutrient interventions were cost-effective in general (*10*). It has also been estimated that iron-containing MNP recover US$ 37 for every US$ 1 invested due to the positive effects of addressing childhood anaemia among children aged 6 to 23 months (*11*).

**Availability**

The following manufacturers were identified in 2016 by UNICEF Supply Division's *Multiple Micronutrient Powder Supply & Market Outlook* as meeting standards (i.e. good manufacturing practice) and having the capacity to provide suitable, age-appropriate dose forms and strengths of multiple micronutrient powders for administration to infants and children (*12*):

1. DSM Europe (Switzerland)
2. DSM (Malaysia) – formerly Fortitech
3. Renata (Bangladesh)
4. Piramal (India)
5. DSM (South Africa)

**Other considerations**

The Committee noted the information provided in the application regarding the submission for MNP to be included in the United States Pharmacopoeia (USP), including a draft of the approved product monograph, which will take effect in May 2019.

### Committee recommendations

The Committee recommended the addition of multiple micronutrient powders to the core list of the EMLc for the prevention of anaemia in infants and children in populations where anaemia is a public health problem. Use should be in line with the recommendations in current WHO guidelines for point-of-use fortification of foods.

## References


1. The global prevalence of anaemia in 2011. Geneva: World Health Organization; 2015. Available from https://apps.who.int/iris/bitstream/handle/10665/177094/9789241564960_eng.pdf, accessed 30 October 2019.
2. Intermittent iron supplementation in pre-school and school-age children. Geneva: World Health Organization; 2011. Available from https://apps.who.int/iris/bitstream/handle/10665/44648/9789241502009_eng.pdf, accessed 30 October 2019.
3. Global health risks: mortality and burden of disease attributable to selected major risks. Geneva: World Health Organization; 2009.
4. Use of multiple micronutrient powders for point-of-use fortification of foods consumed by infants and young children aged 6–23 months and children aged 2–12 years. Geneva: World Health Organization; 2016. Available from https://apps.who.int/iris/bitstream/handle/10665/252540/9789241549943-eng.pdf, accessed 29 September 2019.
5. De-Regil LM, Suchdev PS, Vist GE, Walleser S, Pena-Rosas JP. Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age. Cochrane Database Syst Rev. 2011(9):CD008959.
6. De-Regil LM, Jefferds MED, Pena-Rosas JP. Point-of-use fortification of foods with micronutrient powders containing iron in children of preschool and school-age. Cochrane Database Syst Rev. 2017;11:CD009666.
7. Neuberger A, Okebe J, Yahav D, Paul M. Oral iron supplements for children in malaria-endemic areas. Cochrane Database Syst Rev. 2016;2:CD006589.
8. UNICEF Supply Catalogue [website]. New York: United Nations Children's Fund. (https://supply.unicef.org/, accessed 29 September 2019).
9. Horton S, Shekar M, Mcdonald C, Mahal A, Brooks J. Scaling up nutrition: what will it cost? Washington, DC: International Bank for Reconstruction and Development/The World Bank; 2010.
10. Horton S, Alderman H, Rivera J A. Copenhagen Consensus 2009 Challenge Paper: Hunger and Malnutrition. [ed.] Bjorn Lomborg. In: Global Crises, Global Solutions. Cambridge: Cambridge University Press; 2009.
11. Sharieff W, Horton SE, Zlotkin S. Economic gains of a home fortification program: evaluation of "Sprinkles" from the provider's perspective. Can J Public Health. 2006;97(1):20–3.
12. Multiple micronutrient powder supply & market outlook. Available from https://www.unicef.org/supply/files/Multiple_Micronutrient_Powder_Supply_and_Market_Update.pdf. Copenhagen: United Nations Children's Fund; 2016.

# Annex 1

## WHO Model List of Essential Medicines (2019)

### Explanatory notes

The **core list** presents a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost–effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

Where the [c] symbol is placed next to an individual medicine or strength of medicine on the core list it signifies that there is a specific indication for restricting its use to children.

The **complementary list** presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost-effectiveness in a variety of settings.

Where the *[c]* symbol is placed next to an individual medicine or strength of medicine on the complementary list it signifies that the medicine(s) require(s) specialist diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training for their use in children.

The **square box symbol** (☐) is primarily intended to indicate similar clinical performance within a pharmacological class. The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. Not all square boxes are applicable to medicine selection for children.

Therapeutic equivalence is indicated only on the basis of reviews of efficacy and safety and when consistent with WHO clinical guidelines. National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price.

The [a] symbol indicates that there is an age or weight restriction on use of the medicine; details for each medicine can be found in Table 1.1.

The presence of an entry on the Essential Medicines List carries no assurance as to pharmaceutical quality. It is the responsibility of the relevant national or regional drug regulatory authority to ensure that each product is of

appropriate pharmaceutical quality (including stability) and that, when relevant, different products are interchangeable.

For recommendations and advice concerning all aspects of the quality assurance of medicines see the WHO Medicines website http://www.who.int/medicines/areas/quality_safety/quality_assurance/en/.

Medicines and dosage forms are listed in alphabetical order within each section and there is no implication of preference for one form over another. Standard treatment guidelines should be consulted for information on appropriate dosage forms.

The main terms used for dosage forms in the Essential Medicines List can be found in Table 1.2.

Definitions of many of these terms and pharmaceutical quality requirements applicable to the different categories are published in the current edition of *The International Pharmacopoeia* http://www.who.int/medicines/publications/pharmacopoeia.

## 1. ANAESTHETICS, PREOPERATIVE MEDICINES AND MEDICAL GASES

### 1.1 General anaesthetics and oxygen

#### 1.1.1 *Inhalational medicines*

| | |
|---|---|
| halothane | **Inhalation.** |
| isoflurane | **Inhalation.** |
| nitrous oxide | **Inhalation.** |
| oxygen | **Inhalation** (medical gas). |

#### 1.1.2 *Injectable medicines*

| | |
|---|---|
| ketamine | **Injection:** 50 mg (as hydrochloride)/ mL in 10- mL vial. |
| propofol* | **Injection:** 10 mg/ mL; 20 mg/ mL.<br>* Thiopental may be used as an alternative depending on local availability and cost. |

### 1.2 Local anaesthetics

| | |
|---|---|
| ☐ bupivacaine | **Injection:** 0.25%; 0.5% (hydrochloride) in vial.<br>**Injection for spinal anaesthesia:** 0.5% (hydrochloride) in 4- mL ampoule to be mixed with 7.5% glucose solution. |
| ☐ lidocaine | **Injection:** 1%; 2% (hydrochloride) in vial.<br>**Injection for spinal anaesthesia:** 5% (hydrochloride) in 2- mL ampoule to be mixed with 7.5% glucose solution.<br>**Topical forms**: 2% to 4% (hydrochloride). |
| lidocaine + epinephrine (adrenaline) | **Dental cartridge:** 2% (hydrochloride) + epinephrine 1:80 000.<br>**Injection:** 1%; 2% (hydrochloride **or** sulfate) + epinephrine 1:200 000 in vial. |
| ***Complementary List*** | |
| *ephedrine** | ***Injection:** 30 mg (hydrochloride)/ mL in 1- mL ampoule.*<br>* *For use in spinal anaesthesia during delivery, to prevent hypotension.* |

| | |
|---|---|
| **1. ANAESTHETICS, PREOPERATIVE MEDICINES AND MEDICAL GASES** *(continued)* | |
| **1.3 Preoperative medication and sedation for short-term procedures** | |
| atropine | **Injection:** 1 mg (sulfate) in 1- mL ampoule. |
| ☐ midazolam | **Injection:** 1 mg/ mL.<br>**Oral liquid:** 2 mg/ mL [c].<br>**Tablet:** 7.5 mg; 15 mg. |
| morphine | **Injection:** 10 mg (sulfate **or** hydrochloride) in 1- mL ampoule. |
| **1.4 Medical gases** | |
| oxygen* | **Inhalation**<br>For use in the management of hypoxaemia.<br>* No more than 30% oxygen should be used to initiate resuscitation of neonates less than or equal to 32 weeks of gestation. |
| **2. MEDICINES FOR PAIN AND PALLIATIVE CARE** | |
| **2.1 Non-opioids and non-steroidal anti-inflammatory medicines (NSAIMs)** | |
| acetylsalicylic acid | **Suppository:** 50 mg to 150 mg.<br>**Tablet:** 100 mg to 500 mg. |
| ibuprofen [a] | **Oral liquid:** 200 mg/5 mL.<br>**Tablet:** 200 mg; 400 mg; 600 mg.<br>[a] Not in children less than 3 months. |
| paracetamol* | **Oral liquid:** 120 mg/5 mL; 125 mg/5 mL.<br>**Suppository:** 100 mg.<br>**Tablet:** 100 mg to 500 mg.<br>* Not recommended for anti-inflammatory use due to lack of proven benefit to that effect. |

| 2. MEDICINES FOR PAIN AND PALLIATIVE CARE *(continued)* | |
|---|---|
| **2.2 Opioid analgesics** | |
| codeine | **Tablet:** 30 mg (phosphate). |
| fentanyl* | **Transdermal patch:** 12 micrograms/hr; 25 micrograms/hr; 50 micrograms/hr; 75 micrograms/hr; 100 micrograms/hr<br>* For the management of cancer pain |
| ☐ morphine* | **Granules (slow-release; to mix with water):** 20 mg–200 mg (morphine sulfate).<br>**Injection:** 10 mg (morphine hydrochloride **or** morphine sulfate) in 1- mL ampoule.<br>**Oral liquid:** 10 mg (morphine hydrochloride **or** morphine sulfate)/5 mL.<br>**Tablet (slow release):** 10 mg–200mg (morphine hydrochloride **or** morphine sulfate).<br>**Tablet (immediate release):** 10 mg (morphine sulfate).<br>* Alternatives limited to hydromorphone and oxycodone |
| ***Complementary list*** | |
| *methadone** | ***Tablet:** 5 mg; 10 mg (as hydrochloride)*<br>***Oral liquid:** 5mg/ 5mL; 10mg/ 5mL (as hydrochloride)*<br>***Concentrate for oral liquid:** 5 mg/ mL; 10mg/ mL (as hydrochloride)*<br>* *For the management of cancer pain.* |
| **2.3 Medicines for other common symptoms in palliative care** | |
| amitriptyline | **Tablet:** 10 mg; 25 mg; 75 mg. |
| cyclizine [c] | **Injection:** 50 mg/ mL.<br>**Tablet:** 50 mg. |
| dexamethasone | **Injection:** 4 mg/ mL in 1- mL ampoule (as disodium phosphate salt).<br>**Oral liquid:** 2 mg/5 mL.<br>**Tablet:** 2 mg [c]; 4 mg. |
| diazepam | **Injection:** 5 mg/ mL.<br>**Oral liquid:** 2 mg/5 mL.<br>**Rectal solution:** 2.5 mg; 5 mg; 10 mg.<br>**Tablet:** 5 mg; 10 mg. |

| **2. MEDICINES FOR PAIN AND PALLIATIVE CARE** *(continued)* | |
|---|---|
| docusate sodium | **Capsule:** 100 mg.<br>**Oral liquid:** 50 mg/5 mL. |
| fluoxetine [a] | **Solid oral dosage form:** 20 mg (as hydrochloride).<br>[a] >8 years. |
| haloperidol | **Injection:** 5 mg in 1- mL ampoule.<br>**Oral liquid:** 2 mg/ mL.<br>**Solid oral dosage form:** 0.5 mg; 2mg; 5 mg. |
| hyoscine butylbromide | **Injection:** 20 mg/ mL. |
| hyoscine hydrobromide [c] | **Injection:** 400 micrograms/ mL; 600 micrograms/ mL.<br>**Transdermal patches:** 1 mg/72 hours. |
| lactulose [c] | **Oral liquid:** 3.1–3.7 g/5 mL. |
| loperamide | **Solid oral dosage form:** 2 mg. |
| metoclopramide | **Injection:** 5 mg (hydrochloride)/mL in 2-mL ampoule.<br>**Oral liquid:** 5 mg/5 mL.<br>**Solid oral form:** 10 mg (hydrochloride). |
| midazolam | **Injection:** 1 mg/ mL; 5 mg/ mL.<br>**Solid oral dosage form:** 7.5 mg; 15 mg.<br>**Oral liquid:** 2mg/ mL [c]. |
| ☐ ondansetron [c] [a] | **Injection:** 2 mg base/ mL in 2- mL ampoule (as hydrochloride).<br>**Oral liquid:** 4 mg base/5 mL.<br>**Solid oral dosage form:** Eq 4 mg base; Eq 8 mg base.<br>[a] >1 month. |
| senna | **Oral liquid:** 7.5 mg/5 mL. |
| **3. ANTIALLERGICS AND MEDICINES USED IN ANAPHYLAXIS** | |
| dexamethasone | **Injection:** 4 mg/ mL in 1- mL ampoule (as disodium phosphate salt). |
| epinephrine (adrenaline) | **Injection:** 1 mg (as hydrochloride or hydrogen tartrate) in 1- mL ampoule. |
| hydrocortisone | **Powder for injection:** 100 mg (as sodium succinate) in vial. |

| | |
|---|---|
| **3. ANTIALLERGICS AND MEDICINES USED IN ANAPHYLAXIS** *(continued)* | |
| ☐ loratadine* | **Oral liquid:** 1 mg/ mL.<br>**Tablet:** 10 mg.<br>* There may be a role for sedating antihistamines for limited indications (EMLc). |
| ☐ prednisolone | **Oral liquid:** 5 mg/ mL [c].<br>**Tablet:** 5 mg; 25 mg. |
| **4. ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS** | |
| **4.1 Non-specific** | |
| charcoal, activated | **Powder.** |
| **4.2 Specific** | |
| acetylcysteine | **Injection:** 200 mg/ mL in 10- mL ampoule.<br>**Oral liquid:** 10% [c]; 20% [c]. |
| atropine | **Injection:** 1 mg (sulfate) in 1- mL ampoule. |
| calcium gluconate | **Injection:** 100 mg/ mL in 10- mL ampoule. |
| methylthioninium chloride (methylene blue) | **Injection:** 10 mg/ mL in 10- mL ampoule. |
| naloxone | **Injection:** 400 micrograms (hydrochloride) in 1- mL ampoule. |
| penicillamine | **Solid oral dosage form:** 250 mg. |
| potassium ferric hexacyano-ferrate(II) -2$H_2O$(Prussian blue) | **Powder for oral administration.** |
| sodium nitrite | **Injection:** 30 mg/ mL in 10- mL ampoule. |
| sodium thiosulfate | **Injection:** 250 mg/ mL in 50- mL ampoule. |
| ***Complementary List*** | |
| *deferoxamine* | ***Powder for injection:*** *500 mg (mesilate) in vial.* |
| *dimercaprol* | ***Injection in oil:*** *50 mg/ mL in 2- mL ampoule.* |
| *fomepizole* | ***Injection:*** *5 mg/ mL (sulfate) in 20- mL ampoule or 1 g/ mL (base) in 1.5- mL ampoule.* |
| *sodium calcium edetate* | **Injection:** *200 mg/ mL in 5- mL ampoule.* |
| *succimer* | ***Solid oral dosage form:*** *100 mg.* |

| 5. ANTICONVULSANTS/ANTIEPILEPTICS | |
|---|---|
| carbamazepine | **Oral liquid:** 100 mg/5 mL.<br>**Tablet (chewable):** 100 mg; 200 mg.<br>**Tablet (scored):** 100 mg; 200 mg. |
| diazepam | **Gel or rectal solution:** 5 mg/ mL in 0.5 mL; 2- mL; 4- mL tubes. |
| lamotrigine* | **Tablet:** 25 mg; 50 mg; 100 mg; 200 mg.<br>**Tablet (chewable, dispersible):** 2 mg; 5 mg; 25 mg; 50 mg; 100 mg; 200 mg.<br>* As adjunctive therapy for treatment-resistant partial or generalized seizures. |
| ☐ lorazepam | **Parenteral formulation:** 2 mg/ mL in 1- mL ampoule; 4 mg/ mL in 1- mL ampoule. |
| magnesium sulfate* | **Injection:** 0.5g/ mL in 2- mL ampoule (equivalent to 1 g in 2 mL; 50% weight/volume); 0.5g/ mL in 10- mL ampoule (equivalent to 5 g in 10 mL; 50% weight/ volume).<br>* For use in eclampsia and severe pre-eclampsia and not for other convulsant disorders. |
| midazolam | **Solution for oromucosal administration:** 5 mg/mL; 10 mg/mL.<br>**Ampoule*:** 1 mg/ mL; 10 mg/mL.<br>* For buccal administration when solution for oromucosal administration is not available. |
| phenobarbital | **Injection:** 200 mg/ mL (sodium).<br>**Oral liquid:** 15 mg/5 mL.<br>**Tablet:** 15 mg to 100 mg. |
| phenytoin | **Injection:** 50 mg/ mL in 5- mL vial (sodium salt).<br>**Oral liquid:** 25 mg to 30 mg/5 mL.*<br>**Solid oral dosage form:** 25 mg; 50 mg; 100 mg (sodium salt).<br>**Tablet (chewable):** 50 mg.<br>* The presence of both 25 mg/5 mL and 30 mg/5 mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided. |
| valproic acid (sodium valproate) | **Oral liquid:** 200 mg/5 mL.<br>**Tablet (crushable):** 100 mg.<br>**Tablet (enteric-coated):** 200 mg; 500 mg (sodium valproate). |

| **5. ANTICONVULSANTS/ANTIEPILEPTICS** *(continued)* | |
|---|---|
| ***Complementary List*** | |
| *ethosuximide* | ***Capsule:*** *250 mg.*<br>***Oral liquid:*** *250 mg/5 mL.* |
| *valproic acid (sodium valproate)* | ***Injection:*** *100 mg/ mL in 4- mL ampoule; 100 mg/ mL in 10- mL ampoule.* |

| **6. ANTI-INFECTIVE MEDICINES** | |
|---|---|
| **6.1 Anthelminthics** | |
| **6.1.1** ***Intestinal anthelminthics*** | |
| albendazole | **Tablet (chewable):** 400 mg. |
| ivermectin | **Tablet (scored):** 3 mg. |
| levamisole | **Tablet:** 50 mg; 150 mg (as hydrochloride). |
| mebendazole | **Tablet (chewable):** 100 mg; 500 mg. |
| niclosamide | **Tablet (chewable):** 500 mg. |
| praziquantel | **Tablet:** 150 mg; 600 mg. |
| pyrantel | **Oral liquid:** 50 mg (as embonate **or** pamoate)/ mL.<br>**Tablet (chewable):** 250 mg (as embonate **or** pamoate). |
| **6.1.2** ***Antifilarials*** | |
| albendazole | **Tablet (chewable):** 400 mg. |
| diethylcarbamazine | **Tablet:** 50 mg; 100 mg (dihydrogen citrate). |
| ivermectin | **Tablet (scored):** 3 mg. |
| **6.1.3** ***Antischistosomals and other antitrematode medicines*** | |
| praziquantel | **Tablet:** 600 mg. |
| triclabendazole | **Tablet:** 250 mg. |
| ***Complementary List*** | |
| *oxamniquine** | ***Capsule:*** *250 mg.*<br>***Oral liquid:*** *250 mg/5 mL.*<br>** Oxamniquine is listed for use when praziquantel treatment fails.* |

## 6. ANTI-INFECTIVE MEDICINES *(continued)*

### 6.2 Antibacterials

To assist in the development of tools for antibiotic stewardship at local, national and global levels and to reduce antimicrobial resistance, the Access, Watch, Reserve (AWaRe) classification of antibiotics was developed – where antibiotics are classified into different groups to emphasize the importance of their appropriate use.

**ACCESS GROUP ANTIBIOTICS**

This group includes antibiotics that have activity against a wide range of commonly encountered susceptible pathogens while also showing lower resistance potential than antibiotics in the other groups. Selected Access group antibiotics are recommended as essential first or second choice empiric treatment options for infectious syndromes reviewed by the EML Expert Committee and are listed as individual medicines on the Model Lists to improve access and promote appropriate use. They are essential antibiotics that should be widely available, affordable and quality assured.

**WATCH GROUP ANTIBIOTICS**

This group includes antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine[1] and/or antibiotics that are at relatively high risk of selection of bacterial resistance. These medicines should be prioritized as key targets of stewardship programs and monitoring. Selected Watch group antibiotics are recommended as essential first or second choice empiric treatment options for a limited number of specific infectious syndromes and are listed as individual medicines on the Model Lists.

[1] http://apps.who.int/iris/bitstream/10665/251715/1/9789241511469-eng.pdf?ua=1

**RESERVE GROUP ANTIBIOTICS**

This group includes antibiotics and antibiotic classes that should be reserved for treatment of confirmed or suspected infections due to multi-drug-resistant organisms. Reserve group antibiotics should be treated as "last resort" options. Selected Reserve group antibiotics are listed as individual medicines on the Model Lists when they have a favourable risk-benefit profile and proven activity against "Critical Priority" or "High Priority" pathogens identified by the WHO Priority Pathogens List[1], notably carbapenem resistant *Enterobacteriaceae*. These antibiotics should be accessible, but their use should be tailored to highly specific patients and settings, when all alternatives have failed or are not suitable. These medicines could be protected and prioritized as key targets of national and international stewardship programs involving monitoring and utilization reporting, to preserve their effectiveness.

[1] https://apps.who.int/iris/handle/10665/311820

## 6. ANTI-INFECTIVE MEDICINES *(continued)*

### 6.2.1 *Access group antibiotics*

| | | |
|---|---|---|
| amikacin | **Injection:** 250 mg (as sulfate)/mL in 2- mL vial | |
| | **FIRST CHOICE**<br>– *pyelonephritis or prostatitis (severe)*<br>– *high-risk febrile neutropenia* | **SECOND CHOICE**<br>– *sepsis in neonates and children* [c] |
| amoxicillin | **Powder for oral liquid:** 125 mg (as trihydrate)/5 mL; 250 mg (as trihydrate)/5 mL [c].<br>**Solid oral dosage form:** 250 mg; 500 mg (as trihydrate).<br>**Powder for injection:** 250 mg; 500 mg; 1 g (as sodium) in vial. | |
| | **FIRST CHOICE**<br>– *community acquired pneumonia (mild to moderate)*<br>– *community acquired pneumonia (severe)* [c]<br>– *complicated severe acute malnutrition* [c]<br>– *exacerbations of COPD*<br>– *lower urinary tract infections*<br>– *otitis media*<br>– *pharyngitis*<br>– *sepsis in neonates and children* [c]<br>– *sinusitis*<br>– *uncomplicated severe acute malnutrition* [c]<br>– *progressive apical dental abscess* | **SECOND CHOICE**<br>– *acute bacterial meningitis* |

**6. ANTI-INFECTIVE MEDICINES** *(continued)*

| | | |
|---|---|---|
| amoxicillin + clavulanic acid | **Oral liquid:** 125 mg amoxicillin + 31.25 mg clavulanic acid/5 mL AND 250 mg amoxicillin + 62.5 mg clavulanic acid/5 mL [c].<br>**Tablet:** 500 mg (as trihydrate) + 125 mg (as potassium salt).<br>**Powder for injection:** 500 mg (as sodium) + 100 mg (as potassium salt); 1000 mg (as sodium) + 200 mg (as potassium salt) in vial. | |
| | **FIRST CHOICE**<br>– *community acquired pneumonia (severe)* [c]<br>– *complicated intraabdominal infections (mild to moderate)*<br>– *exacerbations of COPD*<br>– *hospital acquired pneumonia*<br>– *low-risk febrile neutropenia*<br>– *lower urinary tract infections*<br>– *sinusitis*<br>– *skin and soft tissue infections* | **SECOND CHOICE**<br>– *bone and joint infections*<br>– *community-acquired pneumonia (mild to moderate)*<br>– *community acquired pneumonia (severe)*<br>– *otitis media*<br>– *surgical prophylaxis* |
| ampicillin | **Powder for injection:** 500 mg; 1 g (as sodium salt) in vial. | |
| | **FIRST CHOICE**<br>– *community acquired pneumonia (severe)* [c]<br>– *complicated severe acute malnutrition* [c]<br>– *sepsis in neonates and children* [c] | **SECOND CHOICE**<br>– *acute bacterial meningitis* |
| benzathine benzylpenicillin | **Powder for injection:** 900 mg benzylpenicillin (= 1.2 million IU) in 5- mL vial [c]; 1.44 g benzylpenicillin (= 2.4 million IU) in 5- mL vial. | |
| | **FIRST CHOICE**<br>– *syphilis* | **SECOND CHOICE** |

**6. ANTI-INFECTIVE MEDICINES** *(continued)*

benzylpenicillin

**Powder for injection:** 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial.

| FIRST CHOICE | SECOND CHOICE |
|---|---|
| – *community acquired pneumonia (severe)* [c]<br>– *complicated severe acute malnutrition* [c]<br>– *sepsis in neonates and children* [c]<br>– *syphilis* | – *acute bacterial meningitis* [c] |

cefalexin

**Powder for reconstitution with water:** 125 mg/5 mL; 250 mg/5 mL (anhydrous).

**Solid oral dosage form:** 250 mg (as monohydrate).

| FIRST CHOICE | SECOND CHOICE |
|---|---|
| | – *exacerbations of COPD*<br>– *pharyngitis*<br>– *skin and soft tissue infections* |

cefazolin [a]

Powder for injection: 1 g (as sodium salt) in vial.

[a] >1 month.

| FIRST CHOICE | SECOND CHOICE |
|---|---|
| – *surgical prophylaxis* | – *bone and joint infections* |

chloramphenicol

**Capsule:** 250 mg.

**Oily suspension for injection*:** 0.5 g (as sodium succinate)/ mL in 2- mL ampoule.

* Only for the presumptive treatment of epidemic meningitis in children older than 2 years and in adults.

**Oral liquid:** 150 mg (as palmitate)/5 mL.

**Powder for injection:** 1 g (sodium succinate) in vial.

| FIRST CHOICE | SECOND CHOICE |
|---|---|
| | – *acute bacterial meningitis* |

clindamycin

**Capsule:** 150 mg (as hydrochloride).

**Injection**: 150 mg (as phosphate)/ mL.

**Oral liquid:** 75 mg/5 mL (as palmitate) [c].

| FIRST CHOICE | SECOND CHOICE |
|---|---|
| | – *bone and joint infections* |

**6. ANTI-INFECTIVE MEDICINES** *(continued)*

☐ cloxacillin*

**Capsule:** 500 mg; 1 g (as sodium salt).

**Powder for injection:** 500 mg (as sodium salt) in vial.

**Powder for oral liquid:** 125 mg (as sodium salt)/5 mL.

* Cloxacillin, dicloxacillin and flucloxacillin are preferred for oral administration due to better bioavailability.

| FIRST CHOICE | SECOND CHOICE |
|---|---|
| – *bone and joint infections*<br>– *skin and soft tissue infections* | – *sepsis in neonates and children* [c] |

doxycycline [a]

**Oral liquid:** 25 mg/5 mL [c]; 50 mg/5 mL (anhydrous) [c].

**Solid oral dosage form:** 50 mg [c]; 100 mg (as hyclate).

**Powder for injection:** 100 mg in vial.

[a] Use in children <8 years only for life-threatening infections when no alternative exists.

| FIRST CHOICE | SECOND CHOICE |
|---|---|
| – *sexually transmitted infection due to Chlamydia trachomatis*<br>– *cholera* | – *cholera* [c]<br>– *community acquired pneumonia (mild to moderate)*<br>– *exacerbations of COPD* |

gentamicin

**Injection:** 10 mg; 40 mg (as sulfate)/ mL in 2- mL vial.

| FIRST CHOICE | SECOND CHOICE |
|---|---|
| – *community acquired pneumonia (severe)* [c]<br>– *complicated severe acute malnutrition* [c]<br>– *sepsis in neonates and children* [c] | – *gonorrhoea*<br>– *surgical prophylaxis* |

**6. ANTI-INFECTIVE MEDICINES** *(continued)*

| | | |
|---|---|---|
| metronidazole | **Injection:** 500 mg in 100- mL vial.<br>**Oral liquid:** 200 mg (as benzoate)/5 mL.<br>**Suppository:** 500 mg; 1 g.<br>**Tablet:** 200 mg to 500 mg. | |
| | **FIRST CHOICE**<br>– *C. difficile infection*<br>– *complicated intraabdominal infections (mild to moderate)*<br>– *complicated intraabdominal infections (severe)*<br>– *trichomoniasis*<br>– *surgical prophylaxis* | **SECOND CHOICE**<br>– *complicated intraabdominal infections (mild to moderate)* |
| nitrofurantoin | **Oral liquid:** 25 mg/5 mL [c].<br>**Tablet:** 100 mg. | |
| | **FIRST CHOICE**<br>– *lower urinary tract infections* | **SECOND CHOICE** |
| phenoxymethylpenicillin | **Powder for oral liquid:** 250 mg (as potassium salt)/5 mL.<br>**Tablet:** 250 mg (as potassium salt). | |
| | **FIRST CHOICE**<br>– *community acquired pneumonia (mild to moderate)*<br>– *pharyngitis*<br>– *progressive apical dental abscess* | **SECOND CHOICE** |
| procaine benzylpenicillin* | **Powder for injection:** 1 g (=1 million IU); 3 g (=3 million IU) in vial.<br>* Procaine benzylpenicillin is not recommended as first-line treatment for neonatal sepsis except in settings with high neonatal mortality, when given by trained health workers in cases where hospital care is not achievable. | |
| | **FIRST CHOICE**<br>– *syphilis* [c] | **SECOND CHOICE**<br>– *syphilis* |

**6. ANTI-INFECTIVE MEDICINES** *(continued)*

spectinomycin

**Powder for injection:** 2 g (as hydrochloride) in vial.

| FIRST CHOICE | SECOND CHOICE |
|---|---|
| | – *gonorrhoea* |

sulfamethoxazole + trimethoprim*

**Injection:**
80 mg + 16 mg/ mL in 5- mL ampoule;
80 mg + 16 mg/ mL in 10- mL ampoule.

**Oral liquid:** 200 mg + 40 mg/5 mL.

**Tablet:** 100 mg + 20 mg; 400 mg + 80 mg; 800 mg + 160 mg.

* Single agent trimethoprim may be an alternative for lower urinary tract infection.

| FIRST CHOICE | SECOND CHOICE |
|---|---|
| – *lower urinary tract infections* | – *acute invasive diarrhoea / bacterial dysentery* |

**6.2.2** ***Watch group antibiotics***

azithromycin*

**Capsule:** 250 mg; 500 mg (anhydrous).

**Oral liquid:** 200 mg/5 mL.

* Also listed for single-dose treatment of trachoma and yaws.

| FIRST CHOICE | SECOND CHOICE |
|---|---|
| – *sexually transmitted infection due to Chlamydia trachomatis*<br>– *cholera* [c]<br>– *gonorrhoea*<br>– *enteric fever* | – *acute invasive bacterial diarrhoea / dysentery*<br>– *gonorrhoea* |

cefixime

**Capsule or tablet:** 200 mg; 400 mg (as trihydrate).

**Powder for oral liquid:** 100 mg /5 mL [c].

| FIRST CHOICE | SECOND CHOICE |
|---|---|
| | – *acute invasive bacterial diarrhoea / dysentery*<br>– *gonorrhoea* |

**6. ANTI-INFECTIVE MEDICINES** *(continued)*

cefotaxime*

**Powder for injection:** 250 mg per vial (as sodium salt).

* 3rd generation cephalosporin of choice for use in hospitalized neonates.

| FIRST CHOICE | SECOND CHOICE |
|---|---|
| – *acute bacterial meningitis*<br>– *community acquired pneumonia (severe)*<br>– *complicated intraabdominal infections (mild to moderate)*<br>– *complicated intraabdominal infections (severe)*<br>– *hospital acquired pneumonia*<br>– *pyelonephritis or prostatitis (severe)* | – *bone and joint infections*<br>– *pyelonephritis or prostatitis (mild to moderate)*<br>– *sepsis in neonates and children* [c] |

ceftriaxone* [a]

**Powder for injection:** 250 mg; 1 g (as sodium salt) in vial.

* Do not administer with calcium and avoid in infants with hyperbilirubinaemia.

[a] >41 weeks corrected gestational age.

| FIRST CHOICE | SECOND CHOICE |
|---|---|
| – *acute bacterial meningitis*<br>– *community acquired pneumonia (severe)*<br>– *complicated intraabdominal infections (mild to moderate)*<br>– *complicated intraabdominal infections (severe)*<br>– *hospital acquired pneumonia*<br>– *gonorrhoea*<br>– *pyelonephritis or prostatitis (severe)*<br>– *enteric fever* | – *acute invasive bacterial diarrhoea / dysentery*<br>– *bone and joint infections*<br>– *pyelonephritis or prostatitis (mild to moderate)*<br>– *sepsis in neonates and children* [c] |

| **6. ANTI-INFECTIVE MEDICINES** *(continued)* | | |
|---|---|---|
| cefuroxime | **Powder for injection:** 250 mg, 750 mg, 1.5 g (as sodium salt) in vial | |
| | **FIRST CHOICE** | **SECOND CHOICE**<br>– *surgical prophylaxis* |
| ciprofloxacin | **Oral liquid:** 250 mg/5 mL (anhydrous) [c].<br>**Solution for IV infusion:** 2 mg/ mL (as hyclate) [c].<br>**Tablet**: 250 mg (as hydrochloride). | |
| | **FIRST CHOICE**<br>– *acute invasive bacterial diarrhoea / dysentery*<br>– *low-risk febrile neutropenia*<br>– *pyelonephritis or prostatitis (mild to moderate)*<br>– *enteric fever* | **SECOND CHOICE**<br>– *cholera*<br>– *complicated intraabdominal infections (mild to moderate)* |
| clarithromycin*† | **Solid oral dosage form:** 500 mg.<br>**Powder for oral liquid:** 125 mg/5 mL; 250 mg/5 mL<br>**Powder for injection:** 500 mg in vial<br>* Erythromycin may be an alternative.<br>† Clarithromycin is also listed for use in combination regimens for eradication of *H. pylori* in adults. | |
| | **FIRST CHOICE**<br>– *community acquired pneumonia (severe)* | **SECOND CHOICE**<br>– *pharyngitis* |
| piperacillin + tazobactam | **Powder for injection:** 2 g (as sodium salt) + 250 mg (as sodium salt); 4 g (as sodium salt) + 500 mg (as sodium salt) in vial | |
| | **FIRST CHOICE**<br>– *complicated intraabdominal infections (severe)*<br>– *high-risk febrile neutropenia*<br>– *hospital acquired pneumonia* | **SECOND CHOICE** |

**6. ANTI-INFECTIVE MEDICINES** *(continued)*

vancomycin — **Capsule:** 125 mg; 250 mg (as hydrochloride).

| | |
|---|---|
| | **SECOND CHOICE**<br>– *C. difficile infection* |

***Complementary List***

*ceftazidime* — ***Powder for injection:*** *250 mg or 1 g (as pentahydrate) in vial.*

*meropenem** [a] — ***Powder for injection:*** *500 mg (as trihydrate); 1 g (as trihydrate) in vial*

[a] >3 months.

* *Imipenem + cilastatin is an alternative except for acute bacterial meningitis where meropenem is preferred.*

| | |
|---|---|
| **FIRST CHOICE** | **SECOND CHOICE**<br>– *acute bacterial meningitis in neonates [c]*<br>– *complicated intraabdominal infections (severe)*<br>– *high-risk febrile neutropenia* |

*vancomycin* — ***Powder for injection:*** *250 mg (as hydrochloride) in vial.*

| | |
|---|---|
| **FIRST CHOICE** | **SECOND CHOICE**<br>– *high-risk febrile neutropenia* |

**6.2.3** ***Reserve group antibiotics***

***Complementary List***

*ceftazidime + avibactam* — ***Powder for injection:*** *2 g + 0.5 g in vial*

*colistin* — ***Powder for injection:*** *1 million I.U. (as colistemethate sodium) in vial*

*fosfomycin* — ***Powder for injection:*** *2 g; 4 g (as sodium) in vial*

*linezolid* — ***Injection for intravenous administration:*** *2 mg/ mL in 300 mL bag.*

***Powder for oral liquid:*** *100 mg/5 mL.*

***Tablet:*** *400 mg; 600 mg.*

| **6. ANTI-INFECTIVE MEDICINES** *(continued)* | |
|---|---|
| *meropenem + vaborbactam* | ***Powder for injection:*** *1 g + 1 g in vial* |
| *plazomicin* | ***Injection****: 500 mg/10 mL* |
| *polymyxin B* | ***Powder for injection:*** *500,000 I.U. in vial* |

**6.2.4** ***Antileprosy medicines***

Medicines used in the treatment of leprosy should never be used except in combination. Combination therapy is essential to prevent the emergence of drug resistance. Colour-coded blister packs (MDT blister packs) containing standard two-medicine (paucibacillary leprosy) or three-medicine (multibacillary leprosy) combinations for adult and childhood leprosy should be used. MDT blister packs can be supplied free of charge through WHO.

| | |
|---|---|
| clofazimine | **Capsule:** 50 mg; 100 mg. |
| dapsone | **Tablet:** 25 mg; 50 mg; 100 mg. |
| rifampicin | **Solid oral dosage form:** 150 mg; 300 mg. |

## 6. ANTI-INFECTIVE MEDICINES *(continued)*

### 6.2.5 *Antituberculosis medicines*

WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.

| | |
|---|---|
| ethambutol | **Oral liquid:** 25 mg/ mL [c].<br>**Tablet:** 100 mg to 400 mg (hydrochloride).<br>**Tablet (dispersible):** 100 mg [c]. |
| ethambutol + isoniazid + pyrazinamide + rifampicin | **Tablet:** 275 mg + 75 mg + 400 mg + 150 mg. |
| ethambutol + isoniazid + rifampicin | **Tablet:** 275 mg + 75 mg + 150 mg. |
| isoniazid | **Oral liquid:** 50 mg/5 mL [c].<br>**Tablet:** 100 mg to 300 mg.<br>**Tablet (scored):** 50 mg.<br>**Tablet (dispersible):** 100 mg [c]. |
| isoniazid + pyrazinamide + rifampicin | **Tablet:** 75 mg + 400 mg + 150 mg.<br>**Tablet (dispersible):** 50 mg + 150 mg + 75 mg [c]. |
| isoniazid + rifampicin | **Tablet:** 75 mg + 150 mg; 150 mg + 300 mg.<br>**Tablet (dispersible):** 50 mg + 75 mg [c]. |
| pyrazinamide | **Oral liquid:** 30 mg/ mL [c].<br>**Tablet:** 400 mg.<br>**Tablet (dispersible):** 150 mg.<br>**Tablet (scored):** 150 mg. |
| rifabutin | Solid oral dosage form: 150 mg.*<br>* For use only in patients with HIV receiving protease inhibitors. |
| rifampicin | **Oral liquid:** 20 mg/ mL [c].<br>**Solid oral dosage form:** 150 mg; 300 mg. |
| rifapentine* | **Tablet:** 150 mg<br>* For treatment of latent TB infection (LTBI) only. |

## 6. ANTI-INFECTIVE MEDICINES *(continued)*

***Complementary List***

***Medicines for the treatment of multidrug-resistant tuberculosis (MDR-TB) should be used in specialized centres adhering to WHO standards for TB control.***

| | |
|---|---|
| *amikacin* | ***Powder for injection:*** *100 mg; 500 mg; 1 g (as sulfate) in vial.* |
| *amoxicillin + clavulanic acid** | ***Oral liquid:*** *125 mg amoxicillin + 31.25 mg clavulanic acid/5 mL; 250 mg amoxicillin + 62.5 mg clavulanic acid/5 mL* **[c]** *.*<br>***Tablet:*** *500 mg (as trihydrate) + 125 mg (as potassium salt).*<br>* *For use only in combination with meropenem or imipenem+cilastatin* |
| *bedaquiline* **a** | ***Tablet:*** *100 mg.*<br>**a** ≥6 years. |
| *clofazimine* | ***Solid oral dosage form:*** *50 mg; 100 mg.* |
| *cycloserine** | ***Solid oral dosage form:*** *125 mg* **[c]** *; 250 mg.*<br>* *Terizidone may be an alternative.* |
| *delamanid* **a** | ***Tablet:*** *50 mg.*<br>**a** ≥6 years |
| *ethionamide** | ***Tablet:*** *125 mg; 250 mg.*<br>***Tablet (dispersible):*** *125 mg* **[c]** *.*<br>* *Protionamide may be an alternative.* |
| *levofloxacin* | ***Tablet:*** *250mg; 500 mg; 750 mg.*<br>***Tablet (dispersible):*** *100 mg* **[c]** *.* |
| *linezolid* | ***Injection for intravenous administration:*** *2 mg/ mL in 300 mL bag.*<br>***Powder for oral liquid:*** *100 mg/5 mL.*<br>***Tablet:*** *400 mg; 600 mg.*<br>***Tablet (dispersible):*** *150 mg* **[c]** *.* |
| *meropenem** | ***Powder for injection:*** *500 mg (as trihydrate); 1 g (as trihydrate) in vial.*<br>* *Imipenem+cilastatin may be an alternatiave.* |
| *moxifloxacin* | ***Tablet:*** *400 mg.*<br>***Tablet (dispersible):*** *100 mg* **[c]** *.* |
| *p-aminosalicylic acid* | ***Granules:*** *4 g in sachet.*<br>***Tablet:*** *500 mg.* |
| *streptomycin* **[c]** | ***Powder for injection:*** *1 g (as sulfate) in vial.* |

## 6. ANTI-INFECTIVE MEDICINES *(continued)*

### 6.3 Antifungal medicines

| | |
|---|---|
| amphotericin B | **Powder for injection:** 50 mg in vial (as sodium deoxycholate **or** liposomal complex). |
| clotrimazole | **Vaginal cream:** 1%; 10%.<br>**Vaginal tablet:** 100 mg; 500 mg. |
| fluconazole | **Capsule:** 50 mg.<br>**Injection:** 2 mg/ mL in vial.<br>**Oral liquid:** 50 mg/5 mL. |
| flucytosine | **Capsule:** 250 mg.<br>**Infusion:** 2.5 g in 250 mL. |
| griseofulvin | **Oral liquid:** 125 mg/5 mL [c].<br>**Solid oral dosage form:** 125 mg; 250 mg. |
| itraconazole* | **Capsule**: 100 mg.<br>**Oral liquid**: 10 mg/mL.<br>* For treatment of chronic pulmonary aspergillosis, histoplasmosis, sporotrichosis, paracoccidiodomycosis, mycoses caused by *T. marneffei* and chromoblastomycosis; and prophylaxis of histoplasmosis and infections caused by *T. marneffei* in AIDS patients. |
| nystatin | **Lozenge:** 100 000 IU.<br>**Oral liquid:** 50 mg/5 mL [c]; 100 000 IU/ mL [c].<br>**Pessary:** 100 000 IU.<br>**Tablet:** 100 000 IU; 500 000 IU. |
| voriconazole* | **Tablet:** 50 mg; 200 mg.<br>**Powder for injection**: 200 mg in vial.<br>P**owder for oral liquid:** 40 mg/mL.<br>* For treatment of chronic pulmonary aspergillosis and acute invasive aspergillosis. |
| ***Complementary List*** | |
| *potassium iodide* | ***Saturated solution.*** |

## 6. ANTI-INFECTIVE MEDICINES *(continued)*

### 6.4 Antiviral medicines

#### 6.4.1 *Antiherpes medicines*

| | |
|---|---|
| ☐ aciclovir | **Oral liquid:** 200 mg/5 mL [c].<br>**Powder for injection:** 250 mg (as sodium salt) in vial.<br>**Tablet:** 200 mg. |

#### 6.4.2 *Antiretrovirals*

Based on current evidence and experience of use, medicines in the following classes of antiretrovirals are included as essential medicines for treatment and prevention of HIV (prevention of mother-to-child transmission, pre-exposure prophylaxis (where indicated) and post-exposure prophylaxis). WHO emphasizes the importance of using these products in accordance with global and national guidelines. WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.

Scored tablets can be used in children and therefore can be considered for inclusion in the listing of tablets, provided that adequate quality products are available.

##### 6.4.2.1 *Nucleoside/Nucleotide reverse transcriptase inhibitors*

| | |
|---|---|
| abacavir (ABC) | **Tablet:** 300 mg (as sulfate).<br>**Tablet (dispersible, scored):** 60 mg (as sulfate) [c]. |
| lamivudine (3TC) | **Oral liquid:** 50 mg/5 mL [c].<br>**Tablet:** 150 mg. |
| tenofovir disoproxil fumarate† (TDF) | **Tablet:** 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil).<br>† Also indicated for pre-exposure prophylaxis. |
| zidovudine (ZDV **or** AZT) | **Capsule:** 250 mg.<br>**Oral liquid:** 50 mg/5 mL.<br>**Solution for IV infusion injection:** 10 mg/ mL in 20- mL vial.<br>**Tablet:** 300 mg. |

##### 6.4.2.2 *Non-nucleoside reverse transcriptase inhibitors*

| | |
|---|---|
| efavirenz (EFV **or** EFZ) [a] | **Tablet:** 200 mg (scored); 600 mg.<br>[a] >3 years or >10 kg weight. |
| nevirapine (NVP) [a] | **Oral liquid:** 50 mg/5 mL.<br>**Tablet:** 50 mg (dispersible); 200 mg.<br>[a] >6 weeks. |

**6. ANTI-INFECTIVE MEDICINES** *(continued)*

**6.4.2.3** ***Protease inhibitors***

Selection of protease inhibitor(s) from the Model List will need to be determined by each country after consideration of international and national treatment guidelines and experience. Ritonavir is recommended for use in combination as a pharmacological booster, and not as an antiretroviral in its own right. All other protease inhibitors should be used in boosted forms (e.g. with ritonavir).

| | |
|---|---|
| atazanavir [a] | **Solid oral dosage form:** 100 mg; 300 mg (as sulfate).<br>[a] >25 kg. |
| atazanavir + ritonavir | **Tablet (heat stable):** 300 mg (as sulfate) + 100 mg. |
| darunavir [a] | **Tablet:** 75 mg; 400 mg; 600 mg; 800 mg.<br>[a] >3 years. |
| lopinavir + ritonavir (LPV/r) | **Oral liquid:** 400 mg + 100 mg/5 mL.<br>**Tablet (heat stable):** 100 mg + 25 mg; 200 mg + 50 mg.<br>**Solid oral dosage form:** 40 mg + 10 mg [c]. |
| ritonavir | **Oral liquid:** 400 mg/5 mL.<br>**Tablet (heat stable):** 25 mg; 100 mg.<br>**Oral powder:** 100 mg in sachet [c]. |

**6. ANTI-INFECTIVE MEDICINES** *(continued)*

**6.4.2.4** ***Integrase inhibitors***

| | |
|---|---|
| dolutegravir [a] | **Tablet:** 50 mg.<br>[a] ≥25 kg. |
| raltegravir* | **Tablet (chewable):** 25 mg; 100 mg.<br>**Tablet:** 400 mg.<br>**Granules for oral suspension:** 100 mg in sachet.<br>* For use in pregnant women and in second-line regimens in accordance with WHO treatemnt guidelines. |

***FIXED-DOSE COMBINATIONS***

| | |
|---|---|
| abacavir + lamivudine | **Tablet (dispersible, scored):** 120 mg (as sulfate) + 60 mg. |
| dolutegravir + lamivudine + tenofovir | **Tablet:** 50 mg + 300 mg + 300 mg (disoproxil fumarate equivalent to 245 mg tenofovir disoproxil). |
| efavirenz + emtricitabine* + tenofovir | **Tablet:** 600 mg + 200 mg + 300 mg (disoproxil fumarate equivalent to 245 mg tenofovir disoproxil).<br>* Emtricitabine (FTC) is an acceptable alternative to 3TC, based on knowledge of the pharmacology, the resistance patterns and clinical trials of antiretrovirals. |
| efavirenz + lamivudine + tenofovir | **Tablet:** 400 mg + 300 mg + 300 mg (disoproxil fumarate equivalent to 245 mg tenofovir disoproxil). |
| emtricitabine* + tenofovir† | **Tablet:** 200 mg + 300 mg (disoproxil fumarate equivalent to 245 mg tenofovir disoproxil).<br>* Emtricitabine (FTC) is an acceptable alternative to 3TC, based on knowledge of the pharmacology, the resistance patterns and clinical trials of antiretrovirals.<br>† Combination also indicated for pre-exposure prophylaxis. |
| lamivudine + nevirapine + zidovudine | **Tablet:** 30 mg + 50 mg + 60 mg [c]; 150 mg + 200 mg + 300 mg. |
| lamivudine + zidovudine | **Tablet:** 30 mg + 60 mg [c]; 150 mg + 300 mg. |

**6.4.2.5** ***Medicines for prevention of HIV-related opportunistic infections***

| | |
|---|---|
| isoniazid + pyridoxine + sulfamethoxazole + trimethoprim | **Tablet (scored):** 300 mg + 25 mg + 800 mg + 160 mg |

| **6. ANTI-INFECTIVE MEDICINES** *(continued)* | |
|---|---|
| **6.4.3** ***Other antivirals*** | |
| ribavirin* | **Injection for intravenous administration:** 800 mg and 1 g in 10- mL phosphate buffer solution.<br>**Solid oral dosage form:** 200 mg; 400 mg; 600 mg.<br>* For the treatment of viral haemorrhagic fevers. |
| valganciclovir* | **Tablet:** 450 mg.<br>* For the treatment of cytomegalovirus retinitis (CMVr). |
| ***Complementary list*** | |
| *oseltamivir** | ***Capsule:*** *30 mg; 45 mg; 75 mg (as phosphate).*<br>***Oral powder:*** *12 mg/ mL.*<br>* *Severe illness due to confirmed or suspected influenza virus infection in critically ill hospitalized patients.* |
| *valganciclovir** ***[c]*** | ***Powder for oral solution:*** *50 mg/ mL.*<br>***Tablet****: 450 mg.*<br>* *For the treatment of cytomegalovirus retinitis (CMVr).* |

## 6. ANTI-INFECTIVE MEDICINES *(continued)*

### 6.4.4 *Antihepatitis medicines*

#### 6.4.4.1 *Medicines for hepatitis B*

##### 6.4.4.1.1 *Nucleoside/Nucleotide reverse transcriptase inhibitors*

| | |
|---|---|
| entecavir | **Oral liquid:** 0.05 mg/ mL.<br>**Tablet:** 0.5 mg; 1 mg. |
| tenofovir disoproxil fumarate (TDF) | **Tablet:** 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil). |

#### 6.4.4.2 *Medicines for hepatitis C*

WHO guidelines recommend the use of pangenotypic direct-acting antiviral (DAA) regimens for the treatment of persons with chronic HCV infection aged 18 years and above.

WHO recommended treatment regimens for adolescents aged 12-17 years or weighing at least 35 kg with chronic HCV infection are genotype-specific.

**Pangenotypic DAAs should be considered as therapeutically equivalent for the purposes of selection and procurement at national level.**

##### 6.4.4.2.1 ☐ *Pangenotypic direct-acting antiviral combinations*

| | |
|---|---|
| daclatasvir* | **Tablet:** 30 mg; 60 mg (as hydrochloride)<br>* Pangenotypic when used in combination with sofosbuvir. |
| glecaprevir + pibrentasvir | **Tablet:** 100 mg + 40 mg |
| sofosbuvir* | **Tablet:** 400 mg<br>* Pangenotypic when used in combination with daclatasvir. |
| sofosbuvir + velpatasvir | **Tablet:** 400 mg + 100 mg |

##### 6.4.4.2.2 *Non-pangenotypic direct-acting antiviral combinations*

| | |
|---|---|
| dasabuvir | **Tablet:** 250 mg |
| ledipasvir + sofosbuvir | **Tablet:** 90 mg + 400 mg. |
| ombitasvir + paritaprevir + ritonavir | **Tablet:** 12.5 mg + 75 mg + 50 mg |

##### 6.4.4.2.3 *Other antivirals for hepatitis C*

| | |
|---|---|
| ribavirin* | **Injection for intravenous administration:** 800 mg and 1 g in 10- mL phosphate buffer solution.<br>**Solid oral dosage form:** 200 mg; 400 mg; 600 mg.<br>* For the treatment of hepatitis C, in combination with direct acting anti-viral medicines. |

| **6. ANTI-INFECTIVE MEDICINES** *(continued)* | |
|---|---|
| ***Complementary list*** | |
| *pegylated interferon alfa (2a or 2b)** | ***Vial or prefilled syringe:*** *180 micrograms (peginterferon alfa-2a), 80 microgram, 100 microgram (peginterferon alfa-2b).* * *To be used in combination with ribavirin.* |
| **6.5 Antiprotozoal medicines** | |
| **6.5.1 Antiamoebic and antigiardiasis medicines** | |
| diloxanide [a] | **Tablet:** 500 mg (furoate). [a] >25 kg. |
| ☐ metronidazole | **Injection:** 500 mg in 100- mL vial. **Oral liquid:** 200 mg (as benzoate)/5 mL. **Tablet:** 200 mg to 500 mg. |
| **6.5.2 *Antileishmaniasis medicines*** | |
| amphotericin B | **Powder for injection:** 50 mg in vial (as sodium deoxycholate or liposomal complex). |
| miltefosine | **Solid oral dosage form:** 10 mg; 50 mg. |
| paromomycin | **Solution for intramuscular injection:** 750 mg of paromomycin base (as the sulfate). |
| sodium stibogluconate **or** meglumine antimoniate | **Injection:** 100 mg/ mL, 1 vial = 30 mL **or** 30%, equivalent to approximately 8.1% antimony (pentavalent) in 5- mL ampoule. |

## 6. ANTI-INFECTIVE MEDICINES *(continued)*

### 6.5.3 *Antimalarial medicines*

#### 6.5.3.1 *For curative treatment*

Medicines for the treatment of *P. falciparum* malaria cases should be used in combination. The list currently recommends combinations according to treatment guidelines. WHO recognizes that not all of the fixed dose combinations (FDCs) in the WHO treatment guidelines exist, and encourages their development and rigorous testing. WHO also encourages development and testing of rectal dosage formulations.

| | |
|---|---|
| amodiaquine* | **Tablet:** 153 mg **or** 200 mg (as hydrochloride).<br>* To be used in combination with artesunate 50 mg. |
| artemether* | **Oily injection:** 80 mg/ mL in 1- mL ampoule.<br>* For use in the management of severe malaria. |
| artemether + lumefantrine* | **Tablet:** 20 mg + 120 mg.<br>**Tablet (dispersible):** 20 mg + 120 mg [c].<br>* Not recommended in the first trimester of pregnancy or in children below 5 kg. |
| artesunate* ** | **Injection:** ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution.<br>* For use in the management of severe malaria.<br>**Rectal dosage form:** 50 mg [c]; 100 mg [c]; 200 mg capsules (for pre-referral treatment of severe malaria only; patients should be taken to an appropriate health facility for follow-up care) [c].<br>**Tablet:** 50 mg.<br>** To be used in combination with either amodiaquine, mefloquine **or** sulfadoxine + pyrimethamine. |
| artesunate + amodiaquine* | **Tablet:** 25 mg + 67.5 mg; 50 mg + 135 mg; 100 mg + 270 mg.<br>* Other combinations that deliver the target doses required such as 153 mg **or** 200 mg (as hydrochloride) with 50 mg artesunate can be alternatives. |
| artesunate + mefloquine | **Tablet:** 25 mg + 55 mg; 100 mg + 220 mg. |
| artesunate + pyronaridine tetraphosphate [a] | **Tablet:** 60 mg + 180 mg<br>**Granules:** 20 mg + 60 mg [c].<br>[a] >5 kg. |

| **6. ANTI-INFECTIVE MEDICINES** *(continued)* | |
|---|---|
| chloroquine* | **Oral liquid:** 50 mg (as phosphate **or** sulfate)/5 mL.<br>**Tablet:** 100 mg; 150 mg (as phosphate **or** sulfate).<br>* For use only for the treatment of *P. vivax* infection. |
| dihydroartemisinin + piperaquine phosphate [a] | **Tablet:** 20 mg + 160 mg; 40 mg + 320 mg.<br>[a] >5 kg. |
| doxycycline* | **Capsule:** 100 mg (as hydrochloride **or** hyclate).<br>**Tablet (dispersible):** 100 mg (as monohydrate).<br>* For use only in combination with quinine. |
| mefloquine* | **Tablet:** 250 mg (as hydrochloride).<br>* To be used in combination with artesunate 50 mg. |
| primaquine* | **Tablet:** 7.5 mg; 15 mg (as diphosphate).<br>* Only for use to achieve radical cure of *P. vivax* and *P. ovale* infections, given for 14 days. |
| quinine* | **Injection:** 300 mg quinine hydrochloride/ mL in 2- mL ampoule.<br>**Tablet:** 300 mg (quinine sulfate) **or** 300 mg (quinine bisulfate).<br>* For use only in the management of severe malaria, and should be used in combination with doxycycline. |
| sulfadoxine + pyrimethamine* | **Tablet:** 500 mg + 25 mg.<br>* Only in combination with artesunate 50 mg. |

| **6. ANTI-INFECTIVE MEDICINES** *(continued)* | |
|---|---|
| **6.5.3.2** ***For chemoprevention*** | |
| amodiaquine – sulfadoxine + pyrimethamine [c] | **Co-packaged dispersible tablets:**<br>amodiaquine 76.5 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 250 mg + 12.5 mg [1];<br>amodiaquine 153 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 500 mg + 25 mg [1]; |
| chloroquine* | **Oral liquid:** 50 mg (as phosphate **or** sulfate)/5 mL.<br>**Tablet:** 150 mg (as phosphate **or** sulfate).<br>* For use only in central American regions, for *P. vivax* infections. |
| doxycycline [a] | **Solid oral dosage form:** 100 mg (as hydrochloride **or** hyclate).<br>[a] >8 years. |
| mefloquine [a] | **Tablet:** 250 mg (as hydrochloride).<br>[a] >5 kg or >3 months. |
| proguanil* | **Tablet:** 100 mg (as hydrochloride).<br>* For use only in combination with chloroquine. |
| sulfadoxine + pyrimethamine | **Tablet:** 250 mg + 12.5 mg [c]; 500 mg + 25 mg. |
| **6.5.4** ***Antipneumocystosis and antitoxoplasmosis medicines*** | |
| pyrimethamine | **Tablet:** 25 mg. |
| sulfadiazine | **Tablet:** 500 mg. |
| sulfamethoxazole + trimethoprim | **Injection:**<br>80 mg + 16 mg/ mL in 5- mL ampoule;<br>80 mg + 16 mg/ mL in 10- mL ampoule.<br>**Oral liquid:** 200 mg + 40 mg/5 mL [c].<br>**Tablet:** 100 mg + 20 mg; 400 mg + 80 mg [c]; 800 mg + 160 mg |
| ***Complementary List*** | |
| *pentamidine* | ***Tablet:*** *200 mg; 300 mg (as isethionate).* |

## 6. ANTI-INFECTIVE MEDICINES *(continued)*

### 6.5.5 *Antitrypanosomal medicines*

#### 6.5.5.1 *African trypanosomiasis*

fexinidazole* — **Tablet:** 600 mg

* For the treatment of 1st and 2nd stage of human African trypanosomiasis due to *Trypanosoma brucei gambiense* infection.

**Medicines for the treatment of 1st stage African trypanosomiasis**

pentamidine* — **Powder for injection:** 200 mg (as isetionate) in vial.

* To be used for the treatment of *Trypanosoma brucei gambiense* infection.

suramin sodium* — **Powder for injection:** 1 g in vial.

* To be used for the treatment of the initial phase of *Trypanosoma brucei rhodesiense* infection.

**Medicines for the treatment of 2nd stage African trypanosomiasis**

eflornithine* — **Injection:** 200 mg (hydrochloride)/ mL in 100- mL bottle.

* To be used for the treatment of *Trypanosoma brucei gambiense* infection.

melarsoprol — **Injection:** 3.6% solution, 5- mL ampoule (180 mg of active compound).

nifurtimox* — **Tablet:** 120 mg.

* Only to be used in combination with eflornithine, for the treatment of *Trypanosoma brucei gambiense* infection.

***Complementary List***

*melarsoprol* [c] — ***Injection:*** *3.6% solution in 5- mL ampoule (180 mg of active compound).*

#### 6.5.5.2 *American trypanosomiasis*

benznidazole — **Tablet:** 12.5 mg [c] ;100 mg.
**Tablet (scored):** 50 mg.

nifurtimox — **Tablet:** 30 mg; 120 mg; 250 mg.

### 6.6 Medicines for ectoparasitic infections

ivermectin — **Tablet (scored):** 3 mg.

## 7. ANTIMIGRAINE MEDICINES

### 7.1 For treatment of acute attack

| | |
|---|---|
| acetylsalicylic acid | **Tablet:** 300 mg to 500 mg. |
| ibuprofen [c] | **Tablet:** 200 mg; 400 mg. |
| paracetamol | **Oral liquid:** 120 mg/5 mL [c]; 125 mg/5 mL [c].<br>**Tablet:** 300 mg to 500 mg. |

### 7.2 For prophylaxis

| | |
|---|---|
| ☐ propranolol | **Tablet:** 20 mg; 40 mg (hydrochloride). |

## 8. IMMUNOMODULATORS AND ANTINEOPLASTICS

### 8.1 Immunomodulators for non-malignant disease

***Complementary List***

| | |
|---|---|
| ☐ *adalimumab** | ***Injection:*** *40 mg/0.8 mL; 40 mg/0.4 mL*<br>* *Certolizumab pegol, etanercept, golimumab and infliximab are alternatives, including quality-assured biosimilars.* |
| *azathioprine* | ***Powder for injection:*** *100 mg (as sodium salt) in vial.*<br>***Tablet (scored):*** *50 mg.* |
| *ciclosporin** | ***Capsule:*** *25 mg.*<br>***Concentrate for injection:*** *50 mg/ mL in 1- mL ampoule.*<br>* *For organ transplantation.* |

## 8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

### 8.2 Antineoplastics and supportive medicines

Medicines listed below should be used according to protocols for treatment of the diseases.

#### 8.2.1 *Cytotoxic medicines*

***Complementary List***

| | |
|---|---|
| *arsenic trioxide* | ***Concentrate for solution for infusion:*** *1 mg/mL*<br>– *Acute promyelocytic leukaemia* |
| *asparaginase* | ***Powder for injection:*** *10 000 IU in vial*<br>– *Acute lymphoblastic leukaemia.* |
| *bendamustine* | ***Injection:*** *45 mg/0.5 mL; 180 mg/2 mL.*<br>– *Chronic lymphocytic leukaemia*<br>– *Follicular lymphoma* |
| *bleomycin* | ***Powder for injection:*** *15 mg (as sulfate) in vial.*<br>– *Hodgkin lymphoma*<br>– *Kaposi sarcoma*<br>– *Ovarian germ cell tumour*<br>– *Testicular germ cell tumour* |
| *calcium folinate* | ***Injection:*** *3 mg/ mL in 10- mL ampoule.*<br>***Tablet:*** *5 mg, 15 mg, 25 mg.*<br>– *Early stage colon cancer*<br>– *Early stage rectal cancer*<br>– *Gestational trophoblastic neoplasia*<br>– *Metastatic colorectal cancer*<br>– *Osteosarcoma*<br>– *Burkitt lymphoma* |
| *capecitabine* | ***Tablet:*** *150 mg; 500 mg.*<br>– *Early stage colon cancer*<br>– *Early stage rectal cancer*<br>– *Metastatic breast cancer*<br>– *Metastatic colorectal cancer* |

| **8. IMMUNOMODULATORS AND ANTINEOPLASTICS** *(continued)* | |
|---|---|
| *carboplatin* | ***Injection:*** *50 mg/5 mL; 150 mg/15 mL; 450 mg/45 mL; 600 mg/60 mL.*<br>– *Early stage breast cancer*<br>– *Epithelial ovarian cancer*<br>– *Nasopharyngeal cancer*<br>– *Non-small cell lung cancer*<br>– *Osteosarcoma*<br>– *Retinoblastoma*<br>– *Cervical cancer* |
| *chlorambucil* | ***Tablet:*** *2 mg.*<br>– *Chronic lymphocytic leukaemia.* |
| *cisplatin* | ***Injection:*** *50 mg/50 mL; 100 mg/100 mL.*<br>– *Cervical cancer*<br>– *Head and neck cancer (as a radio-sensitizer)*<br>– *Nasopharyngeal cancer (as a radio-sensitizer)*<br>– *Non-small cell lung cancer*<br>– *Osteosarcoma*<br>– *Ovarian germ cell tumour*<br>– *Testicular germ cell tumour* |
| *cyclophosphamide* | ***Powder for injection:*** *500 mg in vial.*<br>***Tablet:*** *25 mg, 50 mg.*<br>– *Chronic lymphocytic leukaemia*<br>– *Diffuse large B-cell lymphoma*<br>– *Early stage breast cancer*<br>– *Gestational trophoblastic neoplasia*<br>– *Hodgkin lymphoma*<br>– *Follicular lymphoma*<br>– *Rhabdomyosarcoma*<br>– *Ewing sarcoma*<br>– *Acute lymphoblastic leukaemia*<br>– *Burkitt lymphoma*<br>– *Metastatic breast cancer*<br>– *Multiple myeloma.* |
| *cytarabine* | ***Powder for injection:*** *100 mg in vial.*<br>– *Acute myeloid leukaemia*<br>– *Acute lymphoblastic leukaemia*<br>– *Acute promyelocytic leukaemia*<br>– *Burkitt lymphoma.* |

| 8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)* | |
|---|---|
| *dacarbazine* | ***Powder for injection:*** *100 mg in vial.*<br>– *Hodgkin lymphoma* |
| *dactinomycin* | ***Powder for injection:*** *500 micrograms in vial.*<br>– *Gestational trophoblastic neoplasia*<br>– *Rhabdomyosarcoma*<br>– *Nephroblastoma (Wilms tumour)* |
| *daunorubicin* | ***Powder for injection:*** *50 mg (hydrochloride) in vial.*<br>– *Acute lymphoblastic leukaemia*<br>– *Acute myeloid leukaemia*<br>– *Acute promyelocytic leukaemia* |
| *docetaxel* | ***Injection:*** *20 mg/ mL; 40 mg/ mL.*<br>– *Early stage breast cancer*<br>– *Metastatic breast cancer*<br>– *Metastatic prostate cancer* |
| *doxorubicin* | ***Powder for injection:*** *10 mg; 50 mg (hydrochloride) in vial.*<br>– *Diffuse large B-cell lymphoma*<br>– *Early stage breast cancer*<br>– *Hodgkin lymphoma*<br>– *Kaposi sarcoma*<br>– *Follicular lymphoma*<br>– *Metastatic breast cancer*<br>– *Osteosarcoma*<br>– *Ewing sarcoma*<br>– *Acute lymphoblastic leukaemia*<br>– *Nephroblastoma (Wilms tumour)*<br>– *Burkitt lymphoma*<br>– *Multiple myeloma.* |
| *etoposide* | ***Capsule:*** *50 mg, 100 mg.*<br>***Injection:*** *20 mg/ mL in 5- mL ampoule.*<br>– *Testicular germ cell tumour*<br>– *Gestational trophoblastic neoplasia*<br>– *Hodgkin lymphoma*<br>– *Non-small cell lung cancer*<br>– *Ovarian germ cell tumour*<br>– *Retinoblastoma*<br>– *Ewing sarcoma*<br>– *Acute lymphoblastic leukaemia*<br>– *Burkitt lymphoma* |

| **8. IMMUNOMODULATORS AND ANTINEOPLASTICS** *(continued)* | |
|---|---|
| *fludarabine* | ***Powder for injection:*** *50 mg (phosphate) in vial.*<br>***Tablet:*** *10 mg*<br>– *Chronic lymphocytic leukaemia.* |
| *fluorouracil* | ***Injection:*** *50 mg/ mL in 5- mL ampoule.*<br>– *Early stage breast cancer*<br>– *Early stage colon cancer*<br>– *Early stage rectal cancer*<br>– *Metastatic colorectal cancer*<br>– *Nasopharyngeal cancer* |
| *gemcitabine* | ***Powder for injection:*** *200 mg in vial, 1 g in vial.*<br>– *Epithelial ovarian cancer*<br>– *Non-small cell lung cancer* |
| *hydroxycarbamide* | ***Solid oral dosage form:*** *200 mg; 250 mg; 300 mg; 400 mg; 500 mg; 1 g.*<br>– *Chronic myeloid leukaemia.* |
| *ifosfamide* | ***Powder for injection:*** *500 mg vial; 1-g vial; 2-g vial.*<br>– *Testicular germ cell tumour*<br>– *Ovarian germ cell tumour*<br>– *Osteosarcoma*<br>– *Rhabdomyosarcoma*<br>– *Ewing sarcoma* |
| *irinotecan* | ***Injection:*** *40 mg/2 mL in 2- mL vial; 100 mg/5 mL in 5- mL vial; 500 mg/25 mL in 25- mL vial.*<br>– *Metastatic colorectal cancer.* |
| *melphalan* | ***Tablet:*** *2 mg*<br>***Powder for injection:*** *50 mg in vial*<br>– *Multiple myeloma.* |
| *mercaptopurine* | ***Tablet:*** *50 mg.*<br>– *Acute lymphoblastic leukaemia*<br>– *Acute promyelocytic leukaemia.* |

| 8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)* | |
|---|---|
| *methotrexate* | ***Powder for injection:*** *50 mg (as sodium salt) in vial.*<br>***Tablet:*** *2.5 mg (as sodium salt).*<br>– *Early stage breast cancer*<br>– *Gestational trophoblastic neoplasia*<br>– *Osteosarcoma*<br>– *Acute lymphoblastic leukaemia*<br>– *Acute promyelocytic leukaemia* |
| *oxaliplatin* | ***Injection:*** *50 mg/10 mL in 10- mL vial; 100 mg/20 mL in 20- mL vial; 200 mg/40 mL in 40- mL vial.*<br>***Powder for injection:*** *50 mg, 100 mg in vial.*<br>– *Early stage colon cancer*<br>– *Metastatic colorectal cancer* |
| *paclitaxel* | ***Powder for injection:*** *6 mg/ mL.*<br>– *Epithelial ovarian cancer*<br>– *Early stage breast cancer*<br>– *Metastatic breast cancer*<br>– *Kaposi sarcoma*<br>– *Nasopharyngeal cancer*<br>– *Non-small cell lung cancer*<br>– *Ovarian germ cell tumour*<br>– *Cervical cancer* |
| *pegaspargase** | ***Injection:*** *3,750 units/5 mL in vial.*<br>– *Acute lymphoblastic leukaemia*<br>* *Including quality-assured biosimilars.* |
| *procarbazine* **[c]** | ***Capsule:*** *50 mg (as hydrochloride).*<br>– *Hodgkin lymphoma* |
| *realgar-Indigo naturalis formulation* | ***Tablet:*** *270 mg (containing tetra-arsenic tetra-sulfide 30 mg).*<br>– *Acute promyelocytic leukaemia* |
| *tioguanine* **[c]** | ***Solid oral dosage form:*** *40 mg.*<br>– *Acute lymphoblastic leukaemia* |
| *vinblastine* | ***Powder for injection:*** *10 mg (sulfate) in vial.*<br>– *Hodgkin lymphoma*<br>– *Kaposi sarcoma*<br>– *Testicular germ cell tumour*<br>– *Ovarian germ cell tumour* |

| **8. IMMUNOMODULATORS AND ANTINEOPLASTICS** *(continued)* | |
|---|---|
| *vincristine* | ***Powder for injection:*** *1 mg; 5 mg (sulfate) in vial.*<br>– *Diffuse large B-cell lymphoma*<br>– *Gestational trophoblastic neoplasia*<br>– *Hodgkin lymphoma*<br>– *Kaposi sarcoma*<br>– *Follicular lymphoma*<br>– *Retinoblastoma*<br>– *Rhabdomyosarcoma*<br>– *Ewing sarcoma*<br>– *Acute lymphoblastic leukaemia*<br>– *Nephroblastoma (Wilms tumour)*<br>– *Burkitt lymphoma* |
| *vinorelbine* | ***Injection:*** *10 mg/mL in 1- mL vial; 50 mg/5 mL in 5- mL vial.*<br>– *Non-small cell lung cancer*<br>– *Metastatic breast cancer* |

## 8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

### 8.2.2 *Targeted therapies*

***Complementary List***

| | |
|---|---|
| *all-trans retinoic acid (ATRA)* | ***Capsule:*** *10 mg.*<br>– *Acute promyelocytic leukaemia.* |
| *bortezomib* | ***Powder for injection:*** *3.5 g in vial.*<br>– *Multiple myeloma* |
| *dasatinib* | ***Tablet:*** *20 mg; 50 mg; 70 mg; 80 mg; 100 mg; 140 mg.*<br>– *Imatinib-resistant chronic myeloid leukaemia* |
| ☐ *erlotinib** | ***Tablet:*** *100 mg, 150 mg*<br>– *EGFR mutation-positive advanced non-small cell lung cancer*<br>* *Gefitinb and afatinb are alternatives.* |
| *imatinib* | ***Tablet:*** *100 mg; 400 mg.*<br>– *Chronic myeloid leukaemia*<br>– *Gastrointestinal stromal tumour* |
| *nilotinib* | ***Capsule:*** *150 mg; 200 mg.*<br>– *Imatinib-resistant chronic myeloid leukaemia* |
| *rituximab** | ***Injection (intravenous):*** *100 mg/10 mL in 10- mL vial; 500 mg/50 mL in 50- mL vial.*<br>– *Diffuse large B-cell lymphoma*<br>– *Chronic lymphocytic leukaemia*<br>– *Follicular lymphoma.*<br>* *Including quality-assured biosimilars.* |
| *trastuzumab** | ***Powder for injection:*** *60 mg; 150 mg; 440 mg in vial.*<br>– *Early stage HER2 positive breast cancer*<br>– *Metastatic HER2 positive breast cancer.*<br>* *Including quality-assured biosimilars.* |

## 8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

### 8.2.3 *Immunomodulators*

***Complementary List***

| | |
|---|---|
| *filgrastim* | ***Injection:*** *120 micrograms/0.2 mL; 300 micrograms/0.5 mL; 480 micrograms/0.8 mL in pre-filled syringe 300 micrograms/mL in 1- mL vial, 480 micrograms/1.6 mL in 1.6- mL vial.*<br>– *Primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy.*<br>– *Secondary prophylaxis for patients who have experienced neutropenia following prior myelotoxic chemotherapy*<br>– *To facilitate administration of dose dense chemotherapy regimens* |
| *lenalidomide* | ***Capsule:*** *25 mg.*<br>– *Multiple myeloma* |
| ☐ *nivolumab** | ***Concentrate solution for infusion:*** *10 mg/mL.*<br>– *Metastatic melanoma*<br>* *Pembrolizumab is an alternative.* |
| *thalidomide* | ***Capsule:*** *50 mg.*<br>– *Multiple myeloma* |

## 8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

### 8.2.4 *Hormones and antihormones*

***Complementary List***

| | |
|---|---|
| *abiraterone* | ***Tablet:*** *250 mg; 500 mg.*<br>– *Metastatic castration-resistant prostate cancer.* |
| ☐ *anastrozole* | ***Tablet:*** *1 mg.*<br>– *Early stage breast cancer*<br>– *Metastatic breast cancer.* |
| ☐ *bicalutamide* | ***Tablet:*** *50 mg.*<br>– *Metastatic prostate cancer.* |
| *dexamethasone* | ***Injection:*** *4 mg/ mL in 1- mL ampoule (as disodium phosphate salt).*<br>***Oral liquid:*** *2 mg/5 mL* ***[c]*** .<br>***Tablet:*** *2 mg* ***[c]*** *; 4 mg.*<br>– *Acute lymphoblastic leukaemia*<br>– *Multiple myeloma.* |
| *hydrocortisone* | ***Powder for injection:*** *100 mg (as sodium succinate) in vial.*<br>– *Acute lymphoblastic leukaemia.* |
| ☐ *leuprorelin* | ***Injection:*** *7.5 mg; 22.5 mg in pre-filled syringe*<br>– *Early stage breast cancer*<br>– *Metastatic prostate cancer.* |
| *methylprednisolone* ***[c]*** | ***Injection:*** *40 mg/ mL (as sodium succinate) in 1- mL single-dose vial and 5- mL multi-dose vials; 80 mg/ mL (as sodium succinate) in 1- mL single-dose vial.*<br>– *Acute lymphoblastic leukamia.* |
| ☐ *prednisolone* | ***Oral liquid:*** *5 mg/ mL* ***[c]*** .<br>***Tablet:*** *5 mg; 25 mg.*<br>– *Chronic lymphocytic leukaemia*<br>– *Diffuse large B-cell lymphoma*<br>– *Hodgkin lymphoma*<br>– *Follicular lymphoma*<br>– *Acute lymphoblastic leukaemia*<br>– *Burkitt lymphoma*<br>– *Metastatic castration-resitsant prostate cancer*<br>– *Multiple myeloma.* |
| *tamoxifen* | ***Tablet:*** *10 mg; 20 mg (as citrate).*<br>– *Early stage breast cancer*<br>– *Metastatic breast cancer.* |

| **8. IMMUNOMODULATORS AND ANTINEOPLASTICS** *(continued)* | |
|---|---|
| **8.2.5** ***Supportive medicines*** | |
| ***Complementary List*** | |
| *allopurinol* ***[c]*** | ***Tablet:*** *100 mg; 300 mg.*<br>– *Tumour lysis syndrome* |
| *mesna* | ***Injection:*** *100 mg/ mL in 4- mL and 10- mL ampoules.*<br>***Tablet:*** *400 mg; 600 mg.*<br>– *Testicular germ cell tumour*<br>– *Ovarian germ cell tumour*<br>– *Osteosarcoma*<br>– *Rhabdomyosarcoma*<br>– *Ewing sarcoma* |
| *zoledronic acid* | ***Concentrate solution for infusion:*** *4 mg/5 mL in 5- mL vial.*<br>***Solution for infusion:*** *4 mg/100 mL in 100- mL bottle.*<br>– *Malignancy-related bone disease* |
| **9. ANTIPARKINSONISM MEDICINES** | |
| ☐ biperiden | **Injection:** 5 mg (lactate) in 1- mL ampoule.<br>**Tablet:** 2 mg (hydrochloride). |
| levodopa + ☐ carbidopa | **Tablet:** 100 mg + 10 mg; 100 mg + 25 mg; 250 mg + 25 mg. |

## 10. MEDICINES AFFECTING THE BLOOD

### 10.1 Antianaemia medicines

| | |
|---|---|
| ferrous salt | **Oral liquid:** equivalent to 25 mg iron (as sulfate)/ mL.<br>**Tablet:** equivalent to 60 mg iron. |
| ferrous salt + folic acid* | **Tablet:** equivalent to 60 mg iron + 400 micrograms folic acid.<br>* Nutritional supplement for use during pregnancy. |
| folic acid | **Tablet:** 400 micrograms*; 1 mg; 5 mg.<br>* Periconceptual use for prevention of first occurrence of neural tube defects. |
| hydroxocobalamin | **Injection:** 1 mg (as acetate, as hydrochloride or as sulfate) in 1- mL ampoule. |
| ***Complementary List*** | |
| ☐ *erythropoiesis-stimulating agents** | ***Injection:*** *pre-filled syringe*<br>*1000IU/ 0.5 mL; 2000IU/ 0.5 mL; 3000IU/ 0.3 mL; 4000IU/ 0.4 mL; 5000IU/ 0.5 mL; 6000IU/ 0.6 mL; 8000IU/ 0.8mL; 10 000IU/ 1 mL; 20 000IU/ 0.5 mL; 40 000IU/ 1 mL*<br>* *The square box applies to epoetin alfa, beta and theta, darbepoetin alfa, methoxy polyethylene glycol-epoetin beta,and their respective biosimilars.* |

## 10. MEDICINES AFFECTING THE BLOOD *(continued)*

### 10.2 Medicines affecting coagulation

| | |
|---|---|
| ☐ dabigatran* | **Capsule:** 110 mg; 150 mg<br>* Apixaban, edoxaban and rivaroxaban are alternatives. |
| ☐ enoxaparin* | **Injection:** ampoule or pre-filled syringe<br>20 mg/0.2 mL; 40 mg/0.4 mL; 60 mg/0.6 mL; 80 mg/ 0.8 mL; 100 mg/1 mL; 120 mg/0.8 mL; 150 mg/1 mL<br>* Alternatives are limited to nadroparin and dalteparin. |
| heparin sodium | **Injection:** 1000 IU/ mL; 5000 IU/ mL; 20 000 IU/ mL in 1- mL ampoule. |
| phytomenadione | **Injection:** 1 mg/ mL [c]; 10 mg/ mL in ampoule.<br>**Tablet:** 10 mg. |
| protamine sulfate | **Injection:** 10 mg/ mL in 5- mL ampoule. |
| tranexamic acid | **Injection:** 100 mg/ mL in 10- mL ampoule. |
| ☐ warfarin | **Tablet:** 1 mg; 2 mg; 5 mg (sodium salt). |
| ***Complementary List*** | |
| *desmopressin* | ***Injection:*** *4 micrograms/ mL (as acetate) in 1- mL ampoule.*<br>***Nasal spray:*** *10 micrograms (as acetate) per dose* |
| *heparin sodium* [c] | ***Injection:*** *1000 IU/ mL; 5000 IU/ mL in 1- mL ampoule.* |
| *protamine sulfate* [c] | ***Injection:*** *10 mg/ mL in 5- mL ampoule.* |
| ☐ *warfarin* [c] | ***Tablet:*** *0.5 mg; 1 mg; 2 mg; 5 mg (sodium salt).* |

### 10.3 Other medicines for haemoglobinopathies

| | |
|---|---|
| ***Complementary List*** | |
| *deferoxamine** | ***Powder for injection:*** *500 mg (mesilate) in vial.*<br>* *Deferasirox oral form may be an alternative, depending on cost and availability.* |
| *hydroxycarbamide* | ***Solid oral dosage form:*** *200 mg; 500 mg; 1 g.* |

## 11. BLOOD PRODUCTS OF HUMAN ORIGIN AND PLASMA SUBSTITUTES

### 11.1 Blood and blood components

In accordance with the World Health Assembly resolution WHA63.12, WHO recognizes that achieving self-sufficiency, unless special circumstances preclude it, in the supply of safe blood components based on voluntary, non-remunerated blood donation, and the security of that supply are important national goals to prevent blood shortages and meet the transfusion requirements of the patient population. All preparations should comply with the WHO requirements.

fresh–frozen plasma

platelets

red blood cells

whole blood

### 11.2 Plasma-derived medicines

All human plasma-derived medicines should comply with the WHO requirements.

#### 11.2.1 *Human immunoglobulins*

| | |
|---|---|
| anti-D immunoglobulin | **Injection:** 250 micrograms in single-dose vial. |
| Anti-rabies immunoglobulin | **Injection:** 150 IU/ mL in vial. |
| Anti-tetanus immunoglobulin | **Injection:** 500 IU in vial. |

***Complementary List***

| | |
|---|---|
| *normal immunoglobulin* | ***Intramuscular administration:*** *16% protein solution.** |
| | ***Intravenous administration:*** *5%; 10% protein solution.*** |
| | ***Subcutaneous administration:*** *15%; 16% protein solution.** |

* *Indicated for primary immune deficiency.*
** *Indicated for primary immune deficiency and Kawasaki disease.*

#### 11.2.2 *Blood coagulation factors*

***Complementary List***

| | |
|---|---|
| ☐ *coagulation factor VIII* | **Powder for injection:** 500 IU/vial. |
| ☐ *coagulation factor IX* | **Powder for injection:** 500 IU/vial, 1000 IU/vial. |

### 11.3 Plasma substitutes

| | |
|---|---|
| ☐ dextran 70* | **Injectable solution:** 6%. |

* Polygeline, injectable solution, 3.5% is considered as equivalent.

## 12. CARDIOVASCULAR MEDICINES

### 12.1 Antianginal medicines

| | |
|---|---|
| ☐ bisoprolol* | **Tablet:** 1.25 mg; 5 mg.<br>* The square box includes metoprolol and carvedilol as alternatives. |
| glyceryl trinitrate | **Tablet (sublingual):** 500 micrograms. |
| ☐ isosorbide dinitrate | **Tablet (sublingual):** 5 mg. |
| verapamil | **Tablet:** 40 mg; 80 mg (hydrochloride). |

### 12.2 Antiarrhythmic medicines

| | |
|---|---|
| ☐ bisoprolol* | **Tablet:** 1.25 mg; 5 mg.<br>* The square box includes metoprolol and carvedilol as alternatives. |
| digoxin | **Injection:** 250 micrograms/ mL in 2- mL ampoule.<br>**Oral liquid:** 50 micrograms/ mL.<br>**Tablet:** 62.5 micrograms; 250 micrograms. |
| epinephrine (adrenaline) | **Injection:** 100 micrograms/ mL (as acid tartrate **or** hydrochloride) in 10- mL ampoule. |
| lidocaine | **Injection:** 20 mg (hydrochloride)/ mL in 5- mL ampoule. |
| verapamil | **Injection:** 2.5 mg (hydrochloride)/ mL in 2- mL ampoule.<br>**Tablet:** 40 mg; 80 mg (hydrochloride). |
| ***Complementary List*** | |
| *amiodarone* | ***Injection:*** *50 mg/ mL in 3- mL ampoule (hydrochloride).*<br>***Tablet:*** *100 mg; 200 mg; 400 mg (hydrochloride).* |

| 12. CARDIOVASCULAR MEDICINES *(continued)* | |
|---|---|
| **12.3 Antihypertensive medicines** | |
| ☐ amlodipine | **Tablet:** 5 mg (as maleate, mesylate or besylate). |
| ☐ bisoprolol* | **Tablet:** 1.25 mg; 5 mg.<br>* The square box includes atenolol, metoprolol and carvedilol as alternatives. Atenolol should not be used as a first-line agent in uncomplicated hypertension in patients >60 years. |
| ☐ enalapril | **Tablet:** 2.5 mg; 5 mg (as hydrogen maleate). |
| hydralazine* | **Powder for injection:** 20 mg (hydrochloride) in ampoule.<br>**Tablet:** 25 mg; 50 mg (hydrochloride).<br>* Hydralazine is listed for use only in the acute management of severe pregnancy-induced hypertension. Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines. |
| ☐ hydrochlorothiazide | **Oral liquid:** 50 mg/5 mL.<br>**Solid oral dosage form:** 12.5 mg; 25 mg. |
| ☐ lisinopril + ☐ amlodipine | **Tablet:** 10 mg + 5 mg; 20 mg + 5 mg; 20 mg + 10 mg. |
| ☐ lisinopril + ☐ hydrochlorothiazide | **Tablet:** 10 mg + 12.5 mg; 20 mg + 12.5 mg; 20 mg + 25 mg |
| ☐ losartan | **Tablet:** 25 mg; 50 mg; 100 mg. |
| methyldopa* | **Tablet:** 250 mg.<br>* Methyldopa is listed for use only in the management of pregnancy-induced hypertension. Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines. |
| ☐ telmisartan + ☐ amlodipine | **Tablet:** 40 mg + 5 mg; 80 mg + 5 mg; 80 mg + 10 mg. |
| ☐ telmisartan + ☐ hydrochlorothiazide | **Tablet:** 40 mg + 12.5 mg; 80 mg + 12.5 mg; 80 mg + 25 mg. |
| ***Complementary List*** | |
| *sodium nitroprusside* | ***Powder for infusion:** 50 mg in ampoule.* |

## 12. CARDIOVASCULAR MEDICINES *(continued)*

### 12.4 Medicines used in heart failure

| | |
|---|---|
| ☐ bisoprolol* | **Tablet:** 1.25 mg; 5 mg.<br>* The square box includes metoprolol and carvedilol as alternatives. |
| digoxin | **Injection:** 250 micrograms/ mL in 2- mL ampoule.<br>**Oral liquid:** 50 micrograms/ mL.<br>**Tablet:** 62.5 micrograms; 250 micrograms. |
| ☐ enalapril | **Tablet:** 2.5 mg; 5 mg (as hydrogen maleate). |
| ☐ furosemide | **Injection:** 10 mg/ mL in 2- mL ampoule.<br>**Oral liquid:** 20 mg/5 mL [c].<br>**Tablet:** 40 mg. |
| ☐ hydrochlorothiazide | **Oral liquid:** 50 mg/5 mL.<br>**Solid oral dosage form:** 25 mg. |
| ☐ losartan | **Tablet:** 25 mg; 50 mg; 100 mg. |
| spironolactone | **Tablet:** 25 mg. |
| ***Complementary List*** | |
| *dopamine* | ***Injection:*** *40 mg/ mL (hydrochloride) in 5- mL vial.* |

### 12.5 Antithrombotic medicines

#### 12.5.1 *Anti-platelet medicines*

| | |
|---|---|
| acetylsalicylic acid | **Tablet:** 100 mg. |
| clopidogrel | **Tablet:** 75 mg; 300 mg |

#### 12.5.2 *Thrombolytic medicines*

| | |
|---|---|
| ***Complementary List*** | |
| *alteplase* | ***Powder for injection:*** *10 mg; 20 mg; 50 mg in vial* |
| *streptokinase* | ***Powder for injection:*** *1.5 million IU in vial.* |

### 12.6 Lipid-lowering agents

| | |
|---|---|
| ☐ simvastatin* | **Tablet:** 5 mg; 10 mg; 20 mg; 40 mg.<br>* For use in high-risk patients. |

| 13. DERMATOLOGICAL MEDICINES (topical) | |
|---|---|
| **13.1 Antifungal medicines** | |
| ☐ miconazole | **Cream or ointment:** 2% (nitrate). |
| selenium sulfide | **Detergent-based suspension:** 2%. |
| sodium thiosulfate | **Solution:** 15%. |
| terbinafine | **Cream:** 1% **or Ointment:** 1% terbinafine hydrochloride. |
| **13.2 Anti-infective medicines** | |
| mupirocin | **Cream (as mupirocin calcium):** 2%.<br>**Ointment:** 2%. |
| potassium permanganate | **Aqueous solution:** 1:10 000. |
| silver sulfadiazine [a] | **Cream:** 1%.<br>[a] >2 months. |
| **13.3 Anti-inflammatory and antipruritic medicines** | |
| ☐ betamethasone [a] | **Cream or ointment:** 0.1% (as valerate).<br>[a] Hydrocortisone preferred in neonates. |
| ☐ calamine | **Lotion.** |
| ☐ hydrocortisone | **Cream or ointment:** 1% (acetate). |
| **13.4 Medicines affecting skin differentiation and proliferation** | |
| benzoyl peroxide | **Cream or lotion:** 5%. |
| coal tar | **Solution:** 5%. |
| fluorouracil | **Ointment:** 5%. |
| ☐ podophyllum resin | **Solution:** 10% to 25%. |
| salicylic acid | **Solution:** 5%. |
| urea | **Cream or ointment:** 5%; 10%. |
| **13.5 Scabicides and pediculicides** | |
| ☐ benzyl benzoate [a] | **Lotion:** 25%.<br>[a] >2 years. |
| permethrin | **Cream:** 5%.<br>**Lotion:** 1%. |

| | |
|---|---|
| **14. DIAGNOSTIC AGENTS** | |
| **14.1 Ophthalmic medicines** | |
| fluorescein | **Eye drops:** 1% (sodium salt). |
| ☐ tropicamide | **Eye drops:** 0.5%. |
| **14.2 Radiocontrast media** | |
| ☐ amidotrizoate | **Injection:** 140 mg to 420 mg iodine (as sodium **or** meglumine salt)/ mL in 20- mL ampoule. |
| barium sulfate | **Aqueous suspension.** |
| ☐ iohexol | **Injection:** 140 mg to 350 mg iodine/ mL in 5- mL; 10- mL; 20- mL ampoules. |
| ***Complementary List*** | |
| *barium sulfate* ***[c]*** | ***Aqueous suspension.*** |
| ☐ *meglumine iotroxate* | ***Solution:*** *5 g to 8 g iodine in 100 mL to 250 mL.* |
| **15. DISINFECTANTS AND ANTISEPTICS** | |
| **15.1 Antiseptics** | |
| ☐ chlorhexidine | **Solution:** 5% (digluconate). |
| ☐ ethanol | **Solution:** 70% (denatured). |
| ☐ povidone iodine | **Solution:** 10% (equivalent to 1% available iodine). |
| **15.2 Disinfectants** | |
| alcohol based hand rub | **Solution:** containing ethanol 80% volume /volume<br>**Solution:** containing isopropyl alcohol 75% volume/ volume. |
| ☐ chlorine base compound | **Powder:** (0.1% available chlorine) for solution. |
| ☐ chloroxylenol | **Solution:** 4.8%. |
| glutaral | **Solution:** 2%. |

| **16. DIURETICS** | |
|---|---|
| amiloride | **Tablet:** 5 mg (hydrochloride). |
| ☐ furosemide | **Injection:** 10 mg/ mL in 2- mL ampoule.<br>**Oral liquid:** 20 mg/5 mL [c].<br>**Tablet:** 10 mg [c]; 20 mg [c]; 40 mg. |
| ☐ hydrochlorothiazide | **Solid oral dosage form:** 25 mg. |
| mannitol | **Injectable solution:** 10%; 20%. |
| spironolactone | **Tablet:** 25 mg. |
| ***Complementary List*** | |
| ☐ *hydrochlorothiazide* [c] | ***Tablet (scored):** 25 mg.* |
| *mannitol* [c] | ***Injectable solution:** 10%; 20%.* |
| *spironolactone* [c] | ***Oral liquid:** 5 mg/5 mL; 10 mg/5 mL; 25 mg/5 mL.*<br>***Tablet:** 25 mg.* |

| | |
|---|---|
| **17. GASTROINTESTINAL MEDICINES** | |
| ***Complementary List*** | |
| ☐ *pancreatic enzymes* [c] | *Age-appropriate formulations and doses including lipase, protease and amylase.* |
| **17.1 Antiulcer medicines** | |
| ☐ omeprazole | **Powder for injection:** 40 mg in vial<br>**Powder for oral liquid:** 20 mg; 40 mg sachets.<br>**Solid oral dosage form:** 10 mg; 20 mg; 40 mg. |
| ☐ ranitidine | **Injection:** 25 mg/ mL (as hydrochloride) in 2- mL ampoule.<br>**Oral liquid:** 75 mg/5 mL (as hydrochloride).<br>**Tablet:** 150 mg (as hydrochloride). |
| **17.2 Antiemetic medicines** | |
| dexamethasone | **Injection:** 4 mg/ mL in 1- mL ampoule (as disodium phosphate salt).<br>**Oral liquid:** 0.5 mg/5 mL; 2 mg/5 mL.<br>**Solid oral dosage form:** 0.5 mg; 0.75 mg; 1.5 mg; 4 mg. |
| metoclopramide [a] | **Injection:** 5 mg (hydrochloride)/ mL in 2- mL ampoule.<br>**Oral liquid:** 5 mg/5 mL [c].<br>**Tablet:** 10 mg (hydrochloride).<br>[a] Not in neonates. |
| ☐ ondansetron [a] | **Injection:** 2 mg base/ mL in 2- mL ampoule (as hydrochloride).<br>**Oral liquid:** 4 mg base/5 mL.<br>**Solid oral dosage form:** Eq 4 mg base; Eq 8 mg base; Eq 24 mg base.<br>[a] >1 month. |
| ***Complementary list*** | |
| *aprepitant* | ***Capsule:*** *80 mg; 125 mg; 165 mg.*<br>***Powder for oral susupension:*** *125 mg in sachet.* |

## 17. GASTROINTESTINAL MEDICINES *(continued)*

### 17.3 Anti-inflammatory medicines

| | |
|---|---|
| ☐ sulfasalazine | **Retention enema.**<br>**Suppository:** 500 mg.<br>**Tablet:** 500 mg. |
| ***Complementary List*** | |
| ☐ *hydrocortisone** | ***Retention enema.***<br>***Suppository:*** *25 mg (acetate).*<br>* The square box only applies to hydrocortisone retention enema). |

### 17.4 Laxatives

| | |
|---|---|
| ☐ senna | **Tablet:** 7.5 mg (sennosides) (or traditional dosage forms). |

### 17.5 Medicines used in diarrhoea

| | |
|---|---|
| oral rehydration salts – zinc sulfate [c] | **Co-package containing:**<br>**ORS powder for dilution** (see Section 17.5.1) – zinc sulfate **solid oral dosage form** 20 mg (see Section 17.5.2) |

#### 17.5.1 *Oral rehydration*

oral rehydration salts — **Powder for dilution** in 200 mL; 500 mL; 1 L.

| | |
|---|---|
| glucose: | 75 mEq |
| sodium: | 75 mEq **or** mmol/L |
| chloride: | 65 mEq or mmol/L |
| potassium: | 20 mEq or mmol/L |
| citrate: | 10 mmol/L |
| osmolarity: | 245 mOsm/L |
| glucose: | 13.5 g/L |
| sodium chloride: | 2.6 g/L |
| potassium chloride: | 1.5 g/L |
| trisodium citrate dihydrate*: | 2.9 g/L |

* Trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/L. However, as the stability of this latter formulation is very poor under tropical conditions, it is recommended only when manufactured for immediate use.

#### 17.5.2 *Medicines for diarrhoea*

| | |
|---|---|
| zinc sulfate* | **Solid oral dosage form:** 20 mg.<br>* In acute diarrhoea zinc sulfate should be used as an adjunct to oral rehydration salts. |

| | |
|---|---|
| **18. MEDICINES FOR ENDOCRINE DISORDERS** | |
| **18.1 Adrenal hormones and synthetic substitutes** | |
| fludrocortisone | **Tablet:** 100 micrograms (acetate). |
| hydrocortisone | **Tablet:** 5 mg; 10 mg; 20 mg. |
| **18.2 Androgens** | |
| ***Complementary List*** | |
| *testosterone* | ***Injection:*** *200 mg (enanthate) in 1- mL ampoule.* |
| **18.3 Estrogens** | — |
| **18.4 Progestogens** | |
| ☐ medroxyprogesterone acetate | **Tablet:** 5 mg. |
| **18.5 Medicines for diabetes** | |
| **18.5.1** ***Insulins*** | |
| insulin injection (soluble) | **Injection:** 40 IU/ mL in 10- mL vial; 100 IU/ mL in 10- mL vial. |
| intermediate-acting insulin | **Injection:** 40 IU/ mL in 10- mL vial; 100 IU/ mL in 10- mL vial (as compound insulin zinc suspension or isophane insulin). |
| **18.5.2** ***Oral hypoglycaemic agents*** | |
| ☐ gliclazide* | **Solid oral dosage form:** (controlled-release tablets) 30 mg; 60 mg; 80 mg.<br>* Glibenclamide not suitable above 60 years. |
| metformin | **Tablet:** 500 mg (hydrochloride). |
| ***Complementary List*** | |
| *metformin* ***[c]*** | ***Tablet:*** *500 mg (hydrochloride).* |
| **18.6 Medicines for hypoglycaemia** | |
| glucagon | **Injection:** 1 mg/ mL. |
| ***Complementary List*** | |
| diazoxide ***[c]*** | **Oral liquid:** 50 mg/mL<br>**Tablet:** 50 mg |

## 18. MEDICINES FOR ENDOCRINE DISORDERS *(continued)*

### 18.7 Thyroid hormones and antithyroid medicines

| | |
|---|---|
| levothyroxine | **Tablet:** 25 micrograms [c]; 50 micrograms; 100 micrograms (sodium salt). |
| potassium iodide | **Tablet:** 60 mg. |
| ☐ methimazole* | **Tablet:** 5mg, 10mg, 20mg.<br>* Carbimazole is an alternative depending on local availability. |
| propylthiouracil* | **Tablet:** 50 mg.<br>* For use when alternative first-line treatment is not appropriate or available; and in patients during the first trimester of pregnancy. |

***Complementary List***

| | |
|---|---|
| *Lugol's solution [c]* | ***Oral liquid:** about 130 mg total iodine/ mL.* |
| ☐ *methimazole* [c]* | ***Tablet:** 5mg, 10mg, 20mg.*<br>* *Carbimazole is an alternative depending on local availability.* |
| *potassium iodide [c]* | ***Tablet:** 60 mg.* |
| *propylthiouracil* [c]* | ***Tablet:** 50 mg.*<br>* *For use when alternative first-line treatment is not appropriate or available.* |

## 19. IMMUNOLOGICALS

### 19.1 Diagnostic agents

All tuberculins should comply with the WHO requirements for tuberculins.

| | |
|---|---|
| tuberculin, purified protein derivative (PPD) | **Injection.** |

### 19.2 Sera and immunoglobulins

All plasma fractions should comply with the WHO requirements.

| | |
|---|---|
| Anti-venom immunoglobulin* | **Injection.**<br>* Exact type to be defined locally. |
| diphtheria antitoxin | **Injection:** 10 000 IU; 20 000 IU in vial. |

## 19. IMMUNOLOGICALS *(continued)*

### 19.3 Vaccines

WHO immunization policy recommendations are published in vaccine position papers on the basis of recommendations made by the Strategic Advisory Group of Experts on Immunization (SAGE).

WHO vaccine position papers are updated three to four times per year. The list below details the vaccines for which there is a recommendation from SAGE and a corresponding WHO position paper as at December 2018. The most recent versions of the WHO position papers, reflecting the current evidence related to a specific vaccine and the related recommendations, can be accessed at any time on the WHO website at: http://www.who.int/immunization/documents/positionpapers/en/index.html.

Vaccine recommendations may be universal or conditional (e.g., in certain regions, in some high-risk populations or as part of immunization programmes with certain characteristics). Details are available in the relevant position papers, and in the Summary Tables of WHO Routine Immunization Recommendations available on the WHO website at: http://www.who.int/immunization/policy/immunization_tables/en/index.html.

Selection of vaccines from the Model List will need to be determined by each country after consideration of international recommendations, epidemiology and national priorities.

All vaccines should comply with the WHO requirements for biological substances.

WHO noted the need for vaccines used in children to be polyvalent.

***Recommendations for all***

BCG vaccine

diphtheria vaccine

Haemophilus influenzae type b vaccine

hepatitis B vaccine

HPV vaccine

measles vaccine

pertussis vaccine

pneumococcal vaccine

poliomyelitis vaccine

rotavirus vaccine

rubella vaccine

tetanus vaccine

| **19. IMMUNOLOGICALS** *(continued)* | |
|---|---|
| ***Recommendations for certain regions*** | |
| Japanese encephalitis vaccine | |
| yellow fever vaccine | |
| tick-borne encephalitis vaccine | |
| ***Recommendations for some high-risk populations*** | |
| cholera vaccine | |
| dengue vaccine | |
| hepatitis A vaccine | |
| meningococcal meningitis vaccine | |
| rabies vaccine | |
| typhoid vaccine | |
| ***Recommendations for immunization programmes with certain characteristics*** | |
| influenza vaccine (seasonal) | |
| mumps vaccine | |
| varicella vaccine | |
| **20. MUSCLE RELAXANTS (PERIPHERALLY-ACTING) AND CHOLINESTERASE INHIBITORS** | |
| ☐ atracurium | **Injection:** 10 mg/ mL (besylate). |
| neostigmine | **Injection:** 500 micrograms in 1- mL ampoule; 2.5 mg (metilsulfate) in 1- mL ampoule.<br>**Tablet:** 15 mg (bromide). |
| suxamethonium | **Injection:** 50 mg (chloride)/ mL in 2- mL ampoule.<br>**Powder for injection** (chloride), in vial. |
| ☐ vecuronium [c] | **Powder for injection:** 10 mg (bromide) in vial. |
| ***Complementary List*** | |
| *pyridostigmine* | ***Injection:*** *1 mg in 1- mL ampoule.*<br>***Tablet:*** *60 mg (bromide).* |
| ☐ *vecuronium* | ***Powder for injection:*** *10 mg (bromide) in vial.* |

## 21. OPHTHALMOLOGICAL PREPARATIONS

### 21.1 Anti-infective agents

| | |
|---|---|
| aciclovir | **Ointment:** 3% W/W. |
| azithromycin | **Solution (eye drops):** 1.5%. |
| erythromycin* | **Ointment:** 0.5% [c].<br>* Infections due to *Chlamydia trachomatis* or *Neisseria gonorrhoea*. |
| ☐ gentamicin | **Solution (eye drops):** 0.3% (sulfate). |
| natamycin | **Suspension: (eye drops):** 5%. |
| ☐ ofloxacin | **Solution (eye drops):** 0.3%. |
| ☐ tetracycline | **Eye ointment:** 1% (hydrochloride). |

### 21.2 Anti-inflammatory agents

| | |
|---|---|
| ☐ prednisolone | **Solution (eye drops):** 0.5% (sodium phosphate). |

### 21.3 Local anaesthetics

| | |
|---|---|
| ☐ tetracaine [a] | **Solution (eye drops):** 0.5% (hydrochloride).<br>[a] Not in preterm neonates. |

### 21.4 Miotics and antiglaucoma medicines

| | |
|---|---|
| acetazolamide | **Tablet:** 250 mg. |
| latanoprost | **Solution (eye drops):** latanoprost 50 micrograms/mL. |
| ☐ pilocarpine | **Solution (eye drops):** 2%; 4% (hydrochloride **or** nitrate). |
| ☐ timolol | **Solution (eye drops):** 0.25%; 0.5% (as hydrogen maleate). |

### 21.5 Mydriatics

| | |
|---|---|
| atropine* [a] | **Solution (eye drops):** 0.1%; 0.5%; 1% (sulfate).<br>* [c] **Or** homatropine (hydrobromide) **or** cyclopentolate (hydrochloride).<br>[a] >3 months. |

***Complementary List***

| | |
|---|---|
| *epinephrine (adrenaline)* | ***Solution (eye drops):** 2% (as hydrochloride).* |

### 21.6 Anti-vascular endothelial growth factor (VEGF) preparations

***Complementary List***

| | |
|---|---|
| *bevacizumab* | ***Injection:** 25 mg/ mL.* |

## 22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE

### 22.1 Contraceptives

#### 22.1.1 *Oral hormonal contraceptives*

| | |
|---|---|
| ☐ ethinylestradiol + ☐ levonorgestrel | **Tablet:** 30 micrograms + 150 micrograms. |
| ☐ ethinylestradiol + ☐ norethisterone | **Tablet:** 35 micrograms + 1 mg. |
| levonorgestrel | **Tablet:** 30 micrograms; 750 micrograms (pack of two); 1.5 mg. |
| ulipristal | **Tablet:** 30 mg (as acetate). |

#### 22.1.2 *Injectable hormonal contraceptives*

| | |
|---|---|
| estradiol cypionate + medroxyprogesterone acetate | **Injection:** 5 mg + 25 mg. |
| medroxyprogesterone acetate | **Injection (intramuscular):** 150 mg/ mL in 1- mL vial.<br>**Injection (subcutaneous):** 104 mg/0.65 mL in pre-filled syringe or single-dose injection delivery system. |
| norethisterone enantate | **Oily solution:** 200 mg/ mL in 1- mL ampoule. |

#### 22.1.3 *Intrauterine devices*

| | |
|---|---|
| copper-containing device | |
| levonorgestrel-releasing intrauterine system | Intrauterine system with reservoir containing 52 mg of levonorestrel. |

#### 22.1.4 *Barrier methods*

condoms

diaphragms

#### 22.1.5 *Implantable contraceptives*

| | |
|---|---|
| etonogestrel-releasing implant | Single-rod etonogestrel-releasing implant, containing 68 mg of etonogestrel. |
| levonorgestrel-releasing implant | Two-rod levonorgestrel-releasing implant, each rod containing 75 mg of levonorgestrel (150 mg total). |

#### 22.1.6 *Intravaginal contraceptives*

| | |
|---|---|
| progesterone vaginal ring* | Progesterone-releasing vaginal ring containing 2.074 g of micronized progesterone.<br>* For use in women actively breastfeeding at least 4 times per day. |

| **22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE** *(continued)* | |
|---|---|
| **22.2 Ovulation inducers** | |
| ***Complementary List*** | |
| *clomifene* | **Tablet:** 50 mg (citrate). |
| **22.3 Uterotonics** | |
| carbetocin | **Injection (heat stable):** 100 micrograms/mL. |
| ☐ ergometrine | **Injection:** 200 micrograms (hydrogen maleate) in 1- mL ampoule. |
| mifepristone – misoprostol<br>Where permitted under national law and where culturally acceptable. | **Tablet** 200 mg – **tablet** 200 micrograms.<br>**Co-package containing:**<br>mifepristone 200 mg tablet [1] and<br>misoprostol 200 microgram tablet [4] |
| misoprostol | **Tablet:** 200 micrograms.<br>– Management of incomplete abortion and miscarriage;<br>– Prevention and treatment of postpartum haemorrhage where oxytocin is not available or cannot be safely used<br>**Vaginal tablet:** 25 micrograms.*<br>* Only for use for induction of labour where appropriate facilities are available. |
| oxytocin | **Injection:** 10 IU in 1- mL. |
| **22.4 Antioxytocics (tocolytics)** | |
| nifedipine | **Immediate-release capsule:** 10 mg. |
| **22.5 Other medicines administered to the mother** | |
| dexamethasone | **Injection:** 4 mg/ mL dexamethasone phosphate (as disodium salt). |
| tranexamic acid | **Injection:** 100 mg/mL in 10-mL ampoule. |

| | |
|---|---|
| **22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE** *(continued)* | |
| **22.6 Medicines administered to the neonate** [c] | |
| caffeine citrate [c] | **Injection:** 20 mg/ mL (equivalent to 10 mg caffeine base/ mL).<br>**Oral liquid:** 20 mg/ mL (equivalent to 10 mg caffeine base/ mL). |
| chlorhexidine* [c] | **Solution or gel:** 7.1% (digluconate) delivering 4% chlorhexidine.<br>* For umbilical cord care. |
| ***Complementary List*** | |
| ☐ *ibuprofen* [c] | ***Solution for injection:*** *5 mg/ mL.* |
| ☐ *prostaglandin E* [c] | ***Solution for injection:***<br>***Prostaglandin E1:*** *0.5 mg/ mL in alcohol.*<br>***Prostaglandin E 2:*** *1 mg/ mL.* |
| *surfactant* [c] | ***Suspension for intratracheal instillation:*** *25 mg/ mL* ***or*** *80 mg/ mL* |
| **23. PERITONEAL DIALYSIS SOLUTION** | |
| ***Complementary List*** | |
| *intraperitoneal dialysis solution (of appropriate composition)* | ***Parenteral solution.*** |

## 24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS

### 24.1 Medicines used in psychotic disorders

| | |
|---|---|
| ☐ chlorpromazine | **Injection:** 25 mg (hydrochloride)/ mL in 2- mL ampoule.<br>**Oral liquid:** 25 mg (hydrochloride)/5 mL.<br>**Tablet:** 100 mg (hydrochloride). |
| ☐ fluphenazine | **Injection:** 25 mg (decanoate or enantate) in 1- mL ampoule. |
| ☐ haloperidol | **Injection:** 5 mg in 1- mL ampoule.<br>**Tablet:** 2 mg; 5 mg. |
| risperidone | **Solid oral dosage form:** 0.25 mg to 6.0 mg. |
| ***Complementary List*** | |
| *chlorpromazine* [c] | **Injection:** 25 mg (hydrochloride)/ mL in 2- mL ampoule.<br>**Oral liquid:** 25 mg (hydrochloride)/5 mL.<br>**Tablet:** 10 mg; 25 mg; 50 mg; 100 mg (hydrochloride). |
| *clozapine* | ***Solid oral dosage form:*** *25 to 200 mg.* |
| *haloperidol* [c] | ***Injection:*** *5 mg in 1- mL ampoule.*<br>***Oral liquid:*** *2 mg/ mL.*<br>***Solid oral dosage form:*** *0.5 mg; 2 mg; 5 mg.* |

### 24.2 Medicines used in mood disorders

#### 24.2.1 *Medicines used in depressive disorders*

| | |
|---|---|
| ☐ amitriptyline | **Tablet:** 25 mg; 75mg. (hydrochloride). |
| ☐ fluoxetine | **Solid oral dosage form:** 20 mg (as hydrochloride). |
| ***Complementary List*** | |
| *fluoxetine* [a] *[c]* | ***Solid oral dosage form:*** *20 mg (as hydrochloride).*<br>[a] >8 years. |

#### 24.2.2 *Medicines used in bipolar disorders*

| | |
|---|---|
| carbamazepine | **Tablet (scored):** 100 mg; 200 mg. |
| lithium carbonate | **Solid oral dosage form:** 300 mg. |
| valproic acid (sodium valproate) | **Tablet (enteric-coated):** 200 mg; 500 mg (sodium valproate). |

### 24.3 Medicines for anxiety disorders

| | |
|---|---|
| ☐ diazepam | **Tablet (scored):** 2 mg; 5 mg. |

| | |
|---|---|
| **24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS** *(continued)* | |
| **24.4 Medicines used for obsessive compulsive disorders** | |
| clomipramine | **Capsule:** 10 mg; 25 mg (hydrochloride). |
| **24.5 Medicines for disorders due to psychoactive substance use** | |
| nicotine replacement therapy (NRT) | **Chewing gum:** 2 mg; 4 mg (as polacrilex).<br>**Transdermal patch:** 5 mg to 30 mg/16 hrs; 7 mg to 21 mg/24 hrs. |
| ***Complementary List*** | |
| ☐ *methadone** | ***Concentrate for oral liquid:*** *5 mg/ mL; 10 mg/ mL (hydrochloride).*<br>***Oral liquid:*** *5 mg/5 mL; 10 mg/5 mL (hydrochloride).*<br>* *The square box is added to include buprenorphine. The medicines should only be used within an established support programme.* |

## 25. MEDICINES ACTING ON THE RESPIRATORY TRACT

### 25.1 Antiasthmatic medicines and medicines for chronic obstructive pulmonary disease

| | |
|---|---|
| ☐ beclometasone | **Inhalation (aerosol):** 50 micrograms (dipropionate) per dose; 100 micrograms (dipropionate) per dose (as CFC free forms). |
| ☐ budesonide [c] | **Inhalation (aerosol):** 100 micrograms per dose; 200 micrograms per dose. |
| ☐ budesonide + formoterol | **Dry powder inhaler:** 100 micrograms + 6 micrograms per dose; 200 micrograms + 6 micrograms per dose |
| epinephrine (adrenaline) | **Injection:** 1 mg (as hydrochloride or hydrogen tartrate) in 1- mL ampoule. |
| ipratropium bromide | **Inhalation (aerosol):** 20 micrograms/metered dose. |
| ☐ salbutamol | **Inhalation (aerosol):** 100 micrograms (as sulfate) per dose.<br>**Injection:** 50 micrograms (as sulfate)/ mL in 5- mL ampoule.<br>**Metered dose inhaler (aerosol):** 100 micrograms (as sulfate) per dose.<br>**Respirator solution for use in nebulizers:** 5 mg (as sulfate)/ mL. |
| ☐ tiotropium | **Powder for inhalaton, capsule:** 18 micrograms.<br>**Inhalation solution:** 1.25 micrograms; 2.5 micrograms per actuation. |

| | |
|---|---|
| **26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID–BASE DISTURBANCES** | |
| **26.1 Oral** | |
| oral rehydration salts | See section 17.5.1. |
| potassium chloride | **Powder for solution.** |
| **26.2 Parenteral** | |
| glucose | **Injectable solution:** 5% (isotonic); 10% (hypertonic); 50% (hypertonic). |
| glucose with sodium chloride | **Injectable solution:** 4% glucose, 0.18% sodium chloride (equivalent to Na+ 30 mmol/L, Cl- 30 mmol/L).<br>**Injectable solution:** 5% glucose, 0.9% sodium chloride (equivalent to Na+ 150 mmol/L and Cl- 150 mmol/L); 5% glucose, 0.45% sodium chloride (equivalent to Na+ 75 mmol/L and Cl- 75 mmol/L) [c] . |
| potassium chloride | **Solution:** 11.2% in 20- mL ampoule (equivalent to K+ 1.5 mmol/ mL, Cl- 1.5 mmol/ mL).<br>**Solution for dilution:** 7.5% (equivalent to K 1 mmol/ mL and Cl 1 mmol/ mL [c] ; 15% (equivalent to K 2 mmol/ mL and Cl 2 mmol/ mL) [c] . |
| sodium chloride | **Injectable solution:** 0.9% isotonic (equivalent to Na+ 154 mmol/L, Cl- 154 mmol/L). |
| sodium hydrogen carbonate | **Injectable solution:** 1.4% isotonic (equivalent to Na+ 167 mmol/L, HCO3- 167 mmol/L).<br>**Solution:** 8.4% in 10- mL ampoule (equivalent to Na+ 1000 mmol/L, HCO3-1000 mmol/L). |
| ☐ sodium lactate, compound solution | **Injectable solution.** |
| **26.3 Miscellaneous** | |
| water for injection | 2- mL; 5- mL; 10- mL ampoules. |

| 27. VITAMINS AND MINERALS | |
|---|---|
| ascorbic acid | **Tablet:** 50 mg. |
| calcium | **Tablet:** 500 mg (elemental). |
| colecalciferol* [c] | **Oral liquid:** 400 IU/ mL.<br>**Solid oral dosage form:** 400 IU; 1000 IU.<br>* Ergocalciferol can be used as an alternative. |
| ☐ ergocalciferol | **Oral liquid:** 250 micrograms/ mL (10 000 IU/ mL).<br>**Solid oral dosage form:** 1.25 mg (50 000 IU). |
| iodine | **Capsule:** 190 mg.<br>**Iodized oil:** 1 mL (480 mg iodine); 0.5 mL (240 mg iodine) in ampoule (oral or injectable); 0.57 mL (308 mg iodine) in dispenser bottle. |
| multiple micronutrient powder [c] | **Sachets containing:**<br>– iron (elemental) 12.5 mg (as coated ferrous fumarate)<br>– zinc (elemental) 5 mg<br>– vitamin A 300 micrograms<br>– with or without other micronutrients at recommended daily values |
| ☐ nicotinamide | **Tablet:** 50 mg. |
| pyridoxine | **Tablet:** 25 mg (hydrochloride). |
| retinol | **Capsule:** 50 000 IU; 100 000 IU; 200 000 IU (as palmitate).<br>**Oral oily solution:** 100 000 IU (as palmitate)/ mL in multidose dispenser.<br>**Tablet (sugar-coated):** 10 000 IU (as palmitate).<br>**Water-miscible injection:** 100 000 IU (as palmitate) in 2- mL ampoule. |
| riboflavin | **Tablet:** 5 mg. |
| sodium fluoride | In any appropriate topical formulation. |
| thiamine | **Tablet:** 50 mg (hydrochloride). |
| ***Complementary List*** | |
| *calcium gluconate* | ***Injection:*** *100 mg/ mL in 10- mL ampoule.* |

| | |
|---|---|
| **28. EAR, NOSE AND THROAT MEDICINES** | |
| acetic acid [c] | **Topical:** 2%, in alcohol. |
| ☐ budesonide [c] | **Nasal spray:** 100 micrograms per dose. |
| ☐ ciprofloxacin [c] | **Topical:** 0.3% drops (as hydrochloride). |
| ☐ xylometazoline [a] [c] | **Nasal spray:** 0.05%.<br>[a] Not in children less than 3 months. |
| **29. MEDICINES FOR DISEASES OF JOINTS** | |
| **29.1 Medicines used to treat gout** | |
| allopurinol | **Tablet:** 100 mg. |
| **29.2 Disease-modifying agents used in rheumatoid disorders (DMARDs)** | |
| chloroquine | **Tablet:** 100 mg; 150 mg (as phosphate or sulfate). |
| ***Complementary List*** | |
| *azathioprine* | ***Tablet:*** *50 mg.* |
| *hydroxychloroquine [c]* | ***Solid oral dosage form:*** *200 mg (as sulfate).* |
| *methotrexate* | ***Tablet:*** *2.5 mg (as sodium salt).* |
| *penicillamine* | ***Solid oral dosage form:*** *250 mg.* |
| *sulfasalazine* | ***Tablet:*** *500 mg.* |
| **29.3 Juvenile joint diseases** | |
| acetylsalicylic acid* (acute or chronic use) | **Suppository:** 50 mg to 150 mg.<br>**Tablet:** 100 mg to 500 mg.<br>* For use for rheumatic fever, juvenile arthritis, Kawasaki disease. |

# Table 1.1: Medicines with age or weight restrictions

| | |
|---|---|
| artesunate + pyronaridine tetraphosphate | >5 kg |
| atazanavir | >25 kg |
| atropine | >3 months |
| bedaquiline | ≥6 years |
| benzyl benzoate | >2 years |
| betamethasone topical preparations | hydrocortisone preferred in neonates |
| cefazolin | >1 month |
| ceftriaxone | >41 weeks corrected gestational age |
| darunavir | >3 years |
| delamanid | ≥6 years |
| dihydroartemisinin + piperaquine phosphate | >5 kg |
| diloxanide | >25 kg |
| dolutegravir | ≥25 kg |
| doxycycline | >8 years (except for serious infections e.g. cholera) |
| efavirenz | >3 years or >10 kg |
| fluoxetine | >8 years |
| ibuprofen | >3 months (except IV form for patent ductus arteriosus) |
| mefloquine | >5 kg or >3 months |
| metoclopramide | Not in neonates |
| nevirapine | >6 weeks |
| ondansetron | >1 month |
| silver sulfadiazine | >2 months |
| tetracaine | Not in preterm neonates |
| xylometazoline | >3 months |

# Table 1.2: Explanation of dosage forms

## A. Principal dosage forms used in EML – oral administration

| Term | Definition |
|---|---|
| **Solid oral dosage form** | Refers to tablets or capsules or other solid dosage forms such as 'melts' that are immediate-release preparations. It implies that there is no difference in clinical efficacy or safety between the available dosage forms, and countries should therefore choose the form(s) to be listed depending on quality and availability.<br>The term 'solid oral dosage form' is *never* intended to allow any type of modified-release tablet. |
| **Tablets** | Refers to:<br>• uncoated or coated (film-coated or sugar-coated) tablets that are intended to be swallowed whole;<br>• unscored and scored*;<br>• tablets that are intended to be chewed before being swallowed;<br>• tablets that are intended to be dispersed or dissolved in water or another suitable liquid before being swallowed;<br>• tablets that are intended to be crushed before being swallowed.<br>The term 'tablet' without qualification is never intended to allow any type of modified-release tablet. |
| **Tablets (qualified)** | Refers to a specific type of tablet:<br>**chewable** - tablets that are intended to be chewed before being swallowed;<br>**dispersible** - tablets that are intended to be dispersed in water or another suitable liquid before being swallowed;<br>**soluble** - tablets that are intended to be dissolved in water or another suitable liquid before being swallowed;<br>**crushable** - tablets that are intended to be crushed before being swallowed;<br>**scored** - tablets bearing a break mark or marks where sub-division is intended in order to provide doses of less than one tablet;<br>**sublingual** - tablets that are intended to be placed beneath the tongue. |

* Scored tablets may be divided for ease of swallowing, provided that dose is a whole number of tablets.

Table 1.2 *continued*

| Term | Definition |
|---|---|
| | The term 'tablet' is *always* qualified with an additional term (in parentheses) in entries where one of the following types of tablet is intended: **gastro-resistant** (such tablets may sometimes be described as enteric-coated or as delayed-release), **prolonged-release** or another modified-release form. |
| **Capsules** | Refers to hard or soft capsules.<br>The term 'capsule' without qualification is *never* intended to allow any type of modified-release capsule. |
| **Capsules (qualified)** | The term 'capsule' with qualification refers to **gastro-resistant** (such capsules may sometimes be described as enteric-coated or as delayed-release), **prolonged-release** or another modified-release form. |
| **Granules** | Preparations that are issued to patient as granules to be swallowed without further preparation, to be chewed, or to be taken in or with water or another suitable liquid.<br>The term 'granules' without further qualification is *never* intended to allow any type of modified-release granules. |
| **Oral powder** | Preparations that are issued to patient as powder (usually as single-dose) to be taken in or with water or another suitable liquid. |
| **Oral liquid** | Liquid preparations intended to be *swallowed* i.e. oral solutions, suspensions, emulsions and oral drops, including those constituted from powders or granules, but *not* those preparations intended for *oromucosal administration* e.g. gargles and mouthwashes.<br>Oral liquids presented as powders or granules may offer benefits in the form of better stability and lower transport costs. If more than one type of oral liquid is available on the same market (e.g. solution, suspension, granules for reconstitution), they may be interchanged and in such cases should be bioequivalent. It is preferable that oral liquids do not contain sugar and that solutions for children do not contain alcohol. |

## B. Principal dosage forms used in EML – parenteral administration

| Term | Definition |
|---|---|
| **Injection** | Refers to solutions, suspensions and emulsions including those constituted from powders or concentrated solutions. |
| **Injection (qualified)** | Route of administration is indicated in parentheses where relevant. |
| **Injection (oily)** | The term 'injection' is qualified by '(oily)' in relevant entries. |
| **Intravenous infusion** | Refers to solutions and emulsions including those constituted from powders or concentrated solutions. |

## C. Other dosage forms

| Mode of administration | Term to be used |
|---|---|
| **To the eye** | Eye drops, eye ointments. |
| **Topical** | For liquids: lotions, paints.<br>For semi-solids: cream, ointment. |
| **Rectal** | Suppositories, gel or solution. |
| **Vaginal** | Pessaries or vaginal tablets. |
| **Inhalation** | Powder for inhalation, pressurized inhalation, nebulizer. |

# Annex 2

## WHO Model List of Essential Medicines for Children (2019)

### Explanatory notes

#### This Model List is intended for use for children up to 12 years of age

The **core list** presents a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

The **complementary list** presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost–effectiveness in a variety of settings.

The **square box symbol** (□) is primarily intended to indicate similar clinical performance within a pharmacological class. The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources.

Therapeutic equivalence is indicated only on the basis of reviews of efficacy and safety and when consistent with WHO clinical guidelines. National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price.

The format and numbering of the 21st WHO Model List of Essential Medicines is used for the 7th WHO Model Essential List for Children. Some sections have been deleted because they contain medicines that are not relevant for children.

The [a] symbol indicates that there is an age or weight restriction on use of the medicine; details for each medicine are in Table 1.1 of Annex 1.

The presence of an entry on the Essential Medicines List carries no assurance as to pharmaceutical quality. It is the responsibility of the relevant national or regional drug regulatory authority to ensure that each product is of appropriate pharmaceutical quality (including stability) and that when relevant, different products are interchangeable.

For recommendations and advice concerning all aspects of the quality assurance of medicines see the WHO Medicines website http://www.who.int/medicines/areas/quality_safety/quality_assurance/en/.

Medicines and dosage forms are listed in alphabetical order within each section and there is no implication of preference for one form over another. Standard treatment guidelines should be consulted for information on appropriate dosage forms.

The main terms used for dosage forms in the Essential Medicines List can be found in Table 1.2 of Annex 1.

Definitions of many of these terms and pharmaceutical quality requirements applicable to the different categories are published in the current edition of *The International Pharmacopoeia* http://www.who.int/medicines/publications/pharmacopoeia.

| | |
|---|---|
| **1. ANAESTHETICS, PREOPERATIVE MEDICINES AND MEDICAL GASES** | |
| **1.1 General anaesthetics and oxygen** | |
| **1.1.1** ***Inhalational medicines*** | |
| halothane | **Inhalation.** |
| isoflurane | **Inhalation.** |
| nitrous oxide | **Inhalation.** |
| oxygen | **Inhalation** (medical gas). |
| **1.1.2** ***Injectable medicines*** | |
| ketamine | **Injection:** 50 mg (as hydrochloride)/mL in 10-mL vial. |
| propofol* | **Injection:** 10 mg/mL; 20 mg/mL.<br>* Thiopental may be used as an alternative depending on local availability and cost. |
| **1.2 Local anaesthetics** | |
| ☐ bupivacaine | **Injection:** 0.25%; 0.5% (hydrochloride) in vial.<br>**Injection for spinal anaesthesia:** 0.5% (hydrochloride) in 4-mL ampoule to be mixed with 7.5% glucose solution. |
| ☐ lidocaine | **Injection:** 1%; 2% (hydrochloride) in vial.<br>**Injection for spinal anaesthesia:** 5% (hydrochloride) in 2-mL ampoule to be mixed with 7.5% glucose solution.<br>**Topical forms:** 2% to 4% (hydrochloride). |
| lidocaine + epinephrine (adrenaline) | **Dental cartridge:** 2% (hydrochloride) + epinephrine 1:80 000.<br>**Injection:** 1%; 2% (hydrochloride **or** sulfate) + epinephrine 1:200 000 in vial. |
| **1.3 Preoperative medication and sedation for short-term procedures** | |
| atropine | **Injection:** 1 mg (sulfate) in 1-mL ampoule. |
| ☐ midazolam | **Injection:** 1 mg/mL.<br>**Oral liquid:** 2 mg/mL.<br>**Tablet:** 7.5 mg; 15 mg. |
| morphine | **Injection:** 10 mg (sulfate **or** hydrochloride) in 1-mL ampoule. |

| | |
|---|---|
| **1. ANAESTHETICS, PREOPERATIVE MEDICINES AND MEDICAL GASES** *(continued)* | |
| **1.4 Medical gases** | |
| oxygen* | **Inhalation**<br>For use in the management of hypoxaemia.<br>* No more than 30% oxygen should be used to initiate resuscitation of neonates less than or equal to 32 weeks of gestation. |
| **2. MEDICINES FOR PAIN AND PALLIATIVE CARE** | |
| **2.1 Non-opioids and non-steroidal anti-inflammatory medicines (NSAIMs)** | |
| ibuprofen [a] | **Oral liquid:** 200 mg/5 mL.<br>**Tablet:** 200 mg; 400 mg; 600 mg.<br>[a] Not in children less than 3 months. |
| paracetamol* | **Oral liquid:** 120 mg/5 mL; 125 mg/5 mL.<br>**Suppository:** 100 mg.<br>**Tablet:** 100 mg to 500 mg.<br>* Not recommended for anti-inflammatory use due to lack of proven benefit to that effect. |
| **2.2 Opioid analgesics** | |
| ☐ morphine* | **Granules (slow release; to mix with water):** 20 mg to 200 mg (morphine sulfate).<br>**Injection:** 10 mg (morphine hydrochloride or morphine sulfate) in 1-mL ampoule.<br>**Oral liquid:** 10 mg (morphine hydrochloride or morphine sulfate)/5 mL.<br>**Tablet (slow release):** 10 mg – 200mg (morphine hydrochloride or morphine sulfate).<br>**Tablet (immediate release):** 10 mg (morphine sulfate).<br>* Alternatives limited to hydromorphone and oxycodone. |
| ***Complementary list*** | |
| *methadone** | ***Tablet:** 5 mg; 10 mg (as hydrochloride).*<br>***Oral liquid:** 5mg/ 5mL; 10mg/ 5mL (as hydrochloride).*<br>***Concentrate for oral liquid:** 5 mg/ mL; 10mg/ mL (as hydrochloride).*<br>* *For the management of cancer pain.* |

| 2. MEDICINES FOR PAIN AND PALLIATIVE CARE *(continued)* | |
|---|---|
| **2.3 Medicines for other symptoms common in palliative care** | |
| amitriptyline | **Tablet:** 10 mg; 25 mg. |
| cyclizine | **Injection:** 50 mg/mL.<br>**Tablet:** 50 mg. |
| dexamethasone | **Injection:** 4 mg/mL in 1-mL ampoule (as disodium phosphate salt).<br>**Oral liquid:** 2 mg/5 mL.<br>**Tablet:** 2 mg. |
| diazepam | **Injection:** 5 mg/mL.<br>**Oral liquid:** 2 mg/5 mL.<br>**Rectal solution:** 2.5 mg; 5 mg; 10 mg.<br>**Tablet:** 5 mg; 10 mg. |
| docusate sodium | **Capsule:** 100 mg.<br>**Oral liquid:** 50 mg/5 mL. |
| fluoxetine [a] | **Solid oral dosage form:** 20 mg (as hydrochloride).<br>[a] >8 years. |
| hyoscine hydrobromide | **Injection:** 400 micrograms/mL; 600 micrograms/mL.<br>**Transdermal patches:** 1 mg/72 hours. |
| lactulose | **Oral liquid:** 3.1–3.7 g/5 mL. |
| midazolam | **Injection:** 1 mg/mL; 5 mg/mL.<br>**Oral liquid:** 2mg/mL.<br>**Solid oral dosage form:** 7.5 mg; 15 mg. |
| ☐ ondansetron [a] | **Injection:** 2 mg base/mL in 2-mL ampoule (as hydrochloride).<br>**Oral liquid:** 4 mg base/5 mL.<br>**Solid oral dosage form:** Eq 4 mg base; Eq 8 mg base.<br>[a] >1 month. |
| senna | **Oral liquid:** 7.5 mg/5 mL. |

| | |
|---|---|
| **3. ANTIALLERGICS AND MEDICINES USED IN ANAPHYLAXIS** | |
| dexamethasone | **Injection:** 4 mg/mL in 1-mL ampoule (as disodium phosphate salt). |
| epinephrine (adrenaline) | **Injection:** 1 mg (as hydrochloride or hydrogen tartrate) in 1-mL ampoule. |
| hydrocortisone | **Powder for injection:** 100 mg (as sodium succinate) in vial. |
| ☐ loratadine* | **Oral liquid:** 1 mg/mL.<br>**Tablet:** 10 mg.<br>* There may be a role for sedating antihistamines for limited indications. |
| ☐ prednisolone | **Oral liquid:** 5 mg/mL.<br>**Tablet:** 5 mg; 25 mg. |
| **4. ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS** | |
| **4.1 Non-specific** | |
| charcoal, activated | **Powder.** |
| **4.2 Specific** | |
| acetylcysteine | **Injection:** 200 mg/mL in 10-mL ampoule.<br>**Oral liquid:** 10%; 20%. |
| atropine | **Injection:** 1 mg (sulfate) in 1-mL ampoule. |
| calcium gluconate | **Injection:** 100 mg/mL in 10-mL ampoule. |
| naloxone | **Injection:** 400 micrograms (hydrochloride) in 1-mL ampoule. |
| ***Complementary List*** | |
| *deferoxamine* | ***Powder for injection:** 500 mg (mesilate) in vial.* |
| *dimercaprol* | ***Injection in oil:** 50 mg/mL in 2-mL ampoule.* |
| *fomepizole* | ***Injection:** 5 mg/mL (sulfate) in 20-mL ampoule or 1 g/mL (base) in 1.5-mL ampoule.* |
| *sodium calcium edetate* | ***Injection:** 200 mg/mL in 5-mL ampoule.* |
| *succimer* | ***Solid oral dosage form:** 100 mg.* |

| 5. ANTICONVULSANTS/ANTIEPILEPTICS | |
|---|---|
| carbamazepine | **Oral liquid:** 100 mg/5 mL.<br>**Tablet (chewable):** 100 mg; 200 mg.<br>**Tablet (scored):** 100 mg; 200 mg. |
| diazepam | **Gel or rectal solution:** 5 mg/mL in 0.5 mL; 2-mL; 4-mL tubes. |
| lamotrigine* | **Tablet:** 25 mg; 50 mg; 100 mg; 200 mg.<br>**Tablet (chewable, dispersible):** 2 mg; 5 mg; 25 mg; 50 mg; 100 mg; 200 mg.<br>* As adjunctive therapy for treatment-resistant partial or generalized seizures. |
| ☐ lorazepam | **Parenteral formulation:** 2 mg/mL in 1-mL ampoule; 4 mg/mL in 1-mL ampoule. |
| midazolam | **Solution for oromucosal administration:** 5 mg/mL; 10 mg/mL.<br>**Ampoule*:** 1 mg/ mL; 10 mg/mL.<br>* For buccal administration when solution for oromucosal administration is not available. |
| phenobarbital | **Injection:** 200 mg/mL (sodium).<br>**Oral liquid:** 15 mg/5 mL.<br>**Tablet:** 15 mg to 100 mg. |
| phenytoin | **Injection:** 50 mg/mL in 5-mL vial (sodium salt).<br>**Oral liquid:** 25 mg to 30 mg/5 mL.*<br>**Solid oral dosage form:** 25 mg; 50 mg; 100 mg (sodium salt).<br>**Tablet (chewable):** 50 mg.<br>* The presence of both 25 mg/5 mL and 30 mg/5 mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided. |
| valproic acid (sodium valproate) | **Oral liquid:** 200 mg/5 mL.<br>**Tablet (crushable):** 100 mg.<br>**Tablet (enteric-coated):** 200 mg; 500 mg (sodium valproate). |
| ***Complementary List*** | |
| *ethosuximide* | ***Capsule*:** *250 mg.*<br>***Oral liquid:*** *250 mg/5 mL.* |
| *valproic acid (sodium valproate)* | ***Injection:*** *100 mg/ mL in 4- mL ampoule; 100 mg/ mL in 10- mL ampoule.* |

## 6. ANTI-INFECTIVE MEDICINES

### 6.1 Anthelminthics

#### 6.1.1 *Intestinal anthelminthics*

| | |
|---|---|
| albendazole | **Tablet (chewable):** 400 mg. |
| ivermectin | **Tablet (scored):** 3 mg. |
| levamisole | **Tablet:** 50 mg; 150 mg (as hydrochloride). |
| mebendazole | **Tablet (chewable):** 100 mg; 500 mg. |
| niclosamide | **Tablet (chewable):** 500 mg. |
| praziquantel | **Tablet:** 150 mg; 600 mg. |
| pyrantel | **Oral liquid:** 50 mg (as embonate or pamoate)/mL.<br>**Tablet (chewable):** 250 mg (as embonate or pamoate). |

#### 6.1.2 *Antifilarials*

| | |
|---|---|
| albendazole | **Tablet (chewable):** 400 mg. |
| diethylcarbamazine | **Tablet:** 50 mg; 100 mg (dihydrogen citrate). |
| ivermectin | **Tablet (scored):** 3 mg. |

#### 6.1.3 *Antischistosomals and other antitrematode medicines*

| | |
|---|---|
| praziquantel | **Tablet:** 600 mg. |
| triclabendazole | **Tablet:** 250 mg. |

***Complementary List***

| | |
|---|---|
| *oxamniquine** | ***Capsule:** 250 mg.*<br>***Oral liquid:** 250 mg/5 mL.* |

* *Oxamniquine is listed for use when praziquantel treatment fails.*

## 6. ANTI-INFECTIVE MEDICINES *(continued)*

### 6.2 Antibacterials

To assist in the development of tools for antibiotic stewardship at local, national and global levels and to reduce antimicrobial resistance, the Access, Watch, Reserve (AWaRe) classification of antibiotics was developed – where antibiotics are classified into different groups to emphasize the importance of their appropriate use.

**ACCESS GROUP ANTIBIOTICS**

This group includes antibiotics that have activity against a wide range of commonly encountered susceptible pathogens while also showing lower resistance potential than antibiotics in the other groups. Selected Access group antibiotics are recommended as essential first or second choice empiric treatment options for infectious syndromes reviewed by the EML Expert Committee and are listed as individual medicines on the Model Lists to improve access and promote appropriate use. They are essential antibiotics that should be widely available, affordable and quality assured.

**WATCH GROUP ANTIBIOTICS**

This group includes antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine[1] and/or antibiotics that are at relatively high risk of selection of bacterial resistance. These medicines should be prioritized as key targets of stewardship programs and monitoring. Selected Watch group antibiotics are recommended as essential first or second choice empiric treatment options for a limited number of specific infectious syndromes and are listed as individual medicines on the Model Lists.

[1] http://apps.who.int/iris/bitstream/10665/251715/1/9789241511469-eng.pdf?ua=1

**RESERVE GROUP ANTIBIOTICS**

This group includes antibiotics and antibiotic classes that should be reserved for treatment of confirmed or suspected infections due to multi-drug-resistant organisms. Reserve group antibiotics should be treated as "last resort" options. Selected Reserve group antibiotics are listed as individual medicines on the Model Lists when they have a favourable risk-benefit profile and proven activity against "Critical Priority" or "High Priority" pathogens identified by the WHO Priority Pathogens List[1], notably carbapenem resistant *Enterobacteriaceae*. These antibiotics should be accessible, but their use should be tailored to highly specific patients and settings, when all alternatives have failed or are not suitable. These medicines could be protected and prioritized as key targets of national and international stewardship programs involving monitoring and utilization reporting, to preserve their effectiveness.

[1] https://apps.who.int/iris/handle/10665/311820

**6. ANTI-INFECTIVE MEDICINES** *(continued)*

**6.2.1** ***Access group antibiotics***

| | | |
|---|---|---|
| amikacin | **Injection:** 250 mg (as sulfate)/mL in 2- mL vial. | |
| | **FIRST CHOICE**<br>– *pyelonephritis (severe)*<br>– *high-risk febrile neutropenia* | **SECOND CHOICE**<br>– *sepsis in neonates and children* |
| amoxicillin | **Powder for oral liquid:** 125 mg (as trihydrate)/5 mL; 250 mg (as trihydrate)/5 mL.<br>**Solid oral dosage form:** 250 mg; 500 mg (as trihydrate).<br>**Powder for injection:** 250 mg; 500 mg; 1 g (as sodium) in vial. | |
| | **FIRST CHOICE**<br>– *community acquired pneumonia (mild to moderate)*<br>– *community acquired pneumonia (severe)*<br>– *complicated severe acute malnutrition*<br>– *lower urinary tract infections*<br>– *otitis media*<br>– *pharyngitis*<br>– *sepsis in neonates and children*<br>– *sinusitis*<br>– *uncomplicated severe acute malnutrition*<br>– *progressive apical dental abscess* | **SECOND CHOICE**<br>– *acute bacterial meningitis* |

**6. ANTI-INFECTIVE MEDICINES** *(continued)*

| | | |
|---|---|---|
| amoxicillin + clavulanic acid | **Oral liquid:** 125 mg amoxicillin + 31.25 mg clavulanic acid/5 mL AND 250 mg amoxicillin + 62.5 mg clavulanic acid/5 mL.<br>**Tablet:** 500 mg (as trihydrate) + 125 mg (as potassium salt).<br>**Powder for injection:** 500 mg (as sodium) + 100 mg (as potassium salt); 1000 mg (as sodium) + 200 mg (as potassium salt) in vial. | |
| | **FIRST CHOICE**<br>– *community acquired pneumonia (severe)*<br>– *complicated intraabdominal infections (mild to moderate)*<br>– *hospital acquired pneumonia*<br>– *low-risk febrile neutropenia*<br>– *lower urinary tract infections*<br>– *sinusitis*<br>– *skin and soft tissue infections* | **SECOND CHOICE**<br>– *bone and joint infections*<br>– *community acquired pneumonia (mild to moderate)*<br>– *community acquired pneumonia (severe)*<br>– *otitis media*<br>– *surgical prophylaxis* |
| ampicillin | **Powder for injection:** 500 mg; 1 g (as sodium salt) in vial. | |
| | **FIRST CHOICE**<br>– *community acquired pneumonia (severe)*<br>– *complicated severe acute malnutrition*<br>– *sepsis in neonates and children* | **SECOND CHOICE**<br>– *acute bacterial meningitis* |
| benzathine benzylpenicillin | **Powder for injection:** 900 mg benzylpenicillin (= 1.2 million IU) in 5- mL vial; 1.44 g benzylpenicillin (= 2.4 million IU) in 5- mL vial. | |
| | **FIRST CHOICE**<br>– *syphilis (congenital)* | **SECOND CHOICE** |

**6. ANTI-INFECTIVE MEDICINES** *(continued)*

| | | |
|---|---|---|
| benzylpenicillin | **Powder for injection:** 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial. | |
| | **FIRST CHOICE**<br>– *community acquired pneumonia (severe)*<br>– *complicated severe acute malnutrition*<br>– *sepsis in neonates and children*<br>– *syphilis (congenital)* | **SECOND CHOICE**<br>– *acute bacterial meningitis* |
| cefalexin | **Powder for reconstitution with water:** 125 mg/5 mL; 250 mg/5 mL (anhydrous).<br>**Solid oral dosage form:** 250 mg (as monohydrate). | |
| | **FIRST CHOICE** | **SECOND CHOICE**<br>– *pharyngitis*<br>– *skin and soft tissue infections* |
| cefazolin [a] | **Powder for injection:** 1 g (as sodium salt) in vial.<br>[a] >1 month. | |
| | **FIRST CHOICE**<br>– *surgical prophylaxis* | **SECOND CHOICE**<br>– *bone and joint infections* |
| chloramphenicol | **Capsule:** 250 mg.<br>**Oily suspension for injection*:** 0.5 g (as sodium succinate)/ mL in 2- mL ampoule.<br>* Only for the presumptive treatment of epidemic meningitis in children older than 2 years.<br>**Oral liquid:** 150 mg (as palmitate)/5 mL.<br>**Powder for injection:** 1 g (sodium succinate) in vial. | |
| | **FIRST CHOICE** | **SECOND CHOICE**<br>– *acute bacterial meningitis* |
| clindamycin | **Capsule:** 150 mg (as hydrochloride).<br>**Injection:** 150 mg (as phosphate)/ mL.<br>**Oral liquid:** 75 mg/5 mL (as palmitate). | |
| | **FIRST CHOICE** | **SECOND CHOICE**<br>– *bone and joint infections* |

**6. ANTI-INFECTIVE MEDICINES** *(continued)*

| | | |
|---|---|---|
| ☐ cloxacillin* | **Capsule:** 500 mg; 1 g (as sodium salt).<br>**Powder for injection:** 500 mg (as sodium salt) in vial.<br>**Powder for oral liquid:** 125 mg (as sodium salt)/5 mL.<br>* Cloxacillin, dicloxacillin and flucloxacillin are preferred for oral administration due to better bioavailability. | |
| | **FIRST CHOICE**<br>– *bone and joint infections*<br>– *skin and soft tissue infections* | **SECOND CHOICE**<br>– *sepsis in neonates and children* |
| doxycycline [a] | **Oral liquid:** 25 mg/5 mL; 50 mg/5 mL (anhydrous).<br>**Solid oral dosage form:** 50 mg; 100 mg (as hyclate).<br>**Powder for injection:** 100 mg in vial.<br>[a] Use in children <8 years only for life-threatening infections when no alternative exists. | |
| | **FIRST CHOICE** | **SECOND CHOICE**<br>– *cholera*<br>– *community acquired pneumonia (mild to moderate)* |
| gentamicin | **Injection:** 10 mg; 40 mg (as sulfate)/ mL in 2- mL vial. | |
| | **FIRST CHOICE**<br>– *community acquired pneumonia (severe)*<br>– *complicated severe acute malnutrition*<br>– *sepsis in neonates and children* | **SECOND CHOICE**<br>– *surgical prophylaxis* |

**6. ANTI-INFECTIVE MEDICINES** *(continued)*

| | | |
|---|---|---|
| metronidazole | **Injection:** 500 mg in 100- mL vial.<br>**Oral liquid:** 200 mg (as benzoate)/5 mL.<br>**Tablet:** 200 mg to 500 mg. | |
| | **FIRST CHOICE**<br>– *C. difficile infection*<br>– *complicated intra-abdominal infections (mild to moderate)*<br>– *complicated intra-abdominal infections (severe)*<br>– *surgical prophylaxis* | **SECOND CHOICE**<br>– *complicated intra-abdominal infections (mild to moderate)* |
| nitrofurantoin | **Oral liquid:** 25 mg/5 mL.<br>**Tablet:** 100 mg. | |
| | **FIRST CHOICE**<br>– *lower urinary tract infections* | **SECOND CHOICE** |
| phenoxymethylpenicillin | **Powder for oral liquid:** 250 mg (as potassium salt)/5 mL.<br>**Tablet:** 250 mg (as potassium salt). | |
| | **FIRST CHOICE**<br>– *community acquired pneumonia (mild to moderate)*<br>– *pharyngitis*<br>– *progressive apical dental abscess* | **SECOND CHOICE** |
| procaine benzylpenicillin* | **Powder for injection:** 1 g (=1 million IU); 3 g (=3 million IU) in vial.<br>* Procaine benzylpenicillin is not recommended as first-line treatment for neonatal sepsis / sepsis except in settings with high neonatal mortality, when given by trained health workers in cases where hospital care is not achievable. | |
| | **FIRST CHOICE**<br>– *syphilis (congenital)* | **SECOND CHOICE** |

**6. ANTI-INFECTIVE MEDICINES** *(continued)*

sulfamethoxazole + trimethoprim*

**Injection:**
80 mg + 16 mg/ mL in 5- mL ampoule;
80 mg + 16 mg/ mL in 10- mL ampoule.

**Oral liquid:** 200 mg + 40 mg/5 mL.

**Tablet:** 100 mg + 20 mg; 400 mg + 80 mg.

* Single agent trimethoprim may be an alternative for lower urinary tract infection.

| FIRST CHOICE | SECOND CHOICE |
|---|---|
| – *lower urinary tract infections* | – *acute invasive bacterial diarrhoea / dysentery* |

**6.2.2** ***Watch group antibiotics***

azithromycin*

**Capsule:** 250 mg; 500 mg (anhydrous).

**Oral liquid:** 200 mg/5 mL.

* Also listed for single-dose treatment of trachoma and yaws.

| FIRST CHOICE | SECOND CHOICE |
|---|---|
| – *cholera*<br>– *enteric fever* | – *acute invasive bacterial diarrhoea / dysentery* |

cefixime

**Capsules or tablets:** 200 mg; 400 mg (as trihydrate).

**Powder for oral liquid:** 100 mg /5 mL.

| FIRST CHOICE | SECOND CHOICE |
|---|---|
| | – *acute invasive bacterial diarrhoea / dysentery* |

**6. ANTI-INFECTIVE MEDICINES** *(continued)*

cefotaxime*

**Powder for injection:** 250 mg per vial (as sodium salt).

* 3rd generation cephalosporin of choice for use in hospitalized neonates.

| FIRST CHOICE | SECOND CHOICE |
|---|---|
| – *acute bacterial meningitis*<br>– *community acquired pneumonia (severe)*<br>– *complicated intraabdominal infections (mild to moderate)*<br>– *complicated intraabdominal infections (severe)*<br>– *hospital acquired pneumonia*<br>– *pyelonephritis (severe)* | – *bone and joint infections*<br>– *pyelonephritis (mild to moderate)*<br>– *sepsis in neonates and children* |

ceftriaxone* [a]

**Powder for injection:** 250 mg; 1 g (as sodium salt) in vial.

* Do not administer with calcium and avoid in infants with hyperbilirubinaemia.

[a] >41 weeks corrected gestational age.

| FIRST CHOICE | SECOND CHOICE |
|---|---|
| – *acute bacterial meningitis*<br>– *community acquired pneumonia (severe)*<br>– *complicated intraabdominal infections (mild to moderate)*<br>– *complicated intraabdominal infections (severe)*<br>– *hospital acquired pneumonia*<br>– *pyelonephritis (severe)*<br>– *enteric fever* | – *acute invasive bacterial diarrhoea / dysentery*<br>– *bone and joint infections*<br>– *pyelohepnritis or prostatitis (mild to moderate)*<br>– *sepsis in neonates and children* |

| **6. ANTI-INFECTIVE MEDICINES** *(continued)* | | |
|---|---|---|
| cefuroxime | **Powder for injection:** 250 mg, 750 mg, 1.5 g (as sodium salt) in vial | |
| | **FIRST CHOICE** | **SECOND CHOICE**<br>– *surgical prophylaxis* |
| ciprofloxacin | **Oral liquid:** 250 mg/5 mL (anhydrous) .<br>**Solution for IV infusion:** 2 mg/ mL (as hyclate).<br>**Tablet:** 250 mg (as hydrochloride). | |
| | **FIRST CHOICE**<br>– *acute invasive bacterial diarrhoea / dysentery*<br>– *low-risk febrile neutropenia*<br>– *pyelonephritis (mild to moderate)*<br>– *enteric fever* | **SECOND CHOICE**<br>– *cholera*<br>– *complicated intraabdominal infections (mild to moderate)* |
| clarithromycin* | **Solid oral dosage form:** 500 mg.<br>**Powder for oral liquid:** 125 mg/5 mL; 250 mg/5 mL.<br>**Powder for injection:** 500 mg in vial.<br>* Erythromycin may be an alternative. | |
| | **FIRST CHOICE** | **SECOND CHOICE**<br>– *pharyngitis* |
| piperacillin + tazobactam | **Powder for injection:** 2 g (as sodium salt) + 250 mg (as sodium salt); 4 g (as sodium salt) + 500 mg (as sodium salt) in vial. | |
| | **FIRST CHOICE**<br>– *complicated intraabdominal infections (severe)*<br>– *high-risk febrile neutropenia*<br>– *hospital acquired pneumonia* | **SECOND CHOICE** |
| vancomycin | **Capsule:** 125 mg; 250 mg (as hydrochloride). | |
| | | **SECOND CHOICE**<br>– *C. difficile infection* |

**6. ANTI-INFECTIVE MEDICINES** *(continued)*

***Complementary List***

| | |
|---|---|
| *ceftazidime* | ***Powder for injection:*** *250 mg* ***or*** *1 g (as pentahydrate) in vial.* |
| *meropenem** [a] | ***Powder for injection:*** *500 mg (as trihydrate); 1 g (as trihydrate) in vial.* |

[a] >3 months.

* *Imipenem + cilastatin is an alternative except for acute bacterial meningitis where meropenen is preferred.*

| FIRST CHOICE | SECOND CHOICE |
|---|---|
| | – *acute bacterial meningitis in neonates*<br>– *complicated intraabdominal infections (severe)*<br>– *high-risk febrile neutropenia* |

| | |
|---|---|
| *vancomycin* | ***Powder for injection:*** *250 mg (as hydrochloride) in vial.* |

| FIRST CHOICE | SECOND CHOICE |
|---|---|
| | – *high-risk febrile neutropenia* |

**6.2.3** ***Reserve group antibiotics***

***Complementary List***

| | |
|---|---|
| *ceftazidime + avibactam* | ***Powder for injection:*** *2 g + 0.5 g in vial.* |
| *colistin* | ***Powder for injection:*** *1 million I.U. (as colistemethate sodium) in vial* |
| *fosfomycin* | ***Powder for injection:*** *2 g; 4 g (as sodium) in vial.* |
| *linezolid* | ***Injection for intravenous administration:*** *2 mg/ mL in 300 mL bag.*<br>***Powder for oral liquid:*** *100 mg/5 mL.*<br>***Tablet:*** *400 mg; 600 mg.* |
| *polymyxin B* | ***Powder for injection:*** *500,000 I.U. in vial.* |

## 6. ANTI-INFECTIVE MEDICINES *(continued)*

### 6.2.4 *Antileprosy medicines*

Medicines used in the treatment of leprosy should never be used except in combination. Combination therapy is essential to prevent the emergence of drug resistance. Colour-coded blister packs (MDT blister packs) containing standard two-medicine (paucibacillary leprosy) or three-medicine (multibacillary leprosy) combinations for adult and childhood leprosy should be used. MDT blister packs can be supplied free of charge through WHO.

| | |
|---|---|
| clofazimine | **Capsule:** 50 mg; 100 mg. |
| dapsone | **Tablet:** 25 mg; 50 mg; 100 mg. |
| rifampicin | **Solid oral dosage form:** 150 mg; 300 mg. |

### 6.2.5 *Antituberculosis medicines*

WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.

| | |
|---|---|
| ethambutol | **Oral liquid:** 25 mg/mL.<br>**Tablet:** 100 mg; 400 mg (hydrochloride).<br>**Tablet (dispersible):** 100 mg. |
| isoniazid | **Oral liquid:** 50 mg/5 mL.<br>**Tablet:** 100 mg to 300 mg.<br>**Tablet (scored):** 50 mg.<br>**Tablet (dispersible):** 100 mg. |
| isoniazid + pyrazinamide + rifampicin | **Tablet (dispersible):** 50 mg + 150 mg + 75 mg. |
| isoniazid + rifampicin | **Tablet (dispersible):** 50 mg + 75 mg. |
| pyrazinamide | **Oral liquid:** 30 mg/mL.<br>**Tablet:** 400 mg.<br>**Tablet (dispersible):** 150 mg.<br>**Tablet (scored):** 150 mg. |
| rifampicin | **Oral liquid:** 20 mg/mL.<br>**Solid oral dosage form:** 150 mg; 300 mg. |
| rifapentine* | **Tablet:** 150 mg<br>* For treatment of latent TB infection (LTBI) only. |

## 6. ANTI-INFECTIVE MEDICINES *(continued)*

***Complementary List***

***Medicines for the treatment of multidrug-resistant tuberculosis (MDR-TB) should be used in specialized centres adhering to WHO standards for TB control.***

| | |
|---|---|
| *amikacin* | ***Powder for injection:*** *100 mg; 500 mg; 1 g (as sulfate) in vial.* |
| *amoxicillin + clavulanic acid** | ***Oral liquid:*** *125 mg amoxicillin + 31.25 mg clavulanic acid/5 mL; 250 mg amoxicillin + 62.5 mg clavulanic acid/5 mL.*<br>***Tablet:*** *500 mg (as trihydrate) + 125 mg (as potassium salt).*<br>* *For use only in combination with meropenem.* |
| *bedaquiline* [a] | ***Tablet:*** *100 mg.*<br>[a] ≥6 years. |
| *clofazimine* | ***Solid oral dosage form:*** *50 mg; 100 mg.* |
| *cycloserine* | ***Solid oral dosage form:*** *125 mg; 250 mg.* |
| *delamanid* [a] | ***Tablet:*** *50 mg.*<br>[a] ≥6 years |
| *ethionamide** | ***Tablet:*** *125 mg; 250 mg.*<br>***Tablet (dispersible):*** *125 mg.*<br>* *Protionamide may be used as an alternative.* |
| *levofloxacin* | ***Tablet:*** *250 mg: 500 mg.*<br>***Tablet (dispersible):*** *100 mg.* |
| *linezolid* | ***Injection for intravenous administration:*** *2 mg/ mL in 300 mL bag.*<br>***Powder for oral liquid:*** *100 mg/5 mL.*<br>***Tablet:*** *400 mg; 600 mg.*<br>***Tablet (dispersible):*** *150 mg.* |
| *meropenem* | ***Powder for injection:*** *500 mg (as trihydrate); 1 g (as trihydrate) in vial.* |
| *moxifloxacin* | ***Tablet:*** *400 mg.*<br>***Tablet (dispersible):*** *100 mg.* |
| *p-aminosalicylic acid* | ***Granules:*** *4 g in sachet.*<br>***Tablet:*** *500 mg.* |
| *streptomycin* | ***Powder for injection:*** *1 g (as sulfate) in vial.* |

| **6. ANTI-INFECTIVE MEDICINES** *(continued)* | |
|---|---|
| **6.3 Antifungal medicines** | |
| amphotericin B | **Powder for injection:** 50 mg in vial (as sodium deoxycholate **or** liposomal complex). |
| fluconazole | **Capsule:** 50 mg.<br>**Injection:** 2 mg/mL in vial.<br>**Oral liquid:** 50 mg/5 mL. |
| flucytosine | **Capsule:** 250 mg.<br>**Infusion:** 2.5 g in 250 mL. |
| griseofulvin | **Oral liquid:** 125 mg/5 mL.<br>**Solid oral dosage form:** 125 mg; 250 mg. |
| itraconazole* | **Capsule:** 100 mg.<br>**Oral liquid:** 10 mg/mL.<br>* For treatment of chronic pulmonary aspergillosis, acute invasive aspergillosis, histoplasmosis, sporotrichosis, paracoccidiodomycosis, mycoses caused by *T. marneffei* and chromoblastomycosis; and prophylaxis of histoplasmosis and infections caused by *T. marneffei* in AIDS patients. |
| nystatin | **Lozenge:** 100 000 IU.<br>**Oral liquid:** 50 mg/5 mL; 100 000 IU/mL.<br>**Tablet:** 100 000 IU; 500 000 IU. |
| voriconazole* | **Tablet:** 50 mg; 200 mg.<br>**Powder for injection:** 200 mg in vial.<br>**Powder for oral liquid:** 40 mg/mL.<br>* For treatment of chronic pulmonary aspergillosis and acute invasive aspergillosis. |
| ***Complementary List*** | |
| *potassium iodide* | ***Saturated solution.*** |

## 6. ANTI-INFECTIVE MEDICINES *(continued)*

### 6.4 Antiviral medicines

#### 6.4.1 *Antiherpes medicines*

| | |
|---|---|
| aciclovir | **Oral liquid:** 200 mg/5 mL.<br>**Powder for injection:** 250 mg (as sodium salt) in vial.<br>**Tablet:** 200 mg. |

#### 6.4.2 *Antiretrovirals*

Based on current evidence and experience of use, medicines in the following classes of antiretrovirals are included as essential medicines for treatment and prevention of HIV (prevention of mother-to-child transmission and post-exposure prophylaxis). WHO emphasizes the importance of using these products in accordance with global and national guidelines. WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.

Scored tablets can be used in children and therefore can be considered for inclusion in the listing of tablets, provided that adequate quality products are available.

##### 6.4.2.1 *Nucleoside/Nucleotide reverse transcriptase inhibitors*

| | |
|---|---|
| abacavir (ABC) | **Tablet (dispersible, scored):** 60 mg (as sulfate). |
| lamivudine (3TC) | **Oral liquid:** 50 mg/5 mL.<br>**Tablet:** 150 mg. |
| zidovudine (ZDV **or** AZT) | **Oral liquid:** 50 mg/5 mL. |

##### 6.4.2.2 *Non-nucleoside reverse transcriptase inhibitors*

| | |
|---|---|
| efavirenz (EFV or EFZ) [a] | **Tablet:** 200 mg (scored).<br>[a] >3 years **or** >10 kg weight. |
| nevirapine (NVP) [a] | **Oral liquid:** 50 mg/5 mL.<br>**Tablet:** 50 mg (dispersible).<br>[a] >6 weeks |

## 6. ANTI-INFECTIVE MEDICINES *(continued)*

### 6.4.2.3 *Protease inhibitors*

Selection of protease inhibitor(s) from the Model List will need to be determined by each country after consideration of international and national treatment guidelines and experience. Ritonavir is recommended for use in combination as a pharmacological booster, and not as an antiretroviral in its own right. All other protease inhibitors should be used in boosted forms (e.g. with ritonavir).

| | |
|---|---|
| atazanavir [a] | **Solid oral dosage form:** 100 mg; (as sulfate).<br>[a] >25 kg. |
| darunavir [a] | **Tablet:** 75 mg.<br>[a] >3 years. |
| lopinavir + ritonavir (LPV/r) | **Oral liquid:** 400 mg + 100 mg/5 mL.<br>**Tablet (heat stable):** 100 mg + 25 mg.<br>**Solid oral dosage form:** 40 mg + 10 mg. |
| ritonavir | **Oral liquid:** 400 mg/5 mL.<br>**Tablet (heat stable):** 25 mg; 100 mg.<br>**Oral powder:** 100 mg in sachet. |

### 6.4.2.4 *Integrase inhibitors*

| | |
|---|---|
| dolutegravir [a] | **Tablet:** 50 mg.<br>[a] ≥25 kg |
| raltegravir* | **Tablet (chewable):** 25 mg; 100 mg.<br>**Tablet:** 400 mg.<br>**Granules for oral suspension:** 100 mg in sachet.<br>* For use in second-line regimens in accordance with WHO treatment guidelines. |

***FIXED-DOSE COMBINATIONS***

| | |
|---|---|
| abacavir + lamivudine | **Tablet (dispersible, scored):** 120 mg (as sulfate) + 60 mg. |
| lamivudine + nevirapine + zidovudine | **Tablet:** 30 mg + 50 mg + 60 mg. |
| lamivudine + zidovudine | **Tablet:** 30 mg + 60 mg. |

### 6.4.2.5 *Medicines for prevention of HIV-related opportunistic infections*

| | |
|---|---|
| isoniazid + pyridoxine + sulfamethoxazole + trimethoprim | **Tablet (scored):** 300 mg + 25 mg + 800 mg + 160 mg. |

**6. ANTI-INFECTIVE MEDICINES** *(continued)*

**6.4.3** ***Other antivirals***

| | |
|---|---|
| ribavirin* | **Injection for intravenous administration:** 800 mg and 1 g in 10-mL phosphate buffer solution.<br>**Solid oral dosage form:** 200 mg; 400 mg; 600 mg.<br>* For the treatment of viral haemorrhagic fevers only. |

***Complementary List***

| | |
|---|---|
| *oseltamivir** | ***Capsule:*** *30 mg; 45 mg; 75 mg (as phosphate).*<br>***Oral powder:*** *12 mg/ mL.*<br>* *Severe illness due to confirmed or suspected influenza virus infection in critically ill hospitalized patients.* |
| *valganciclovir** | ***Powder for oral solution:*** *50 mg/mL.*<br>***Tablet:*** *450 mg.*<br>* *For the treatment of cytomegalovirus retinitis (CMVr).* |

**6.4.4** ***Antihepatitis medicines***

**6.4.4.1** ***Medicines for hepatitis B***

**6.4.4.1.1** ***Nucleoside/Nucleotide reverse transcriptase inhibitors***

| | |
|---|---|
| entecavir | **Oral liquid:** 0.05 mg/ mL.<br>**Tablet:** 0.5 mg; 1 mg. |

~~***6.4.4.2 Medicines for hepatitis C***~~

**6.5 Antiprotozoal medicines**

**6.5.1 Antiamoebic and antigiardiasis medicines**

| | |
|---|---|
| diloxanide [a] | **Tablet:** 500 mg (furoate).<br>[a] >25 kg. |
| ☐ metronidazole | **Injection:** 500 mg in 100-mL vial.<br>**Oral liquid:** 200 mg (as benzoate)/5 mL.<br>**Tablet:** 200 mg to 500 mg. |

**6. ANTI-INFECTIVE MEDICINES** *(continued)*

**6.5.2** ***Antileishmaniasis medicines***

| | |
|---|---|
| amphotericin B | **Powder for injection:** 50 mg in vial.<br>As sodium deoxycholate **or** liposomal complex. |
| miltefosine | **Solid oral dosage form:** 10 mg; 50 mg. |
| paromomycin | **Solution for intramuscular injection:** 750 mg of paromomycin base (as the sulfate). |
| sodium stibogluconate **or** meglumine antimoniate | **Injection:** 100 mg/mL, 1 vial = 30 mL or 30%, equivalent to approximately 8.1% antimony (pentavalent) in 5-mL ampoule. |

**6.5.3** ***Antimalarial medicines***

**6.5.3.1** ***For curative treatment***

Medicines for the treatment of *P. falciparum* malaria cases should be used in combination. The list currently recommends combinations according to treatment guidelines. WHO recognizes that not all of the fixed dose combinations (FDCs in the WHO treatment guidelines exist, and encourages their development and rigorous testing. WHO also encourages development and testing of rectal dosage formulations.

| | |
|---|---|
| amodiaquine* | **Tablet:** 153 mg **or** 200 mg (as hydrochloride).<br>* To be used in combination with artesunate 50 mg. |
| artemether* | **Oily injection:** 80 mg/mL in 1-mL ampoule.<br>* For use in the management of severe malaria. |
| artemether + lumefantrine* | **Tablet:** 20 mg + 120 mg.<br>**Tablet (dispersible):** 20 mg + 120 mg.<br>* Not recommended in the first trimester of pregnancy or in children below 5 kg. |
| artesunate* ** | **Injection:** ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution.<br>* For use in the management of severe malaria.<br>**Rectal dosage form:** 50 mg; 100 mg; 200 mg capsules (for pre-referral treatment of severe malaria only; patients should be taken to an appropriate health facility for follow-up care).<br>**Tablet:** 50 mg.<br>** To be used in combination with either amodiaquine, mefloquine or sulfadoxine + pyrimethamine. |

| **6. ANTI-INFECTIVE MEDICINES** *(continued)* | |
|---|---|
| artesunate + amodiaquine* | **Tablet:** 25 mg + 67.5 mg; 50 mg + 135 mg; 100 mg + 270 mg.<br>* Other combinations that deliver the target doses required such as 153 mg or 200 mg (as hydrochloride) with 50 mg artesunate can be alternatives. |
| artesunate + mefloquine | **Tablet:** 25 mg + 55 mg; 100 mg + 220 mg. |
| artesunate + pyronaridine tetraphosphate [a] | **Tablet:** 60 mg + 180 mg.<br>**Granules:** 20 mg + 60 mg.<br>[a] >5 kg |
| chloroquine* | **Oral liquid:** 50 mg (as phosphate or sulfate)/5 mL.<br>**Tablet:** 100 mg; 150 mg (as phosphate or sulfate).<br>* For use only for the treatment of *P. vivax* infection. |
| dihydroartemisinin + piperaquine phosphate [a] | **Tablet:** 20 mg + 160 mg; 40 mg + 320 mg<br>[a] >5 kg. |
| doxycycline* | **Capsule:** 100 mg (as hydrochloride **or** hyclate).<br>**Tablet (dispersible):** 100 mg (as monohydrate).<br>* For use only in combination with quinine. |
| mefloquine* | **Tablet:** 250 mg (as hydrochloride).<br>* To be used in combination with artesunate 50 mg. |
| primaquine* | **Tablet:** 7.5 mg; 15 mg (as diphosphate).<br>* Only for use to achieve radical cure of *P. vivax* and *P. ovale* infections, given for 14 days. |
| quinine* | **Injection:** 300 mg quinine hydrochloride/mL in 2-mL ampoule.<br>**Tablet:** 300 mg (quinine sulfate) **or** 300 mg (quinine bisulfate).<br>* For use only in the management of severe malaria, and should be used in combination with doxycycline. |
| sulfadoxine + pyrimethamine* | **Tablet:** 500 mg + 25 mg.<br>* Only in combination with artesunate 50 mg. |

| 6. ANTI-INFECTIVE MEDICINES *(continued)* | |
|---|---|
| **6.5.3.2** ***For chemoprevention*** | |
| amodiaquine – sulfadoxine + pyrimethamine | **Co-packaged dispersible tablets:**<br>amodiaquine 76.5 mg (as hydrochloride [3] and sulfadoxine + pyrimethamine 250 mg + 12.5 mg [1];<br>amodiaquine 153 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 500 mg + 25 mg [1]; |
| chloroquine* | **Oral liquid:** 50 mg (as phosphate **or** sulfate)/5 mL.<br>**Tablet:** 150 mg (as phosphate **or** sulfate).<br>* For use only for the treatment of *P. vivax* infection. |
| doxycycline [a] | **Solid oral dosage form:** 100 mg (as hydrochloride **or** hyclate).<br>[a] >8 years. |
| mefloquine [a] | **Tablet:** 250 mg (as hydrochloride).<br>[a] >5 kg **or** >3 months. |
| proguanil* | **Tablet:** 100 mg (as hydrochloride).<br>* For use only in combination with chloroquine. |
| sulfadoxine + pyrimethamine | **Tablet:** 250 mg + 12.5 mg. |
| **6.5.4** ***Antipneumocystosis and antitoxoplasmosis medicines*** | |
| pyrimethamine | **Tablet:** 25 mg. |
| sulfadiazine | **Tablet:** 500 mg. |
| sulfamethoxazole + trimethoprim | **Injection:**<br>80 mg + 16 mg/mL in 5-mL ampoule;<br>80 mg + 16 mg/mL in 10-mL ampoule.<br>**Oral liquid:** 200 mg + 40 mg/5 mL.<br>**Tablet:** 100 mg + 20 mg; 400 mg + 80 mg. |

## 6. ANTI-INFECTIVE MEDICINES *(continued)*

### 6.5.5 *Antitrypanosomal medicines*

#### 6.5.5.1 *African trypanosomiasis*

| | |
|---|---|
| fexinidazole* | **Tablet:** 600 mg<br>* For the treatment of 1st and 2nd stage of human African trypanosomiasis due to *Trypanosoma brucei gambiense* infection. |

**Medicines for the treatment of 1st stage African trypanosomiasis**

| | |
|---|---|
| pentamidine* | **Powder for injection:** 200 mg (as isetionate) in vial.<br>* To be used for the treatment of *Trypanosoma brucei gambiense* infection. |
| suramin sodium* | **Powder for injection:** 1 g in vial.<br>* To be used for the treatment of the initial phase of *Trypanosoma brucei rhodesiense* infection. |

**Medicines for the treatment of 2nd stage African trypanosomiasis**

| | |
|---|---|
| eflornithine* | **Injection:** 200 mg (hydrochloride)/mL in 100-mL bottle.<br>* To be used for the treatment of *Trypanosoma brucei gambiense* infection. |
| nifurtimox* | **Tablet:** 120 mg.<br>* Only to be used in combination with eflornithine, for the treatment of *Trypanosoma brucei gambiense* infection. |
| ***Complementary List*** | |
| *melarsoprol* | ***Injection:** 3.6% solution in 5-mL ampoule (180 mg of active compound).* |

#### 6.5.5.2 *American trypanosomiasis*

| | |
|---|---|
| benznidazole | **Tablet:** 12.5 mg; 100 mg.<br>**Tablet (scored):** 50 mg. |
| nifurtimox | **Tablet:** 30 mg; 120 mg; 250 mg. |

### 6.6 Medicines for ectoparasitic infections

| | |
|---|---|
| ivermectin | **Tablet (scored):** 3 mg. |

| | |
|---|---|
| **7. ANTIMIGRAINE MEDICINES** | |
| **7.1 For treatment of acute attack** | |
| ibuprofen | **Tablet:** 200 mg; 400 mg. |
| paracetamol | **Oral liquid:** 120 mg/5 mL; 125 mg/5 mL.<br>**Tablet:** 300 mg to 500 mg. |
| **7.2 For prophylaxis** | |
| propranolol | **Tablet:** 20 mg; 40 mg (hydrochloride). |
| **8. IMMUNOMODULATORS AND ANTINEOPLASTICS** | |
| **8.1 Immunomodulators for non-malignant disease** | |
| ***Complementary List*** | |
| ☐ *adalimumab** | ***Injection:*** *40 mg/0.8 mL; 40 mg/0.4 mL.*<br>* *Etanercept and infliximab are alternatives, including quality-assured biosimilars.* |
| *azathioprine* | ***Powder for injection:*** *100 mg (as sodium salt) in vial.*<br>***Tablet (scored):*** *50 mg.* |
| *ciclosporin* | ***Capsule:*** *25 mg.*<br>***Concentrate for injection:*** *50 mg/mL in 1-mL ampoule.*<br>* *For organ transplantation.* |

## 8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

### 8.2 Antineoplastic and supportive medicines

Medicines listed below should be used according to protocols for treatment of the diseases.

#### 8.2.1 *Cytotoxic medicines*

***Complementary List***

| | |
|---|---|
| *arsenic trioxide* | ***Concentrate for solution for infusion:*** *1 mg/mL.*<br>– *Acute promyelocytic leukaemia* |
| *asparaginase* | ***Powder for injection:*** *10 000 IU in vial.*<br>– *Acute lymphoblastic leukaemia* |
| *bleomycin* | ***Powder for injection:*** *15 mg (as sulfate) in vial.*<br>– *Hodgkin lymphoma*<br>– *Testicular germ cell tumours*<br>– *Ovarian germ cell tumours*<br>– *Kaposi sarcoma* |
| *calcium folinate* | ***Injection:*** *3 mg/ mL in 10- mL ampoule.*<br>***Tablet:*** *5 mg; 15 mg; 25 mg.*<br>– *Osteosarcoma*<br>– *Burkitt lymphoma* |
| *carboplatin* | ***Injection:*** *50 mg/5 mL; 150 mg/15 mL; 450 mg/45 mL; 600 mg/60 mL.*<br>– *Osteosarcoma*<br>– *Retinoblastoma* |
| *cisplatin* | ***Injection:*** *50 mg/50 mL; 100 mg/100 mL.*<br>– *Osteosarcoma*<br>– *Testicular germ cell tumours*<br>– *Ovarian germ cell tumours*<br>– *Nasopharyngeal cancer* |
| *cyclophosphamide* | ***Powder for injection:*** *500 mg in vial.*<br>***Tablet:*** *25 mg; 50 mg.*<br>– *Rhabdomyosarcoma*<br>– *Ewing sarcoma*<br>– *Acute lymphoblastic leukaemia*<br>– *Burkitt lymphoma*<br>– *Hodgkin lymphoma*<br>– *Diffuse large B-cell lymphoma* |

| 8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)* | |
|---|---|
| *cytarabine* | ***Powder for injection:*** *100 mg in vial.*<br>– *Acute lymphoblastic leukaemia*<br>– *Burkitt lymphoma.*<br>– *Acute myeloid leukaemia*<br>– *Acute promyelocytic leukaemia* |
| *dacarbazine* | ***Powder for injection:*** *100 mg in vial.*<br>– *Hodgkin lymphoma* |
| *dactinomycin* | ***Powder for injection:*** *500 micrograms in vial.*<br>– *Rhabdomyosarcoma*<br>– *Nephroblastoma (Wilms tumour)* |
| *daunorubicin* | ***Powder for injection:*** *50 mg (hydrochloride) in vial.*<br>– *Acute lymphoblastic leukaemia*<br>– *Acute promyelocytic leukaemia* |
| *doxorubicin* | ***Powder for injection:*** *10 mg; 50 mg (hydrochloride) in vial.*<br>– *Osteosarcoma*<br>– *Ewing sarcoma*<br>– *Acute lymphoblastic leukaemia*<br>– *Nephroblastoma (Wilms tumour)*<br>– *Burkitt lymphoma*<br>– *Hodgkin lymphoma*<br>– *Diffuse large B-cell lymphoma*<br>– *Kaposi sarcoma* |
| *etoposide* | ***Capsule:*** *50 mg; 100 mg.*<br>***Injection:*** *20 mg/ mL in 5- mL ampoule.*<br>– *Retinoblastoma*<br>– *Ewing sarcoma*<br>– *Acute lymphoblastic leukaemia*<br>– *Burkitt lymphoma*<br>– *Hodgkin lymphoma*<br>– *Testicular germ cell tumours*<br>– *Ovarian germ cell tumours* |
| *fluorouracil* | ***Injection:*** *50 mg/ mL in 5- mL ampoule.*<br>– *Nasopharyngeal cancer*<br>– *Metastatic colorectal cancer*<br>– *Early stage colon cancer*<br>– *Early stage rectal cancer* |

| **8. IMMUNOMODULATORS AND ANTINEOPLASTICS** *(continued)* | |
|---|---|
| *hydroxycarbamide* | ***Solid oral dosage form:*** *200 mg; 250 mg; 300 mg; 400 mg; 500 mg; 1 g.*<br>– *Chronic myeloid leukaemia* |
| *ifosfamide* | ***Powder for injection:*** *500 mg vial 1-g vial; 2-g vial.*<br>– *Osteosarcoma*<br>– *Rhabdomyosarcoma*<br>– *Ewing sarcoma*<br>– *Testicular germ cell tumours*<br>– *Ovarian germ cell tumours* |
| *irinotecan* | ***Injection:*** *40 mg/2 mL in 2- mL vial; 100 mg/5 mL in 5- mL vial; 500 mg/25 mL in 25- mL vial.*<br>– *Metastatic colorectal cancer* |
| *mercaptopurine* | ***Tablet:*** *50 mg.*<br>– *Acute lymphoblastic leukaemia*<br>– *Acute promyelocytic leukaemia* |
| *methotrexate* | ***Powder for injection:*** *50 mg (as sodium salt) in vial.*<br>***Tablet:*** *2.5 mg (as sodium salt).*<br>– *Osteosarcoma*<br>– *Acute lymphoblastic leukaemia*<br>– *Acute promyelocytic leukaemia* |
| *oxaliplatin* | ***Injection:*** *50 mg/10 mL in 10- mL vial; 100 mg/20 mL in 20- mL vial; 200 mg/40 mL in 40- mL vial.*<br>***Powder for injection:*** *50 mg, 100 mg in vial.*<br>– *Early stage colon cancer*<br>– *Metastatic colorectal cancer* |
| *paclitaxel* | ***Powder for injection:*** *6 mg/ mL.*<br>– *Ovarian germ cell tumours* |
| *pegaspargase** | ***Injection:*** *3,750 units/5 mL in vial.*<br>– *Acute lymphoblastic leukaemia*<br>* *Including quality-assured biosimilars.* |
| *procarbazine* | ***Capsule:*** *50 mg (as hydrochloride).*<br>– *Hodgkin lymphoma* |
| *realgar-Indigo naturalis formulation* | ***Tablet:*** *270 mg (containing tetra-arsenic tetra-sulfide 30 mg).*<br>– *Acute promyelocytic leukaemia* |

| **8. IMMUNOMODULATORS AND ANTINEOPLASTICS** *(continued)* | |
|---|---|
| *tioguanine* | ***Solid oral dosage form:*** *40 mg.*<br>– *Acute lymphoblastic leukaemia* |
| *vinblastine* | ***Powder for injection:*** *10 mg (sulfate) in vial.*<br>– *Testicular germ cell tumours*<br>– *Ovarian germ cell tumours*<br>– *Hodgkin lymphoma* |
| *vincristine* | ***Powder for injection:*** *1 mg; 5 mg (sulfate) in vial.*<br>– *Retinoblastoma*<br>– *Rhabdomyosarcoma*<br>– *Ewing sarcoma*<br>– *Acute lymphoblastic leukaemia*<br>– *Nephroblastoma (Wilms tumour)*<br>– *Burkitt lymphoma*<br>– *Hodgkin lymphoma*<br>– *Diffuse large B-cell lymphoma*<br>– *Kaposi sarcoma* |

## 8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

### 8.2.2 *Targeted therapies*

***Complementary List***

| | |
|---|---|
| *all-trans retinoic acid (ATRA)* | ***Capsule:*** *10 mg.*<br>– *Acute promyelocytic leukaemia* |
| *dasatinib* | ***Tablet:*** *20 mg; 50 mg; 70 mg; 80 mg; 100 mg; 140 mg.*<br>– *Imatinib-resistant chronic myeloid leukaemia* |
| *imatinib* | ***Tablet:*** *100 mg; 400 mg.*<br>– *Chronic myeloid leukaemia*<br>– *Gastrointestinal stromal tumour* |
| *nilotinib* | ***Capsule:*** *150 mg; 200 mg.*<br>– *Imatinib-resistant chronic myeloid leukaemia* |
| *rituximab** | ***Injection (intravenous):*** *100 mg/10 mL in 10- mL vial; 500 mg/50 mL in 50- mL vial.*<br>– *Diffuse large B-cell lymphoma* |

* *Including quality-assured biosimilars.*

### 8.2.3 *Immunomodulators*

***Complementary List***

| | |
|---|---|
| *filgrastim* | ***Injection:*** *120 micrograms/0.2 mL; 300 micrograms/0.5 mL; 480 micrograms/0.8 mL in pre-filled syringe*<br>*300 micrograms/mL in 1- mL vial, 480 micrograms/1.6 mL in 1.6- mL vial.*<br>– *Primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy.*<br>– *Secondary prophylaxis for patients who have experienced neutropenia following prior myelotoxic chemotherapy*<br>– *To facilitate administration of dose dense chemotherapy regimens* |

## 8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

### 8.2.4 *Hormones and antihormones*

***Complementary List***

| | |
|---|---|
| *dexamethasone* | ***Injection:*** *4 mg/ mL in 1- mL ampoule (as disodium phosphate salt).*<br>***Oral liquid:*** *2 mg/5 mL.*<br>***Tablet:*** *2 mg; 4 mg.*<br>– *Acute lymphoblastic leukaemia* |
| *hydrocortisone* | ***Powder for injection:*** *100 mg (as sodium succinate) in vial.*<br>– *Acute lymphoblastic leukaemia.* |
| *methylprednisolone* | ***Injection:*** *40 mg/ mL (as sodium succinate) in 1- mL single-dose vial and 5- mL multi-dose vials; 80 mg/ mL (as sodium succinate) in 1- mL single-dose vial.*<br>– *Acute lymphoblastic leukamia* |
| ☐ *prednisolone* | ***Oral liquid:*** *5 mg/ mL.*<br>***Tablet:*** *5 mg; 25 mg.*<br>– *Acute lymphoblastic leukaemia*<br>– *Burkitt lymphoma*<br>– *Hodgkin lymphoma*<br>– *Diffuse large B-cell lymphoma* |

### 8.2.5 *Supportive medicines*

***Complementary List***

| | |
|---|---|
| *allopurinol* | ***Tablet:*** *100 mg; 300 mg.*<br>– *Tumour lysis syndrome* |
| *mesna* | ***Injection:*** *100 mg/ mL in 4- mL and 10- mL ampoules.*<br>***Tablet:*** *400 mg; 600 mg.*<br>– *Osteosarcoma*<br>– *Rhabdomyosarcoma*<br>– *Ewing sarcoma*<br>– *Testicular germ cell tumours*<br>– *Ovarian germ cell tumours* |

## ~~9. ANTIPARKINSONISM MEDICINES~~

## 10. MEDICINES AFFECTING THE BLOOD

### 10.1 Antianaemia medicines

| | |
|---|---|
| ferrous salt | **Oral liquid:** equivalent to 25 mg iron (as sulfate)/mL.<br>**Tablet:** equivalent to 60 mg iron. |
| folic acid | **Tablet:** 1 mg; 5 mg. |
| hydroxocobalamin | **Injection:** 1 mg (as acetate, as hydrochloride or as sulfate) in 1-mL ampoule. |
| ***Complementary List*** | |
| ☐ *erythropoiesis-stimulating agents** | ***Injection:** pre-filled syringe*<br>*1000IU/ 0.5 mL; 2000IU/ 0.5 mL; 3000IU/ 0.3 mL; 4000IU/ 0.4 mL; 5000IU/ 0.5 mL; 6000IU/ 0.6 mL; 8000IU/ 0.8mL; 10 000IU/ 1 mL; 20 000IU/ 0.5 mL; 40 000IU/ 1 mL*<br>* *The square box applies to epoetin alfa, beta and theta, darbepoetin alfa, and their respective biosimilars.* |

### 10.2 Medicines affecting coagulation

| | |
|---|---|
| ☐ enoxaparin* | **Injection:** ampoule or pre-filled syringe<br>20 mg/0.2 mL; 40 mg/0.4 mL; 60 mg/0.6 mL; 80 mg/ 0.8 mL; 100 mg/1 mL; 120 mg/0.8 mL; 150 mg/1 mL<br>* Alternatives are limited to nadroparin and dalteparin. |
| phytomenadione | **Injection:** 1 mg/mL; 10 mg/mL in ampoule.<br>**Tablet:** 10 mg. |
| ***Complementary List*** | |
| *desmopressin* | ***Injection:** 4 micrograms/ mL (as acetate) in 1- mL ampoule.*<br>***Nasal spray:** 10 micrograms (as acetate) per dose.* |
| *heparin sodium* | ***Injection:** 1000 IU/mL; 5000 IU/mL in 1-mL ampoule.* |
| *protamine sulfate* | ***Injection:** 10 mg/mL in 5-mL ampoule.* |
| ☐ *warfarin* | ***Tablet:** 0.5 mg; 1 mg; 2 mg; 5 mg (sodium salt).* |

### 10.3 Other medicines for haemoglobinopathies

| | |
|---|---|
| ***Complementary list*** | |
| *deferoxamine** | ***Powder for injection:** 500 mg (mesilate) in vial.*<br>* *Deferasirox oral form may be an alternative, depending on cost and availability.* |
| *hydroxycarbamide* | ***Solid oral dosage form:** 200 mg; 500 mg; 1 g.* |

## 11. BLOOD PRODUCTS OF HUMAN ORIGIN AND PLASMA SUBSTITUTES

### 11.1 Blood and blood components

In accordance with the World Health Assembly resolution WHA63.12, WHO recognizes that achieving self-sufficiency, unless special circumstances preclude it, in the supply of safe blood components based on voluntary, non-remunerated blood donation, and the security of that supply are important national goals to prevent blood shortages and meet the transfusion requirements of the patient population. All preparations should comply with the WHO requirements.

fresh–frozen plasma

platelets

red blood cells

whole blood

### 11.2 Plasma-derived medicines

All human plasma-derived medicines should comply with the WHO requirements.

#### 11.2.1 *Human immunoglobulins*

| | |
|---|---|
| anti-rabies immunoglobulin | **Injection:** 150 IU/ mL in vial. |
| anti-tetanus immunoglobulin | **Injection:** 500 IU in vial. |

***Complementary List***

| | |
|---|---|
| *normal immunoglobulin* | ***Intramuscular administration:*** *16% protein solution.** <br> ***Intravenous administration:*** *5%; 10% protein solution.*** <br> ***Subcutaneous administration:*** *15%; 16% protein solution.** |

* *Indicated for primary immune deficiency.*
** *Indicated for primary immune deficiency and Kawasaki disease.*

#### 11.2.2 *Blood coagulation factors*

***Complementary List***

| | |
|---|---|
| ☐ *coagulation factor VIII* | ***Powder for injection:*** *500 IU/vial.* |
| ☐ *coagulation factor IX* | ***Powder for injection:*** *500 IU/vial, 1000 IU/vial.* |

### 11.3 Plasma substitutes

| | |
|---|---|
| ☐ dextran 70* | **Injectable solution:** 6%. <br> * Polygeline, injectable solution, 3.5% is considered as equivalent. |

| | |
|---|---|
| **12. CARDIOVASCULAR MEDICINES** | |
| ~~**12.1 Antianginal medicines**~~ | |
| ~~**12.2 Antiarrhythmic medicines**~~ | |
| **12.3 Antihypertensive medicines** | |
| ☐ enalapril | **Tablet:** 2.5 mg; 5 mg (as hydrogen maleate). |
| **12.4 Medicines used in heart failure** | |
| digoxin | **Injection:** 250 micrograms/mL in 2-mL ampoule.<br>**Oral liquid:** 50 micrograms/mL.<br>**Tablet:** 62.5 micrograms; 250 micrograms. |
| furosemide | **Injection:** 10 mg/mL in 2-mL ampoule.<br>**Oral liquid:** 20 mg/5 mL.<br>**Tablet:** 40 mg. |
| ***Complementary List*** | |
| *dopamine* | ***Injection:*** *40 mg (hydrochloride) in 5-mL vial.* |
| ~~**12.5 Antithrombotic medicines**~~ | |
| ~~**12.6 Lipid-lowering agents**~~ | |

| | |
|---|---|
| **13. DERMATOLOGICAL MEDICINES (topical)** | |
| **13.1 Antifungal medicines** | |
| ☐ miconazole | **Cream or ointment:** 2% (nitrate). |
| terbinafine | **Cream:** 1% **or Ointment:** 1% terbinafine hydrochloride. |
| **13.2 Anti-infective medicines** | |
| mupirocin | **Cream (as mupirocin calcium):** 2%.<br>**Ointment:** 2%. |
| potassium permanganate | **Aqueous solution:** 1:10 000. |
| silver sulfadiazine [a] | **Cream:** 1%.<br>[a] >2 months. |
| **13.3 Anti-inflammatory and antipruritic medicines** | |
| ☐ betamethasone [a] | **Cream or ointment:** 0.1% (as valerate).<br>[a] Hydrocortisone preferred in neonates. |
| calamine | **Lotion.** |
| hydrocortisone | **Cream or ointment:** 1% (acetate). |
| **13.4 Medicines affecting skin differentiation and proliferation** | |
| benzoyl peroxide | **Cream or lotion:** 5%. |
| coal tar | **Solution:** 5%. |
| ☐ podophyllum resin | **Solution:** 10% to 25%. |
| salicylic acid | **Solution:** 5%. |
| urea | **Cream or ointment:** 5%; 10%. |
| **13.5 Scabicides and pediculicides** | |
| ☐ benzyl benzoate [a] | **Lotion:** 25%.<br>[a] >2 years. |
| permethrin | **Cream:** 5%.<br>**Lotion:** 1%. |

| | |
|---|---|
| **14. DIAGNOSTIC AGENTS** | |
| **14.1 Ophthalmic medicines** | |
| fluorescein | **Eye drops:** 1% (sodium salt). |
| ☐ tropicamide | **Eye drops:** 0.5%. |
| **14.2 Radiocontrast media** | |
| ***Complementary List*** | |
| *barium sulfate* | ***Aqueous suspension.*** |
| **15. DISINFECTANTS AND ANTISEPTICS** | |
| **15.1 Antiseptics** | |
| ☐ chlorhexidine | **Solution:** 5% (digluconate).<br>**Gel:** 4%. |
| ☐ ethanol | **Solution:** 70% (denatured). |
| ☐ povidone iodine | **Solution:** 10% (equivalent to 1% available iodine). |
| **15.2 Disinfectants** | |
| alcohol based hand rub | **Solution** containing ethanol 80% volume /volume<br>**Solution** containing isopropyl alcohol 75% volume/ volume |
| ☐ chlorine base compound | **Powder:** (0.1% available chlorine) for solution. |
| ☐ chloroxylenol | **Solution:** 4.8%. |
| glutaral | **Solution:** 2%. |
| **16. DIURETICS** | |
| furosemide | **Injection:** 10 mg/mL in 2-mL ampoule.<br>**Oral liquid:** 20 mg/5 mL.<br>**Tablet:** 10 mg; 20 mg; 40 mg. |
| ***Complementary List*** | |
| ☐ *hydrochlorothiazide* | ***Tablet (scored):** 25 mg.* |
| *mannitol* | ***Injectable solution:** 10%; 20%.* |
| *spironolactone* | ***Oral liquid:** 5 mg/5 mL; 10 mg/5 mL; 25 mg/5 mL.*<br>***Tablet:** 25 mg.* |

| 17. GASTROINTESTINAL MEDICINES | |
|---|---|
| ***Complementary List*** | |
| ☐ *pancreatic enzymes* | *Age-appropriate formulations and doses including lipase, protease and amylase.* |
| **17.1 Antiulcer medicines** | |
| ☐ omeprazole | **Powder for oral liquid:** 20-mg; 40-mg sachets.<br>**Solid oral dosage form:** 10 mg; 20 mg; 40 mg. |
| ☐ ranitidine | **Injection:** 25 mg/mL (as hydrochloride) in 2-mL ampoule.<br>**Oral liquid:** 75 mg/5 mL (as hydrochloride).<br>**Tablet:** 150 mg (as hydrochloride). |
| **17.2 Antiemetic medicines** | |
| dexamethasone | **Injection:** 4 mg/mL in 1-mL ampoule (as disodium phosphate salt).<br>**Oral liquid:** 0.5 mg/5 mL; 2 mg/5 mL.<br>**Solid oral dosage form:** 0.5 mg; 0.75 mg; 1.5 mg; 4 mg. |
| metoclopramide [a] | **Injection:** 5 mg (hydrochloride)/mL in 2-mL ampoule.<br>**Oral liquid:** 5 mg/5 mL.<br>**Tablet:** 10 mg (hydrochloride).<br>[a] Not in neonates. |
| ☐ ondansetron [a] | **Injection:** 2 mg base/mL in 2-mL ampoule (as hydrochloride).<br>**Oral liquid:** 4 mg base/5 mL.<br>**Solid oral dosage form:** Eq 4 mg base; Eq 8 mg base.<br>[a] >1 month. |
| ***Complementary list*** | |
| *aprepitant* | ***Capsule:*** *80 mg; 125 mg; 165 mg.*<br>***Powder for oral susupension:*** *125 mg in sachet.* |

## 17. GASTROINTESTINAL MEDICINES *(continued)*

~~**17.3 Anti-inflammatory medicines**~~

~~**17.4 Laxatives**~~

### 17.5 Medicines used in diarrhoea

| | |
|---|---|
| oral rehydration salts – zinc sulfate | **Co-package containing:**<br>**ORS powder for dilution** (see Section 17.5.1) – zinc sulfate **solid oral dosage form** 20 mg (see Section 17.5.2) |

#### 17.5.1 *Oral rehydration*

oral rehydration salts — **Powder for dilution** in 200 mL; 500 mL; 1 L.

| | |
|---|---|
| glucose: | 75 mEq |
| sodium: | 75 mEq **or** mmol/L |
| chloride: | 65 mEq **or** mmol/L |
| potassium: | 20 mEq **or** mmol/L |
| citrate: | 10 mmol/L |
| osmolarity: | 245 mOsm/L |
| glucose: | 13.5 g/L |
| sodium chloride: | 2.6 g/L |
| potassium chloride: | 1.5 g/L |
| trisodium citrate dihydrate*: | 2.9 g/L |

* Trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/L. However, as the stability of this latter formulation is very poor under tropical conditions, it is recommended only when manufactured for immediate use.

#### 17.5.2 *Medicines for diarrhoea*

zinc sulfate* — **Solid oral dosage form:** 20 mg.

* In acute diarrhoea, zinc sulfate should be used as an adjunct to oral rehydration salts.

## 18. MEDICINES FOR ENDOCRINE DISORDERS

### 18.1 Adrenal hormones and synthetic substitutes

| | |
|---|---|
| fludrocortisone | **Tablet:** 100 micrograms (acetate). |
| hydrocortisone | **Tablet:** 5 mg; 10 mg; 20 mg. |

~~**18.2 Androgens**~~

~~**18.3 Estrogens**~~

~~**18.4 Progestogens**~~

### 18.5 Medicines for diabetes

#### 18.5.1 *Insulins*

| | |
|---|---|
| insulin injection (soluble) | **Injection:** 100 IU/mL in 10-mL vial. |
| intermediate-acting insulin | **Injection:** 100 IU/mL in 10-mL vial (as compound insulin zinc suspension or isophane insulin). |

#### 18.5.2 *Oral hypoglycaemic agents*

***Complementary List***

| | |
|---|---|
| *metformin* | ***Tablet:** 500 mg (hydrochloride).* |

### 18.6 Medicines for hypoglycaemia

| | |
|---|---|
| glucagon | **Injection:** 1 mg/mL. |

***Complementary List***

| | |
|---|---|
| *diazoxide* | ***Oral liquid:** 50 mg/mL*<br>***Tablet:** 50 mg* |

### 18.7 Thyroid hormones and antithyroid medicines

| | |
|---|---|
| levothyroxine | **Tablet:** 25 micrograms; 50 micrograms; 100 micrograms (sodium salt). |

***Complementary List***

| | |
|---|---|
| *Lugol's solution* | ***Oral liquid:** about 130 mg total iodine/mL.* |
| ☐ *methimazole** | ***Tablet:** 5mg, 10mg, 20mg.*<br>* *Carbimazole is an alternative depending on local availability.* |
| *potassium iodide* | ***Tablet:** 60 mg.* |
| *propylthiouracil** | ***Tablet:** 50 mg.*<br>* *For use in patients for whom alternative first-line treatment is not appropriate or available.* |

## 19. IMMUNOLOGICALS

### 19.1 Diagnostic agents

All tuberculins should comply with the WHO requirements for tuberculins.

| | |
|---|---|
| tuberculin, purified protein derivative (PPD) | **Injection.** |

### 19.2 Sera and immunoglobulins

All plasma fractions should comply with the WHO requirements.

| | |
|---|---|
| anti-venom immunoglobulin* | **Injection.**<br>* Exact type to be defined locally. |
| diphtheria antitoxin | **Injection:** 10 000 IU; 20 000 IU in vial. |

### 19.3 Vaccines

WHO immunization policy recommendations are published in vaccine position papers on the basis of recommendations made by the Strategic Advisory Group of Experts on Immunization (SAGE).

WHO vaccine position papers are updated three to four times per year. The list below details the vaccines for which there is a recommendation from SAGE and a corresponding WHO position paper as at December 2018. The most recent versions of the WHO position papers, reflecting the current evidence related to a specific vaccine and the related recommendations, can be accessed at any time on the WHO website at: http://www.who.int/immunization/documents/positionpapers/en/index.html.

Vaccine recommendations may be universal or conditional (e.g., in certain regions, in some high-risk populations or as part of immunization programmes with certain characteristics). Details are available in the relevant position papers, and in the Summary Tables of WHO Routine Immunization Recommendations available on the WHO website at: http://www.who.int/immunization/policy/immunization_tables/en/index.html.

Selection of vaccines from the Model List will need to be determined by each country after consideration of international recommendations, epidemiology and national priorities.

All vaccines should comply with the WHO requirements for biological substances.

WHO noted the need for vaccines used in children to be polyvalent.

***Recommendations for all***

BCG vaccine

diphtheria vaccine

Haemophilus influenzae type b vaccine

hepatitis B vaccine

**19. IMMUNOLOGICALS** *(continued)*

HPV vaccine

measles vaccine

pertussis vaccine

pneumococcal vaccine

poliomyelitis vaccine

rotavirus vaccine

rubella vaccine

tetanus vaccine

***Recommendations for certain regions***

Japanese encephalitis vaccine

yellow fever vaccine

tick-borne encephalitis vaccine

***Recommendations for some high-risk populations***

cholera vaccine

dengue vaccine

hepatitis A vaccine

meningococcal meningitis vaccine

rabies vaccine

typhoid vaccine

***Recommendations for immunization programmes with certain characteristics***

influenza vaccine (seasonal)

mumps vaccine

varicella vaccine

| | |
|---|---|
| **20. MUSCLE RELAXANTS (PERIPHERALLY-ACTING) AND CHOLINESTERASE INHIBITORS** | |
| neostigmine | **Injection:** 500 micrograms in 1-mL ampoule; 2.5 mg (metilsulfate) in 1-mL ampoule.<br>**Tablet:** 15 mg (bromide). |
| suxamethonium | **Injection:** 50 mg (chloride)/mL in 2-mL ampoule.<br>**Powder for injection:** (chloride), in vial. |
| ☐ vecuronium | **Powder for injection**: 10 mg (bromide) in vial. |
| ***Complementary List*** | |
| *pyridostigmine* | ***Injection:*** *1 mg in 1-mL ampoule.*<br>***Tablet:*** *60 mg (bromide).* |
| **21. OPHTHALMOLOGICAL PREPARATIONS** | |
| **21.1 Anti-infective agents** | |
| aciclovir | **Ointment:** 3% W/W. |
| azithromycin | **Solution (eye drops):** 1.5% |
| erythromycin* | **Ointment:** 0.5%<br>* Infections due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae.* |
| ☐ gentamicin | **Solution (eye drops):** 0.3% (sulfate). |
| natamycin | **Suspension: (eye drops):** 5%. |
| ☐ ofloxacin | **Solution (eye drops):** 0.3%. |
| ☐ tetracycline | **Eye ointment:** 1% (hydrochloride). |
| **21.2 Anti-inflammatory agents** | |
| ☐ prednisolone | **Solution (eye drops):** 0.5% (sodium phosphate). |
| **21.3 Local anaesthetics** | |
| ☐ tetracaine [a] | Solution (eye drops): 0.5% (hydrochloride).<br>[a] Not in preterm neonates. |
| ~~**21.4 Miotics and antiglaucoma medicines**~~ | |

| | |
|---|---|
| **21. OPHTHALMOLOGICAL PREPARATIONS** *(continued)* | |
| **21.5 Mydriatics** | |
| atropine* [a] | **Solution (eye drops):** 0.1%; 0.5%; 1% (sulfate).<br>* Or homatropine (hydrobromide) or cyclopentolate (hydrochloride).<br>[a] >3 months. |
| ***Complementary List*** | |
| *epinephrine (adrenaline)* | ***Solution (eye drops):** 2% (as hydrochloride).* |
| ~~**21.6 Anti-vascular endothelial growth factor (VEGF) preparations**~~ | |
| **22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE** | |
| ~~**22.1 Contraceptives**~~ | |
| ~~**22.2 Ovulation inducers**~~ | |
| ~~**22.3 Uterotonics**~~ | |
| ~~**22.4 Antioxytocics (tocolytics)**~~ | |
| ~~**22.5 Other medicines administered to the mother**~~ | |
| **22.6 Medicines administered to the neonate** | |
| caffeine citrate | **Injection:** 20 mg/mL (equivalent to 10 mg caffeine base/mL).<br>**Oral liquid:** 20 mg/mL (equivalent to 10 mg caffeine base/mL). |
| chlorhexidine* | **Solution or gel:** 7.1% (digluconate) delivering 4% chlorhexidine.<br>* For umbilical cord care. |
| ***Complementary List*** | |
| ☐ *ibuprofen* | ***Solution for injection**: 5 mg/mL.* |
| ☐ *prostaglandin E* | ***Solution for injection:***<br>***Prostaglandin E1:** 0.5 mg/mL in alcohol.*<br>***Prostaglandin E2:** 1 mg/mL.* |
| *surfactant* | ***Suspension for intratracheal instillation:** 25 mg/mL **or** 80 mg/mL.* |

## 23. PERITONEAL DIALYSIS SOLUTION

***Complementary List***

| | |
|---|---|
| *intraperitoneal dialysis solution (of appropriate composition)* | ***Parenteral solution.*** |

## 24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS

### 24.1 Medicines used in psychotic disorders

***Complementary List***

| | |
|---|---|
| *chlorpromazine* | ***Injection**: 25 mg (hydrochloride)/mL in 2-mL ampoule.*<br>***Oral liquid:** 25 mg (hydrochloride)/5 mL.*<br>***Tablet:** 10 mg; 25 mg; 50 mg; 100 mg (hydrochloride).* |
| *haloperidol* | ***Injection:** 5 mg in 1-mL ampoule.*<br>***Oral liquid:** 2 mg/mL.*<br>***Solid oral dosage form:** 0.5 mg; 2 mg; 5 mg.* |

### 24.2 Medicines used in mood disorders

#### 24.2.1 *Medicines used in depressive disorders*

***Complementary List***

| | |
|---|---|
| *fluoxetine* [a] | ***Solid oral dosage form:** 20 mg (as hydrochloride).*<br>[a] >8 years. |

~~**24.2.2 *Medicines used in bipolar disorders***~~

~~**24.3 Medicines for anxiety disorders**~~

~~**24.4 Medicines used for obsessive compulsive disorders**~~

~~**24.5 Medicines for disorders due to psychoactive substance use**~~

| | |
|---|---|
| **25. MEDICINES ACTING ON THE RESPIRATORY TRACT** | |
| **25.1 Antiasthmatic medicines** | |
| ☐ budesonide | **Inhalation (aerosol):** 100 micrograms per dose; 200 micrograms per dose. |
| epinephrine (adrenaline) | **Injection:** 1 mg (as hydrochloride or hydrogen tartrate) in 1-mL ampoule. |
| ☐ salbutamol | **Injection:** 50 micrograms (as sulfate)/mL in 5-mL ampoule.<br>**Metered dose inhaler (aerosol):** 100 micrograms (as sulfate) per dose.<br>**Respirator solution for use in nebulizers:** 5 mg (as sulfate)/mL. |
| **26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID–BASE DISTURBANCES** | |
| **26.1 Oral** | |
| oral rehydration salts | See section 17.5.1. |
| potassium chloride | **Powder for solution.** |
| **26.2 Parenteral** | |
| glucose | **Injectable solution:** 5% (isotonic); 10% (hypertonic); 50% (hypertonic). |
| glucose with sodium chloride | **Injectable solution:** 5% glucose, 0.9% sodium chloride (equivalent to Na+ 150 mmol/L and Cl- 150 mmol/L); 5% glucose, 0.45% sodium chloride (equivalent to Na+ 75 mmol/L and Cl- 75 mmol/L). |
| potassium chloride | **Solution for dilution:** 7.5% (equivalent to K+ 1 mmol/mL and Cl- 1 mmol/mL); 15% (equivalent to K+ 2 mmol/mL and Cl- 2 mmol/mL). |
| sodium chloride | **Injectable solution:** 0.9% isotonic (equivalent to Na+ 154 mmol/L, Cl- 154 mmol/L). |
| sodium hydrogen carbonate | **Injectable solution:** 1.4% isotonic (equivalent to Na+ 167 mmol/L, HCO3- 167 mmol/L).<br>**Solution:** 8.4% in 10-mL ampoule (equivalent to Na+ 1000 mmol/L, HCO3-1000 mmol/L). |
| ☐ sodium lactate, compound solution | **Injectable solution.** |

| | |
|---|---|
| **26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID–BASE DISTURBANCES** *(continued)* | |
| **26.3 Miscellaneous** | |
| water for injection | 2-mL; 5-mL; 10-mL ampoules. |
| **27. VITAMINS AND MINERALS** | |
| ascorbic acid | **Tablet:** 50 mg. |
| colecalciferol* | **Oral liquid:** 400 IU/mL.<br>**Solid oral dosage form**: 400 IU; 1000 IU.<br>* Ergocalciferol can be used as an alternative. |
| iodine | **Capsule:** 190 mg.<br>**Iodized oil:** 1 mL (480 mg iodine); 0.5 mL (240 mg iodine) in ampoule (oral or injectable); 0.57 mL (308 mg iodine) in dispenser bottle. |
| multiple micronutrient powder | **Sachets containing:**<br>– iron (elemental) 12.5 mg (as coated ferrous fumarate)<br>– zinc (elemental) 5 mg<br>– vitamin A 300 micrograms<br>– with or without other micronutrients at recommended daily values |
| pyridoxine | **Tablet:** 25 mg (hydrochloride). |
| retinol | **Capsule:** 100 000 IU; 200 000 IU (as palmitate).<br>**Oral oily solution:** 100 000 IU (as palmitate)/mL in multidose dispenser.<br>**Tablet (sugar-coated):** 10 000 IU (as palmitate).<br>**Water-miscible injection:** 100 000 IU (as palmitate) in 2-mL ampoule. |
| riboflavin | **Tablet:** 5 mg. |
| sodium fluoride | In any appropriate topical formulation. |
| thiamine | **Tablet:** 50 mg (hydrochloride). |
| ***Complementary List*** | |
| *calcium gluconate* | ***Injection:** 100 mg/mL in 10-mL ampoule.* |

| | |
|---|---|
| **28. EAR, NOSE AND THROAT MEDICINES** | |
| acetic acid | **Topical:** 2%, in alcohol. |
| ☐ budesonide | **Nasal spray:** 100 micrograms per dose. |
| ☐ ciprofloxacin | **Topical:** 0.3% drops (as hydrochloride). |
| ☐ xylometazoline [a] | **Nasal spray:** 0.05%.<br>[a] Not in children less than 3 months. |
| **29. MEDICINES FOR DISEASES OF JOINTS** | |
| ~~**29.1 Medicines used to treat gout**~~ | |
| **29.2 Disease-modifying agents used in rheumatoid disorders (DMARDs)** | |
| ***Complementary List*** | |
| *hydroxychloroquine* | ***Solid oral dosage form:*** *200 mg (as sulfate).* |
| *methotrexate* | ***Tablet:*** *2.5 mg (as sodium salt).* |
| **29.3 Juvenile joint diseases** | |
| acetylsalicylic acid* (acute or chronic use) | **Suppository:** 50 mg to 150 mg.<br>**Tablet:** 100 mg to 500 mg.<br>* For use for rheumatic fever, juvenile arthritis, Kawasaki disease. |

# Annex 3

## The Anatomical Therapeutic Chemical (ATC) Classification System

The following list provides the corresponding Anatomical Therapeutic Chemical (ATC) classification codes for all items on the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children, sorted by ATC code number.

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| **A** | **ALIMENTARY TRACT AND METABOLISM** | |
| **A02** | **Drugs for acid related disorders** | |
| A02B | Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD) | |
| A02BA | *H2-receptor antagonists* | |
| A02BA02 | ranitidine | 17.1 |
| A02BC | *Proton pump inhibitors* | |
| A02BC01 | omeprazole | 17.1 |
| **A03** | **Drugs for functional gastrointestinal disorders** | |
| A03B | Belladonna and derivatives, plain | |
| A03BA | *Belladonna alkaloids, tertiary amines* | |
| A03BA01 | atropine | 1.3; 4.2 |
| A03BB | *Belladonna alkaloids, semisynthetic, quaternary ammonium compounds* | |
| A03BB01 | hyoscine butylbromide* | 2.3 |
| A03F | Propulsives | |
| A03FA | *Propulsives* | |
| A03FA01 | metoclopramide | 2.3; 17.2 |
| **A04** | **Antiemetics and antinauseants** | |
| A04A | Antiemetics and antinauseants | |
| A04AA | *Serotonin (5HT3) antagonists* | |
| A04AA01 | ondansetron | 2.3; 17.2 |
| A04AD | *Other antiemetics* | |
| A04AD01 | hyoscine hydrobromide* | 2.3 |
| A04AD12 | aprepitant | 17.2 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| **A06** | **Drugs for constipation** | |
| A06A | Laxatives | |
| A06AA | *Softeners, emollients* | |
| A06AA02 | docusate sodium | 2.3 |
| A06AB | *Contact laxatives* | |
| A06AB06 | senna glycosides* | 2.3; 17.4 |
| A06AD | *Osmotically acting laxatives* | |
| A06AD11 | lactulose | 2.3 |
| **A07** | **Antidiarrheals, intestinal antiinflammatory/antiinfective agents** | |
| A07A | Intestinal antiinfectives | |
| A07AA | *Antibiotics* | |
| A07AA06 | paromomycin | 6.5.2 |
| A07B | Intestinal adsorbents | |
| A07BA | *Charcoal preparations* | |
| A07BA01 | medicinal charcoal* | 4.1 |
| A07C | Electrolytes with carbohydrates | |
| A07CA | *Oral rehydration salt formulations** | 17.5; 17.5.1; 26.1 |
| A07DA | *Antipropulsives* | |
| A07DA03 | loperamide | 2.3 |
| A07E | Intestinal antiinflammatory agents | |
| A07EA | *Corticosteroids for local use* | |
| A07EA02 | hydrocortisone | 17.3 |
| A07EC | *Aminosalicylic acid and similar agents* | |
| A07EC01 | sulfasalazine | 17.3; 29.2 |
| **A09** | **Digestives, incl. enzymes** | |
| A09A | Digestives, incl. enzymes | |
| A09AA | *Enzyme preparations* | |
| A09AA02 | multienzymes (lipase, protease, etc.)* | 17 |
| **A10** | **Drugs used in diabetes** | |
| A10A | Insulins and analogues | |
| A10AB | *Insulins and analogues for injection, fast-acting* | |
| A10AB01 | insulin (human)* | 18.5.1 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| A10AC | *Insulins and analogues for injection, intermediate-acting* | |
| A10AC01 | insulin (human)* | 18.5.1 |
| A10B | Blood glucose lowering drugs, excl. insulins | |
| A10BA | *Biguanides* | |
| A10BA02 | metformin | 18.5.2 |
| A10BB | *Sulfonamides, urea derivatives* | |
| A10BB09 | gliclazide | 18.5.2 |
| **A11** | **Vitamins** | |
| A11C | Vitamin A and D, incl. combinations of the two | |
| A11CA | *Vitamin A, plain* | |
| A11CA01 | retinol | 27 |
| A11CC | *Vitamin D and analogues* | |
| A11CC01 | ergocalciferol | 27 |
| A11CC05 | colecalciferol | 27 |
| A11D | Vitamin B1, plain and in combination with vitamin B6 and B12 | |
| A11DA | *Vitamin B1, plain* | |
| A11DA01 | thiamine | 27 |
| A11G | Ascorbic acid (vitamin C), incl. combinations | |
| A11GA | *Ascorbic acid (vitamin C), plain* | |
| A11GA01 | ascorbic acid | 27 |
| A11H | Other plain vitamin preparations | |
| A11HA | *Other plain vitamin preparations* | |
| A11HA01 | nicotinamide | 27 |
| A11HA02 | pyridoxine | 27 |
| A11HA04 | riboflavin | 27 |
| **A12** | **Mineral supplements** | |
| A12A | Calcium | |
| A12AA | *Calcium* | |
| A12AA03 | calcium gluconate | 4.2; 27 |
| A12C | Other mineral supplements | |
| A12CB | *Zinc* | |
| A12CB01 | zinc sulfate | 17.5; 17.5.2 |
| A12CD | *Fluoride* | |
| A12CD01 | sodium fluoride | 27 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| **B** | **BLOOD AND BLOOD FORMING ORGANS** | |
| **B01** | **Antithrombotic agents** | |
| B01A | Antithrombotic agents | |
| B01AA | *Vitamin K antagonists* | |
| B01AA03 | warfarin | 10.2 |
| B01AB | *Heparin group* | |
| B01AB01 | heparin | 10.2 |
| B01AB05 | enoxaparin | 10.2 |
| B01AC | *Platelet aggregation inhibitors excl. heparin* | |
| B01AC04 | clopidogrel | 12.5.1 |
| B01AC06 | acetylsalicylic acid | 12.5.1 |
| B01AD | *Enzymes* | |
| B01AD01 | streptokinase | 12.5.2 |
| B01AD02 | alteplase | 12.5.2 |
| B01AE | *Direct thrombin inhibitors* | |
| B01AE07 | dabigatran etexilate | 10.2 |
| **B02** | **Antihemorrhagics** | |
| B02A | Antifibrinolytics | |
| B02AA | *Amino acids* | |
| B02AA02 | tranexamic acid | 10.2, 22.5 |
| B02B | Vitamin K and other hemostatics | |
| B02BA | *Vitamin K* | |
| B02BA01 | phytomenadione | 10.2 |
| B02BD | *Blood coagulation factors* | |
| B02BD01 | coagulation factor IX, II, VII and X in combination* | 11.2.2 |
| B02BD02 | coagulation factor VIII* | 11.2.2 |
| **B03** | **Antianemic preparations** | |
| B03A | Iron preparations | 10.1 |
| B03AA | *Iron bivalent, oral preparations** | 10.1 |
| B03AB | *Iron trivalent, oral preparations** | 10.1 |
| B03AD | *Iron in combination with folic acid** | 10.1 |
| B03AE | *Iron in other combinations** | |
| B03AE10 | various combinations* | 27 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| B03B | Vitamin B12 and folic acid | |
| B03BA | *Vitamin B12 (cyanocobalamin and analogues)* | |
| B03BA03 | hydroxocobalamin | 10.1 |
| B03BB | *Folic acid and derivatives* | |
| B03BB01 | folic acid | 10.1 |
| B03X | Other antianemic preparations | |
| B03XA | *Other antianemic preparations* | |
| B03XA01 | erythropoietin | 10.1 |
| B03XA02 | darbepoetin alfa | 10.1 |
| B03XA03 | methoxy polyethylene glycol-epoetin beta | 10.1 |
| **B05** | **Blood substitutes and perfusion solutions** | |
| B05A | Blood and related products | |
| B05A | platelet concentrates | 11.1 |
| B05A | whole blood* | 11.1 |
| B05AA | *Blood substitutes and plasma protein fractions* | |
| B05AA05 | dextran* | 11.3 |
| B05AX | *Other blood products* | |
| B05AX01 | red blood cells* | 11.1 |
| B05AX03 | fresh frozen plasma* | 11.1 |
| B05B | I.V. solutions | |
| B05BA | *Solutions for parenteral nutrition* | |
| B05BA03 | carbohydrates* | 26.2 |
| B05BB | *Solutions affecting the electrolyte balance* | |
| B05BB01 | electrolytes* | 26.2 |
| B05BB02 | electrolytes with carbohydrates* | 26.2 |
| B05BC | *Solutions producing osmotic diuresis* | |
| B05BC01 | mannitol | 16 |
| B05D | Peritoneal dialytics | |
| B05DA | *Isotonic solutions** | 23 |
| B05X | I.V. solution additives | |
| B05XA | *Electrolyte solutions* | |
| B05XA01 | potassium chloride | 26.1; 26.2 |
| B05XA02 | sodium bicarbonate* | 26.2 |
| B05XA03 | sodium chloride | 26.2 |
| B05XA05 | magnesium sulfate | 5 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| **C** | **CARDIOVASCULAR SYSTEM** | |
| **C01** | **Cardiac therapy** | |
| C01A | Cardiac glycosides | |
| C01AA | *Digitalis glycosides* | |
| C01AA05 | digoxin | 12.2; 12.4 |
| C01B | Antiarrhythmics, class I and III | |
| C01BB | *Antiarrhythmics, class Ib* | |
| C01BB01 | lidocaine | 12.2 |
| C01BD | *Antiarrhythmics, class III* | |
| C01BD01 | amiodarone | 12.2 |
| C01C | Cardiac stimulants excl. cardiac glycosides | |
| C01CA | *Adrenergic and dopaminergic agents* | |
| C01CA04 | dopamine | 12.4 |
| C01CA24 | epinephrine (adrenaline) | 3; 12.2; 25.1 |
| C01CA26 | ephedrine | 1.2 |
| C01D | Vasodilators used in cardiac diseases | |
| C01DA | *Organic nitrates* | |
| C01DA02 | glyceryl trinitrate | 12.1 |
| C01DA08 | isosorbide dinitrate | 12.1 |
| C01E | Other cardiac preparations | |
| C01EA | *Prostaglandins* | 22.6 |
| **C02** | **Antihypertensives** | |
| C02A | Antiadrenergic agents, centrally acting | |
| C02AB | *Methyldopa* | |
| C02AB01 | methyldopa (levorotatory)* | 12.3 |
| C02D | Arteriolar smooth muscle, agents acting on | |
| C02DB | *Hydrazinophthalazine derivatives* | |
| C02DB02 | hydrazaline | 12.3 |
| C02DD | *Nitroferricyanide derivatives* | |
| C02DD01 | nitroprusside* | 12.3 |
| **C03** | **Diuretics** | |
| C03A | Low-ceiling diuretics, thiazides | |
| C03AA | *Thiazides, plain* | |
| C03AA03 | hydrochlorothiazide | 12.3; 12.4; 16 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| C03C | High-ceiling diuretics | |
| C03CA | *Sulfonamides, plain* | |
| C03CA01 | furosemide | 12.4; 16 |
| C03D | Potassium-sparing agents | |
| C03DA | *Aldosterone antagonists* | |
| C03DA01 | spironolactone | 12.4; 16 |
| C03DB | *Other potassium-sparing agents* | |
| C03DB01 | amiloride | 16 |
| **C07** | **Beta blocking agents** | |
| C07A | Beta blocking agents | |
| C07AA | *Beta blocking agents, non-selective* | |
| C07AA05 | propranolol | 7.2 |
| C07AB | *Beta blocking agents, selective* | |
| C07AB07 | bisoprolol | 12.1; 12.2; 12.3; 12.4 |
| **C08** | **Calcium channel blockers** | |
| C08C | Selective calcium channel blockers with mainly vascular effects | |
| C08CA | *Dihydropyridine derivatives* | |
| C08CA01 | amlodipine | 12.3 |
| C08CA05 | nifedipine | 22.4 |
| C08D | Selective calcium channel blockers with direct cardiac effects | |
| C08DA | *Phenylalkylamine derivatives* | |
| C08DA01 | verapamil | 12.1; 12.2 |
| **C09** | **Agents acting on the renin-angiotensin system** | |
| C09A | ACE inhibitors, plain | |
| C09AA | *ACE inhibitors, plain* | |
| C09AA02 | enalapril | 12.3; 12.4 |
| C09B | ACE inhibitors, combinations | |
| C09BA | *ACE inhibitors and diuretics* | |
| C09BA03 | lisinopril and diuretics* | 12.3 |
| C09BB | *ACE inhibitors and calcium channel blockers* | |
| C09BB03 | lisinopril and amlodipine | 12.3 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| C09C | Antiotensin II receptor blockers (ARBs), plain | |
| C09CA | *Antiotensin II receptor blockers (ARBs), plain* | |
| C09CA01 | losartan | 12.3; 12.4 |
| C09D | Antiotensin II receptor blockers (ARBs), combinations | |
| C09DA | *Antiotensin II receptor blockers (ARBs) and diuretics* | |
| C09DA07 | telmisartan and diuretics* | 12.3 |
| C09DB | *Antiotensin II receptor blockers (ARBs) and calcium channel blockers* | |
| C09DB04 | telmisartan and amlodipine | 12.3 |
| **C10** | **Lipid modifying agents** | |
| C10A | Lipid modifying agents, plain | |
| C10AA | *HMG CoA reductase inhibitors* | |
| C10AA01 | simvastatin | 12.6 |
| **D** | **DERMATOLOGICALS** | |
| **D01** | **Antifungals for dermatological use** | |
| D01A | Antifungals for topical use | |
| D01AA | *Antibiotics* | |
| D01AA01 | nystatin | 6.3 |
| D01AC | *Imidazole and triazole derivatives* | |
| D01AC02 | miconazole | 13.1 |
| D01AE | *Other antifungals for topical use* | |
| D01AE12 | salicylic acid | 13.4 |
| D01AE13 | selenium sulfide | 13.1 |
| D01B | Antifungals for systemic use | |
| D01BA | *Antifungals for systemic use* | |
| D01BA01 | griseofulvin | 6.3 |
| D01BA02 | terbinafine | 13.1 |
| **D02** | **Emollients and protectives** | |
| D02A | Emollients and protectives | |
| D02AB | *Zinc products** | 13.3 |
| D02AE | *Carbamide products* | |
| D02AE01 | carbamide* | 13.4 |
| **D05** | **Antipsoriatics** | |
| D05A | Antipsoriatics for topical use | |
| D05AA | *Tars** | 13.4 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| **D06** | **Antibiotics and chemotherapeutics for dermatological use** | |
| D06A | Antibiotics for topical use | |
| D06AX | *Other antibiotics for topical use* | |
| D06AX09 | mupirocin | 13.2 |
| D06B | Chemotherapeutics for topical use | |
| D06BA | *Sulfonamides* | |
| D06BA01 | silver sulfadiazine | 13.2 |
| D06BB | *Antivirals* | |
| D06BB04 | podophyllotoxin* | 13.4 |
| **D07** | **Corticosteroids, dermatological preparations** | |
| D07A | Corticosteroids, plain | |
| D07AA | *Corticosteroids, weak (group I)* | |
| D07AA02 | hydrocortisone | 13.3 |
| D07AC | *Corticosteroids, potent (group III)* | |
| D07AC01 | betamethasone | 13.3 |
| **D08** | **Antiseptics and disinfectants** | |
| D08A | Antiseptics and disinfectants | |
| D08AC | *Biguanides and amidines* | |
| D08AC02 | chlorhexidine | 15.1; 22.6 |
| D08AE | *Phenol and derivatives* | |
| D08AE05 | chloroxylenol | 15.2 |
| D08AG | *Iodine products* | |
| D08AG02 | povidone-iodine | 15.1 |
| D08AG03 | iodine* | 6.3 |
| D08AX | *Other antiseptics and disinfectants** | 15 |
| D08AX05 | isopropanol* | 15.2 |
| D08AX06 | potassium permanganate | 13.2 |
| D08AX08 | ethanol | 15.1; 15.2 |
| **D10** | **Anti-acne preparations** | |
| D10A | Anti-acne preparations for topical use | |
| D10AE | *Peroxides* | |
| D10AE01 | benzoyl peroxide | 13.4 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| **G** | **GENITO URINARY SYSTEM AND SEX HORMONES** | |
| **G01** | **Gynecological antiinfectives and antiseptics** | |
| G01A | Antiinfectives and antiseptics, excl. combinations with corticosteroids | |
| G01AF | *Imidazole derivatives* | |
| G01AF02 | clotrimazole | 6.3 |
| **G02** | **Other gynecologicals** | |
| G02A | Oxytocics | |
| G02AB | *Ergot alkaloids* | |
| G02AB03 | ergometrine | 22.3 |
| G02AD | *Prostaglandins* | |
| G02AD06 | misoprostol | 22.3 |
| G02B | Contraceptives for topical use | |
| G02BA | *Intrauterine contraceptives* | |
| G02BA02 | plastic IUD with copper* | 22.1.3 |
| G02BA03 | plastic IUD with progestogen* | 22.1.3 |
| G02BB | *Intravaginal contraceptives* | |
| G02BB02 | vaginal ring with progestogen* | 22.1.6 |
| **G03** | **Sex hormones and modulators of the genital system** | |
| G03A | Hormonal contraceptives for systemic use | |
| G03AA | *Progestogens and estrogens, fixed combinations* | |
| G03AA05 | norethisterone and ethinylestradiol | 22.1.1 |
| G03AA07 | levonorgestrel and ethinylestradiol | 22.1.1 |
| G03AA08 | medroxyprogesterone and estrogen* | 22.1.2 |
| G03AC | *Progestogens* | |
| G03AC01 | norethisterone* | 22.1.2 |
| G03AC03 | levonorgestrel | 22.1.1; 22.1.5 |
| G03AC06 | medroxyprogesterone* | 18.4; 22.1.2 |
| G03AC08 | etonorgestrel | 22.1.5 |
| G03AD | *Emergency contraceptives* | |
| G03AD01 | levonorgestrel | 22.1.1 |
| G03AD02 | ulipristal | 22.1.1 |
| G03B | Androgens | |
| G03BA | *3-oxoandrosten (4) derivatives* | |
| G03BA03 | testosterone | 18.2 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| G03G | Gonadotropins and other ovulation stimulants | |
| G03GB | *Ovulation stimulants, synthetic* | |
| G03GB02 | clomifene | 22.2 |
| G03X | Other sex hormones and modulators of the genital system | |
| G03XB | *Antiprogesterons* | |
| G03XB01 | mifepristone | 22.3 |
| **H** | **SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS** | |
| **H01** | **Pituitary, hypothalamic hormones and analogues** | |
| H01B | Posterior pituitary lobe hormones | |
| H01BA | *Vasopressin and analogues* | |
| H01BA02 | desmopressin | 10.2 |
| H01BB | *Oxytocin and analogues* | |
| H01BB02 | oxytocin | 22.3 |
| H01BB03 | carbetocin | 22.3 |
| **H02** | **Corticosteroids for systemic use** | |
| H02A | Corticosteroids for systemic use, plain | |
| H02AA | *Mineralocorticoids* | |
| H02AA02 | fludrocortisone | 18.1 |
| H02AB | *Glucocorticoids* | |
| H02AB02 | dexamethasone | 2.3; 3; 8.2.4; 17.2; 22.5 |
| H02AB04 | methylprednisolone | 8.2.4 |
| H02AB06 | prednisolone | 3; 8.2.4 |
| H02AB09 | hydrocortisone | 3; 8.2.4; 18.1 |
| **H03** | **Thyroid therapy** | |
| H03A | Thyroid preparations | |
| H03AA | *Thyroid hormones* | |
| H03AA01 | levothyroxine sodium* | 18.7 |
| H03B | Antithyroid preparations | |
| H03BA | *Thiouracils* | |
| H03BA02 | propylthiouracil | 18.7 |
| H03BB | *Sulfur-containine imidazole derivatives* | |
| H03BB01 | carbimazole* | 18.7 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| H03C | Iodine therapy | |
| H03CA | *Iodine therapy** | 18.7; 27 |
| **H04** | **Pancreatic hormones** | |
| H04A | Glycogenolytic hormones | |
| H04AA | *Glycogenolytic hormones* | |
| H04AA01 | glucagon | 18.6 |
| **J** | **ANTIINFECTIVES FOR SYSTEMIC USE** | |
| **J01** | **Antibacterials for systemic use** | |
| J01A | Tetracyclines | |
| J01AA | *Tetracyclines* | |
| J01AA02 | doxycycline | 6.2.1; 6.5.3.1; 6.5.3.2 |
| J01B | Amphenicols | |
| J01BA | *Amphenicols* | |
| J01BA01 | chloramphenicol | 6.2.1 |
| J01C | Beta-lactam antibacterials, penicillins | |
| J01CA | *Penicillins with extended spectrum* | |
| J01CA01 | ampicillin | 6.2.1 |
| J01CA04 | amoxicillin | 6.2.1 |
| J01CE | *Beta-lactamase sensitive penicillins* | |
| J01CE01 | benzylpenicillin | 6.2.1 |
| J01CE02 | phenoxymethylpenicillin | 6.2.1 |
| J01CE08 | benzathine benzylpenicillin | 6.2.1 |
| J01CE09 | procaine benzylpenicillin | 6.2.1 |
| J01CF | *Beta-lactamase resistant penicillins* | |
| J01CF02 | cloxacillin | 6.2.1 |
| J01CR | *Combinations of penicillins, incl. beta-lactamase inhibitors* | |
| J01CR02 | amoxicillin and beta-lactamase inhibitor* | 6.2.1; 6.2.5 |
| J01CR05 | piperacillin and beta-lactamase inhibitor* | 6.2.2 |
| J01D | Other beta-lactam antibacterials | |
| J01DB | *First-generation cephalosporins* | |
| J01DB01 | cefalexin | 6.2.1 |
| J01DB04 | cefazolin | 6.2.1 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| J01DC | *Second-generation cephalosporins* | |
| J01DC02 | cefuroxime | 6.2.2 |
| J01DD | *Third-generation cephalosporins* | |
| J01DD01 | cefotaxime | 6.2.2 |
| J01DD02 | ceftazidime | 6.2.2 |
| J01DD04 | ceftriaxone | 6.2.2 |
| J01DD08 | cefixime | 6.2.2 |
| J01DD52 | ceftazidime and beta-lactamase inhibitor* | 6.2.3 |
| J01DH | *Carbapenems* | |
| J01DH02 | meropenem | 6.2.2 |
| J01DH52 | meropenem + vaborbactam | 6.2.3 |
| J01E | Sulfonamides and trimethoprim | |
| J01EC | *Intermediate-acting sulfonamides* | |
| J01EC02 | sulfadiazine | 6.5.4 |
| J01EE | *Combinations of sulfonamides and trimethoprim, incl. derivatives* | |
| J01EE01 | sulfamethoxazole + trimethoprim | 6.2.1; 6.5.4 |
| J01F | Macrolides, lincosamides and streptogramins | |
| J01FA | *Macrolides* | |
| J01FA09 | clarithromycin | 6.2.2 |
| J01FA10 | azithromycin | 6.2.2 |
| J01FF | *Lincosamides* | |
| J01FF01 | clindamycin | 6.2.1 |
| J01G | Aminoglycoside antibacterials | |
| J01GA | *Streptomycins* | |
| J01GA01 | streptomycin | 6.2.5 |
| J01GB | *Other aminoglycosides* | |
| J01GB03 | gentamicin | 6.2.1 |
| J01GB06 | amikacin | 6.2.1; 6.2.5 |
| TBA | plazomicin | 6.2.3 |
| J01M | Quinolone antibacterials | |
| J01MA | *Fluoroquinolones* | |
| J01MA02 | ciprofloxacin | 6.2.2 |
| J01MA12 | levofloxacin | 6.2.5 |
| J01MA14 | moxifloxacin | 6.2.5 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| J01X | Other antibacterials | |
| J01XA | *Glycopeptide antibacterials* | |
| J01XA01 | vancomycin | 6.2.2 |
| J01XB | *Polymyxins* | |
| J01XB01 | colistin | 6.2.3 |
| J01XB02 | polymyxin B | 6.2.3 |
| J01XD | *Imidazole derivatives* | |
| J01XD01 | metronidazole | 6.2.1; 6.5.1 |
| J01XE | *Nitrofuran derivatives* | |
| J01XE01 | nitrofurantoin | 6.2.1 |
| J01XX | *Other antibacterials* | |
| J01XX01 | fosfomycin | 6.2.3 |
| J01XX04 | spectinomycin | 6.2.1 |
| J01XX08 | linezolid | 6.2.3; 6.2.5 |
| **J02** | **Antimycotics for systemic use** | |
| J02A | Antimycotics for systemic use | |
| J02AA | *Antibiotics* | |
| J02AA01 | amphotericin B | 6.3; 6.5.2 |
| J02AC | *Triazole derivatives* | |
| J02AC01 | fluconazole | 6.3 |
| J02AC02 | itraconazole | 6.3 |
| J02AC03 | voriconazole | 6.3 |
| J02AX | *Other antimycotics for systemic use* | |
| J02AX01 | flucytosine | 6.3 |
| **J04** | **Antimycobacterials** | |
| J04A | Drugs for treatment of tuberculosis | |
| J04AA | *Aminosalicylic acid and derivatives* | |
| J04AA01 | p-aminosalicylic acid* | 6.2.5 |
| J04AB | *Antibiotics* | |
| J04AB01 | cycloserine | 6.2.5 |
| J04AB02 | rifampicin | 6.2.4; 6.2.5 |
| J04AB04 | rifabutin | 6.2.5 |
| J04AB05 | rifapentine | 6.2.5 |
| J04AC | *Hydrazides* | |
| J04AC01 | isoniazid | 6.2.5 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| J04AD | *Thiocarbamide derivatives* | |
| J04AD03 | ethionamide | 6.2.5 |
| J04AD01 | protionamide | 6.2.5 |
| J04AK | *Other drugs for treatment of tuberculosis* | |
| J04AK01 | pyrazinamide | 6.2.5 |
| J04AK02 | ethambutol | 6.2.5 |
| J04AK05 | bedaquiline | 6.2.5 |
| J04AK06 | delamanid | 6.2.5 |
| J04AM | *Combinations of drugs for treatment of tuberculosis** | |
| J04AM02 | rifampicin and isoniazid* | 6.2.5 |
| J04AM05 | rifampicin, pyrazinamide and isoniazid* | 6.2.5 |
| J04AM06 | rifampicin, pyrazinamide, ethambutol and isoniazid* | 6.2.5 |
| J04AM08 | isoniazid, sulfamethoxazole, trimethoprim and pyridoxine* | 6.4.2.5 |
| J04B | Drugs for treatment of lepra | |
| J04BA | *Drugs for treatment of lepra* | |
| J04BA01 | clofazimine | 6.2.4; 6.2.5 |
| J04BA02 | dapsone | 6.2.4 |
| **J05** | **Antivirals for systemic use** | |
| J05A | Direct acting antivirals | |
| J05AB | *Nucleosides and nucleotides excl. reverse transcriptase inhibitors* | |
| J05AB01 | aciclovir | 6.4.1 |
| J05AB14 | valganciclovir | 6.4.3 |
| J05AE | *Protease inhibitors* | |
| J05AE03 | ritonavir | 6.4.2.3 |
| J05AE08 | atazanavir | 6.4.2.3 |
| J05AE10 | darunavir | 6.4.2.3 |
| J05AF | *Nucleoside and nucleotide reverse transcriptase inhibitors* | |
| J05AF01 | zidovudine (ZDV or AZT) | 6.4.2.1 |
| J05AF05 | lamivudine (3TC) | 6.4.2.1 |
| J05AF06 | abacavir (ABC) | 6.4.2.1 |
| J05AF07 | tenofovir disoproxil | 6.4.2.1; 6.4.4.1.1 |
| J05AF10 | entecavir | 6.4.4.1.1 |
| J05AG | *Non-nucleoside reverse transcriptase inhibitors* | |
| J05AG01 | nevirapine (NVP) | 6.4.2.2 |
| J05AG03 | efavirenz (EFV or EFZ) | 6.4.2.2 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| J05AH | *Neuraminidase inhibitors* | |
| J05AH02 | oseltamivir | 6.4.3 |
| J05AP | *Antivirals for treatment of HCV infections* | |
| J05AP01 | ribavirin | 6.4.3; 6.4.4.2.3 |
| J05AP07 | daclatasvir | 6.4.4.2.1 |
| J05AP08 | sofosbuvir | 6.4.4.2.1 |
| J05AP09 | dasabuvir | 6.4.4.2.2 |
| J05AP51 | ledipasvir + sofosbuvir | 6.4.4.2.2 |
| J05AP53 | ombitasvir + paritaprevir + ritonavir | 6.4.4.2.2 |
| J05AP55 | sofosbuvir + velpatasvir | 6.4.4.2.1 |
| J05AP57 | glecaprevir + pibrentasvir | 6.4.4.2.1 |
| J05AR | *Antivirals for treatment of HIV infections, combinations* | |
| J05AR01 | lamivudine + zidovudine (ZDV or AZT) | 6.4.2 |
| J05AR02 | abacavir + lamivudine | 6.4.2 |
| J05AR03 | tenofovir disoproxil + emtricitabine | 6.4.2 |
| J05AR05 | lamivudine + nevirapine + zidovudine | 6.4.2 |
| J05AR06 | emtricitabine + tenofovir disoproxil + efavirenz | 6.4.2 |
| J05AR10 | lopinavir + ritonavir (LPV/r)* | 6.4.2.3 |
| J05AR11 | lamivudine + tenofovir disoproxil + efavirenz | 6.4.2 |
| J05AR23 | atazanavir + ritonavir | 6.4.2.3 |
| TBA | dolutegravir + lamivudine + tenofovir | 6.4.2 |
| J05AX | *Other antivirals* | |
| J05AX08 | raltegravir | 6.4.2.4 |
| J05AX12 | dolutegravir | 6.4.2.4 |
| **J06** | **Immune sera and immunoglobulins** | |
| J06A | Immune sera | |
| J06AA | Immune sera | |
| J06AA01 | diphtheria antitoxin | 19.2 |
| J06AA03 | snake venom antiserum* | 19.2 |
| J06B | Immunoglobulins | |
| J06BA | Immunoglobulins, normal human | |
| J06BA01 | immunoglobulins, normal human, for extravascular admin* | 11.2.1 |
| J06BA02 | immunoglobulins, normal human, for intravascular admin* | 11.2.1 |
| J06BB | Specific immunoglobulins | |
| J06BB01 | anti-D immunoglobulin | 11.2.1 |
| J06BB02 | tetanus immunoglobulin* | 11.2.1 |
| J06BB05 | rabies immunoglobulin* | 11.2.1 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| **J07** | **Vaccines** | |
| J07A | Bacterial vaccines | |
| J07AE | *Cholera vaccines** | 19.3 |
| J07AF | *Diphtheria vaccines* | |
| J07AF01 | diphtheria toxoid* | 19.3 |
| J07AG | *Hemophilus influenzae B vaccines* | |
| J07AG01 | hemophilus influenzae B, purified antigen conjugated* | 19.3 |
| J07AH | *Meningococcal vaccines** | 19.3 |
| J07AJ | *Pertussis vaccines* | |
| J07AJ01 | pertussis vaccine | 19.3 |
| J07AL | *Pneumococcal vaccines* | |
| J07AL01 | pneumococcus, purified polysaccharides antigen* | 19.3 |
| J07AM | *Tetanus vaccines* | |
| J07AM01 | tetanus toxoid* | 19.3 |
| J07AN | *Tuberculosis vaccines* | |
| J07AN01 | tuberculosis, live attenuated* | 19.3 |
| J07AP | *Typhoid vaccines** | 19.3 |
| J07B | Viral vaccines | |
| J07BA | *Encephalitis vaccines* | |
| J07BA01 | encephalitis, tick-borne, inactivated, whole virus | 19.3 |
| J07BA02 | encephalitis, Japanese, inactivated, whole virus | 19.3 |
| J07BB | *Influenza vaccines** | 19.3 |
| J07BC | *Hepatitis vaccines* | |
| J07BC01 | hepatitis B vaccine | 19.3 |
| J07BC02 | hepatitis A vaccine | 19.3 |
| J07BD | *Measles vaccine** | |
| J07BD01 | measles vaccine, live attenuated* | 19.3 |
| J07BE | *Mumps vaccines* | |
| J07BE01 | mumps vaccine, live attenuated* | 19.3 |
| J07BF | *Poliomyelitis vaccine* | 19.3 |
| J07BG | *Rabies vaccine* | 19.3 |
| J07BH | *Rota virus diarrhea vaccines** | 19.3 |
| J07BJ | *Rubella vaccines* | 19.3 |
| J07BK | *Varicella zoster vaccines** | 19.3 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| J07BL | *Yellow fever vaccines* | 19.3 |
| J07BM | *Papillomavirus vaccines* | |
| J07BM01 | papillomavirus (human types 6, 11, 16, 18)* | 19.3 |
| J07BM02 | papillomavirus (human types 16, 18)* | 19.3 |
| J07BX | *Other viral vaccines** | 19.3 |
| J07C | Bacterial and viral vaccines, combined | |
| J07CA | *Bacterial and viral vaccines, combined** | 19.3 |
| **L** | **ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS** | |
| **L01** | **Antineoplastic agents** | |
| L01A | Alkylating agents | |
| L01AA | *Nitrogen mustard analogues* | |
| L01AA01 | cyclophosphamide | 8.2.1 |
| L01AA02 | chlorambucil | 8.2.1 |
| L01AA03 | melphalan | 8.2.1 |
| L01AA06 | ifosfamide | 8.2.1 |
| L01AA09 | bendamustine | 8.2.1 |
| L01AX | *Other alkylating agents* | |
| L01AX04 | dacarbazine | 8.2.1 |
| L01B | Antimetabolites | |
| L01BA | *Folic acid analogues* | |
| L01BA01 | methotrexate | 8.2.1 |
| L01BB | *Purine analogues* | |
| L01BB02 | mercaptopurine | 8.2.1 |
| L01BB03 | tioguanine | 8.2.1 |
| L01BB05 | fludarabine | 8.2.1 |
| L01BC | *Pyrimidine analogues* | |
| L01BC01 | cytarabine | 8.2.1 |
| L01BC02 | fluorouracil | 8.2.1; 13.4 |
| L01BC05 | gemcitabine | 8.2.1 |
| L01BC06 | capecitabine | 8.2.1 |
| L01C | Plant alkaloids and other natural products | |
| L01CA | *Vinca alkaloids and analogues* | |
| L01CA01 | vinblastine | 8.2.1 |
| L01CA02 | vincristine | 8.2.1 |
| L01CA04 | vinorelbine | 8.2.1 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| L01CB | *Podophyllotoxin derivatives* | |
| L01CB01 | etoposide | 8.2.1 |
| L01CD | *Taxanes* | |
| L01CD01 | paclitaxel | 8.2.1 |
| L01CD02 | docetaxel | 8.2.1 |
| L01D | Cytotoxic antibiotics and related substances | |
| L01DA | *Actinomycines* | |
| L01DA01 | dactinomycin | 8.2.1 |
| L01DB | *Anthracyclines and related substances* | |
| L01DB01 | doxorubicin | 8.2.1 |
| L01DB02 | daunorubicin | 8.2.1 |
| L01DC | *Other cytotoxic antibiotics* | |
| L01DC01 | bleomycin | 8.2.1 |
| L01X | Other antineoplastic agents | |
| L01XA | *Platinum compounds* | |
| L01XA01 | cisplatin | 8.2.1 |
| L01XA02 | carboplatin | 8.2.1 |
| L01XA03 | oxaliplatin | 8.2.1 |
| L01XB | *Methylhydrazines* | |
| L01XB01 | procarbazine | 8.2.1 |
| L01X | Other antineoplastic agents | |
| L01XC | *Monoclonal antibodies* | |
| L01XC02 | rituximab | 8.2.2 |
| L01XC03 | trastuzumab | 8.2.2 |
| L01XC07 | bevacizumab | 21.6 |
| L01XC17 | nivolumab | 8.2.3 |
| L01XE | *Protein kinase inhibitors* | |
| L01XE01 | imatinib | 8.2.2 |
| L01XE03 | erlotinib | 8.2.2 |
| L01XE06 | dasatinib | 8.2.2 |
| L01XE08 | nilotinib | 8.2.2 |
| L01XX | *Other antineoplastic agents* | |
| L01XX02 | asparaginase | 8.2.1 |
| L01XX05 | hydroxycarbamide | 8.2.1; 10.3 |
| L01XX09 | miltefosine | 6.5.2 |
| L01XX14 | tretinoin* | 8.2.2 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| L01XX19 | irinotecan | 8.2.1 |
| L01XX24 | pegaspargase | 8.2.1 |
| L01XX27 | arsenic trioxide | 8.2.1 |
| L01XX32 | bortezomib | 8.2.2 |
| TBA | realgar-Indigo naturalis formula | 8.2.1 |
| **L02** | **Endocrine therapy** | |
| L02A | Hormones and related agents | |
| L02AE | *Gonadotrophin releasing hormone analogues* | |
| L02AE02 | leuprorelin | 8.2.4 |
| L02B | Hormone antagonists and related agents | |
| L02BA | *Anti-estrogens* | |
| L02BA01 | tamoxifen | 8.2.4 |
| L02BB | *Anti-androgens* | |
| L02BB03 | bicalutamide | 8.2.4 |
| L02BG | *Aromatase inhibitors* | |
| L02BG03 | anastrozole | 8.2.4 |
| L02BX | *Other hormone antagonists and related agents* | |
| L02BX03 | abiraterone | 8.2.4 |
| **L03** | **Immunostimulants** | |
| L03A | Immunostimulants | |
| L03AA | *Colony stimulating factors* | |
| L03AA02 | filgrastim | 8.2.3 |
| L03AB | *Interferons* | |
| L03AB10 | peginterferon alfa-2b* | 6.4.4.2.3 |
| L03AB11 | peginterferon alfa-2a* | 6.4.4.2.3 |
| **L04** | **Immunosuppressants** | |
| L04A | Immunosuppressants | |
| L04AB | *Tumor necrosis factor alfa (TNF-a) inhibitors* | |
| L04AB04 | adalimumab | 8.1 |
| L04AD | *Calcineurin inhibitors* | |
| L04AD01 | ciclosporin | 8.1 |
| L04AX | *Other immunosuppressants* | |
| L04AX01 | azathioprine | 8.1; 29.2 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| L04AX02 | thalidomide | 8.2.3 |
| L04AX03 | methotrexate | 29.2 |
| L04AX04 | lenalidomide | 8.2.3 |
| **M** | **MUSCULO-SKELETAL SYSTEM** | |
| **M01** | **Antiinflammatory and antirheumatic products** | |
| M01A | Antiinflammatory and antirheumatic products, non-steroids | |
| M01AE | *Propionic acid derivatives* | |
| M01AE01 | ibuprofen | 2.1; 7.1; 22.6 |
| M01C | Specific antirheumatic agents | |
| M01CC | *Penicillamine and similar agents* | |
| M01CC01 | penicillamine | 4.2; 29.2 |
| **M03** | **Muscle relaxants** | |
| M03A | Muscle relaxants, peripherally acting agents | |
| M03AB | *Choline derivatives* | |
| M03AB01 | suxamethonium | 20 |
| M03AC | *Other quaternary ammonium compounds* | |
| M03AC03 | vecuronium | 20 |
| M03AC04 | atracurium | 20 |
| **M04** | **Antigout preparations** | |
| M04A | Antigout preparations | |
| M04AA | *Preparations inhibiting uric acid production* | |
| M04AA01 | allopurinol | 8.2.5; 29.1 |
| **M05** | **Drugs for treatment of bone diseases** | |
| M05B | Drugs affecting bone structure and mineralization | |
| M05BA | *Bisphosphonates* | |
| M05BA08 | zoledronic acid | 8.2.5 |
| **N** | **NERVOUS SYSTEM** | |
| **N01** | **Anesthetics** | |
| N01A | Anesthetics, general | |
| N01AB | *Halogenated hydrocarbons* | |
| N01AB01 | halothane | 1.1.1 |
| N01AB06 | isoflurane | 1.1.1 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| N01AX | *Other general anesthetics* | |
| N01AX03 | ketamine | 1.1.2 |
| N01AX10 | propofol | 1.1.2 |
| N01AX13 | nitrous oxide | 1.1.1 |
| N01B | Anesthetics, local | |
| N01BB | *Amides* | |
| N01BB01 | bupivacaine | 1.2 |
| N01BB02 | lidocaine | 1.2 |
| N01BB52 | lidocaine, combinations* | 1.2 |
| **N02** | **Analgesics** | |
| N02A | Opioids | |
| N02AA | *Natural opium alkaloids* | |
| N02AA01 | morphine | 1.3; 2.2 |
| N02AB | *Phenylpiperidine derivatives* | |
| N02AB03 | fentanyl | 2.2 |
| N02B | Other analgesics and antipyretics | |
| N02BA | *Salicylic acid and derivatives* | |
| N02BA01 | acetylsalicylic acid | 2.1; 7.1; 29.3 |
| N02BE | *Anilides* | |
| N02BE01 | paracetamol | 2.1; 7.1 |
| **N03** | **Antiepileptics** | |
| N03A | Antiepileptics | |
| N03AA | *Barbiturates and derivatives* | |
| N03AA02 | phenobarbital | 5 |
| N03AB | *Hydantoin derivatives* | |
| N03AB02 | phenytoin | 5 |
| N03AD | *Succinimide derivatives* | |
| N03AD01 | ethosuximide | 5 |
| N03AF | *Carboxamide derivatives* | |
| N03AF01 | carbamazepine | 5; 24.2.2 |
| N03AG | *Fatty acid derivatives* | |
| N03AG01 | valproic acid | 5; 24.2.2 |
| N03AX | *Other antiepileptics* | |
| N03AX09 | lamotrigine | 5 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| **N04** | **Anti-parkinson drugs** | |
| N04A | Anticholinergic agents | |
| N04AA | *Tertiary amines* | |
| N04AA02 | biperiden | 9 |
| N04B | Dopaminergic agents | |
| N04BA | *Dopa and dopa derivatives* | |
| N04BA02 | levodopa and decarboxylase inhibitor* | 9 |
| **N05** | **Psycholeptics** | |
| N05A | Antipsychotics | |
| N05AA | *Phenothiazines with aliphatic side-chain* | |
| N05AA01 | chlorpromazine | 24.1 |
| N05AB | *Phenothiazines with piperazine structure* | |
| N05AB02 | fluphenazine | 24.1 |
| N05AH | *Diazepines, oxazepines, thiazepines and oxepines* | |
| N05AH02 | clozapine | 24.1 |
| N05AD | *Butyrophenone derivatives* | |
| N05AD01 | haloperidol | 2.3; 24.1 |
| N05AN | *Lithium* | |
| N05AN01 | lithium* | 24.2.2 |
| N05AX | *Other antipsychotics* | |
| N05AX08 | risperidone | 24.1 |
| N05B | Anxiolytics | |
| N05BA | *Benzodiazepine derivatives* | |
| N05BA01 | diazepam | 2.3; 5; 24.3 |
| N05BA06 | lorazepam | 5 |
| N05C | Hypnotics and sedatives | |
| N05CD | *Benzodiazepine derivatives* | |
| N05CD08 | midazolam | 1.3; 2.3; 5 |
| **N06** | **Psychoanaleptics** | |
| N06A | Antidepressants | |
| N06AA | *Non-selective monoamine reuptake inhibitors* | |
| N06AA04 | clomipramine | 24.4 |
| N06AA09 | amitriptyline | 2.3; 24.2.1 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| N06AB | *Selective serotonin reuptake inhibitors* | |
| N06AB03 | fluoxetine | 2.3; 24.2.1 |
| N06B | Psychostimulants, agents used for ADHD and nootropics | |
| N06BC | Xanthine derivatives | |
| N06BC01 | caffeine citrate | 22.6 |
| **N07** | **Other nervous system drugs** | |
| N07A | Parasympathomimetics | |
| N07AA | *Anticholinesterases* | |
| N07AA01 | neostigmine | 20 |
| N07AA02 | pyridostigmine | 20 |
| N07B | Drugs used in addictive disorders | |
| N07BA | *Drugs used in nicotine dependence* | |
| N07BA01 | nicotine* | 24.5 |
| N07BC | *Drugs used in opioid dependence* | |
| N07BC02 | methadone | 2.2; 24.5 |
| **P** | **ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS** | |
| **P01** | **Antiprotozoals** | |
| P01A | Agents against amoebiasis and other protozoal diseases | |
| P01AB | *Nitroimidazole derivatives* | |
| P01AB01 | metronidazole | 6.5.1 |
| P01AC | *Dichloroacetamide derivatives* | |
| P01AC01 | diloxanide | 6.5.1 |
| P01B | Antimalarials | |
| P01BA | *Aminoquinolines* | |
| P01BA01 | chloroquine | 6.5.3.1; 6.5.3.2; 29.2 |
| P01BA02 | hydroxychloroquine | 29.2 |
| P01BA03 | primaquine | 6.5.3.1 |
| P01BA06 | amodiaquine | 6.5.3.1 |
| P01BB | *Biguanides* | |
| P01BB01 | proguanil | 6.5.3.2 |
| P01BC | *Methanolquinolines* | |
| P01BC01 | quinine | 6.5.3.1 |
| P01BC02 | mefloquine | 6.5.3.1; 6.5.3.2 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| P01BD | *Diaminopyrimidines* | |
| P01BD01 | pyrimethamine | 6.5.4 |
| P01BD51 | pyrimethamine, combinations* | 6.5.3.1; 6.5.3.2 |
| P01BE | *Artemisinin and derivatives* | |
| P01BE02 | artemether | 6.5.3.1 |
| P01BE03 | artesunate | 6.5.3.1 |
| P01BF01 | artemether and lumefantrine | 6.5.3.1 |
| P01BF02 | artesunate and mefloquine | 6.5.3.1 |
| P01BF03 | artesunate and amodiaquine | 6.5.3.1 |
| P01BF05 | artenimol and piperaquine | 6.5.3.1 |
| P01BF06 | artesunate and pyronaridine | 6.5.3.1 |
| P01C | Agents against leishmaniasis and trypanosomiasis | |
| P01CA | *Nitroimidazole derivatives* | |
| P01CA02 | benznidazole | 6.5.5.2 |
| P01CA03 | fexinidazole | 6.5.5.1 |
| P01CB | *Antimony compounds* | |
| P01CB01 | meglumine antimoniate | 6.5.2 |
| P01CB02 | sodium stibogluconate | 6.5.2 |
| P01CC | *Nitrofuran derivatives* | |
| P01CC01 | nifurtimox | 6.5.5.1; 6.5.5.2 |
| P01CD | *Arsenic compounds* | |
| P01CD01 | melarsoprol | 6.5.5.1 |
| P01CX | *Other agents against leishmaniasis and trypanosomiasis* | |
| P01CX01 | pentamidine isethionate* | 6.5.4; 6.5.5.1 |
| P01CX02 | suramin sodium | 6.5.5.1 |
| P01CX03 | eflornithine | 6.5.5.1 |
| **P02** | **Anthelmintics** | |
| P02B | Antitrematodals | |
| P02BA | *Quinoline derivatives and related substances* | |
| P02BA01 | praziquantel | 6.1.1; 6.1.3 |
| P02BA02 | oxamniquine | 6.1.3 |
| P02BX | *Other antitrematodal agents* | |
| P02BX04 | triclabendazole | 6.1.3 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| P02C | Antinematodal agents | |
| P02CA | *Benzimidazole derivatives* | |
| P02CA01 | mebendazole | 6.1.1 |
| P02CA03 | albendazole | 6.1.1; 6.1.2 |
| P02CB | *Piperazine and derivatives* | |
| P02CB02 | diethylcarbamazine | 6.1.2 |
| P02CC | *Tetrahydropyrimidine derivatives* | |
| P02CC01 | pyrantel | 6.1.1 |
| P02CE | *Imidazothiazole derivatives* | |
| P02CE01 | levamisole | 6.1.1 |
| P02CF | *Avermectines* | |
| P02CF01 | ivermectin | 6.1.1; 6.1.2; 6.6 |
| P02D | Anticestodals | |
| P02DA | *Salicylic acid derivatives* | |
| P02DA01 | niclosamide | 6.1.1 |
| **P03** | **Ectoparasiticides, incl. scabicides, insecticides and repellents** | |
| P03A | Ectoparasiticides, incl. scabicides | |
| P03AC | *Pyrethrines, incl. synthetic compounds* | |
| P03AC04 | permethrin | 13.5 |
| P03AX | *Other ectoparasiticides, incl. scabicides* | |
| P03AX01 | benzyl benzoate | 13.5 |
| **R** | **RESPIRATORY SYSTEM** | |
| **R01** | **Nasal preparations** | |
| R01A | Decongestants and other nasal preparations for topical use | |
| R01AA | *Sympathomimetics, plain* | |
| R01AA07 | xylometazoline | 28 |
| R01AD | *Corticosteroids* | |
| R01AD05 | budesonide | 28 |
| **R03** | **Drugs for obstructive airway diseases** | |
| R03A | Adrenergics, inhalants | |
| R03AC | *Selective beta-2-adrenoreceptor agonists* | |
| R03AC02 | salbutamol | 25.1 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| R03AK | *Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics* | |
| R03AK07 | formoterol and budesonide | 25.1 |
| R03B | Other drugs for obstructive airway diseases, inhalants | |
| R03BA | *Glucocorticoids* | |
| R03BA01 | beclometasone | 25.1 |
| R03BA02 | budesonide | 25.1 |
| R03BB | *Anticholinergics* | |
| R03BB01 | ipratropium bromide | 25.1 |
| R03BB04 | tiotropium | 25.1 |
| R03C | Adrenergics for systemic use | |
| R03CC | *Selective beta-2-adrenoreceptor agonists* | |
| R03CC02 | salbutamol | 25.1 |
| **R05** | **Cough and cold preparations** | |
| R05D | Cough suppressants, excl. combinations with expectorants | |
| R05DA | *Opium alkaloids and derivatives* | |
| R05DA04 | codeine | 2.2 |
| **R06** | **Antihistamines for systemic use** | |
| R06A | Antihistamines for systemic use | |
| R06AE | *Piperazine derivatives* | |
| R06AE3 | cyclizine | 2.3 |
| R06AX | *Other antihistamines for systemic use* | |
| R06AX13 | loratadine | 3 |
| **R07** | **Other respiratory system products** | |
| R07A | Other respiratory system products | |
| R07AA | *Lung surfactants* | 22.6 |
| **S** | **SENSORY ORGANS** | |
| **S01** | **Ophthalmologicals** | |
| S01A | Antiinfectives | |
| S01AA | *Antibiotics* | |
| S01AA09 | tetracycline | 21.1 |
| S01AA10 | natamycin | 21.1 |
| S01AA11 | gentamicin | 21.1 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| S01AA17 | erythromycin | 21.1 |
| S01AA26 | azithromycin | 21.1 |
| S01AD | *Antivirals* | |
| S01AD03 | aciclovir | 21.1 |
| S01AE | *Fluoroquinolones* | |
| S01AE01 | ofloxacin | 21.1 |
| S01B | Antiinflammatory agents | |
| S01BA | *Corticosteroids, plain* | |
| S01BA04 | prednisolone | 21.2 |
| S01E | Antiglaucoma preparations and miotics | |
| S01EA | *Sympathomimetics in glaucoma therapy* | |
| S01EA01 | epinephrine | 21.5 |
| S01EB | *Parasympathomimetics* | |
| S01EB01 | pilocarpine | 21.4 |
| S01EC | *Carbonic anhydrase inhibitors* | |
| S01EC01 | acetazolamide | 21.4 |
| S01ED | *Beta blocking agents* | |
| S01ED01 | timolol | 21.4 |
| S01EE | *Prostaglandin analogues* | |
| S01EE01 | latanoprost | 21.4 |
| S01F | Mydriatics and cycloplegics | |
| S01FA | *Anticholinergics* | |
| S01FA01 | atropine | 21.5 |
| S01FA06 | tropicamide | 14.1 |
| S01H | Local anesthetics | |
| S01HA | *Local anesthetics* | |
| S01HA03 | tetracaine | 21.3 |
| S01J | Diagnostic agents | |
| S01JA | *Colouring agents* | |
| S01JA01 | fluorescein | 14.1 |
| **S02** | **Otologicals** | |
| S02A | Antiinfectives | |
| S02AA | *Antiinfectives* | |
| S02AA10 | acetic acid | 28 |
| S02AA15 | ciprofloxacin | 28 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| **V** | **VARIOUS** | |
| **V03** | **All other therapeutic products** | |
| V03A | All other therapeutic products | |
| V03AB | *Antidotes* | |
| V03AB03 | edetates* | 4.2 |
| V03AB06 | thiosulfate* | 4.2; 13.1 |
| V03AB08 | sodium nitrite | 4.2 |
| V03AB09 | dimercaprol | 4.2 |
| V03AB14 | protamine* | 10.2 |
| V03AB15 | naloxone | 4.2 |
| V03AB17 | methylthioninium chloride (methylene blue) | 4.2 |
| V03AB23 | acetylcysteine | 4.2 |
| V03AB31 | potassium ferric hexacyanoferrate (II) ·2H2O (Prussian blue) | 4.2 |
| V03AB34 | fomepizole | 4.2 |
| V03AC | *Iron chelating agents* | |
| V03AC01 | deferoxamine | 4.2; 10.3 |
| V03AF | *Detoxifying agents for antineoplastic treatment* | |
| V03AF01 | mesna | 8.2.5 |
| V03AF03 | calcium folinate | 8.2.1 |
| V03AH | *Drugs for treatment of hypoglycaemia* | |
| V03AH01 | diazoxide | 18.6 |
| V03AN | *Medical gases* | |
| V03AN01 | oxygen | 1.1.1; 1.4 |
| **V04** | **Diagnostic agents** | |
| V04C | Other diagnostic agents | |
| V04CF | *Tuberculosis diagnostics* | |
| V04CF01 | tuberculin, purified protein derivative (PPD) - BCG* | 19.1 |
| **V07** | **All other non-therapeutic products** | |
| V07A | All other non-therapeutic products | |
| V07AB | *Solvents and diluting agents, incl. irrigating solutions** | 26.3 |
| V07AB | *Water for Injection* | 26.3 |
| V07AV | *Technical disinfectants** | 15.2 |
| **V08** | **Contrast media** | |
| V08A | X-ray contrast media, iodinated | |
| V08AA | *Watersoluble, nephrotropic, high osmolar X-ray contrast media* | |
| V08AA01 | diatrizoic acid* | 14.2 |

| ATC code | ATC group/medicine or item | Section |
|---|---|---|
| V08AB | *Watersoluble, nephrotropic, low osmolar X-ray contrast media* | |
| V08AB02 | iohexol | 14.2 |
| V08AC | *Watersoluble, hepatotropic X-ray contrast media* | |
| V08AC02 | iotroxic acid* | 14.2 |
| V08B | X-ray contrast media, non-iodinated | |
| V08BA | *Barium sulfate containing X-ray contrast media* | |
| V08BA01 | barium sulfate with suspending agents* | 14.2 |



* Medicine or item name differs slightly from the name used.

# Annex 4

## Alphabetical list of essential medicines (with ATC classification code numbers)

| Medicine or item as in EML | ATC code | Section |
|---|---|---|
| abacavir (ABC) | J05AF06 | 6.4.2.1 |
| abacavir + lamivudine | J05AR02 | 6.4.2 |
| abiraterone | L02BX03 | 8.2.4 |
| acetazolamide | S01EC01 | 21.4 |
| acetic acid | S02AA10 | 28 |
| acetylcysteine | V03AB23 | 4.2 |
| acetylsalicylic acid | B01AC06 | 12.5.1 |
| acetylsalicylic acid | N02BA01 | 2.1; 7.1; 29.3 |
| aciclovir | J05AB01 | 6.4.1 |
| aciclovir | S01AD03 | 21.1 |
| adalimumab | L04AB04 | 8.1 |
| albendazole | P02CA03 | 6.1.1; 6.1.2 |
| allopurinol | M04AA01 | 8.2.5; 29.1 |
| alteplase | B01AD02 | 12.5.2 |
| amikacin | J01GB06 | 6.2.1; 6.2.5 |
| amiloride | C03DB01 | 16 |
| amiodarone | C01BD01 | 12.2 |
| amitriptyline | N06AA09 | 2.3; 24.2.1 |
| amlodipine | C08CA01 | 12.3 |
| amodiaquine | P01BA06 | 6.5.3.1 |
| amoxicillin | J01CA04 | 6.2.1 |
| amoxicillin and enzyme inhibitor* | J01CR02 | 6.2.1; 6.2.5 |
| amphotericin B | J02AA01 | 6.3; 6.5.2 |
| ampicillin | J01CA01 | 6.2.1 |
| anastrozole | L02BG03 | 8.2.4 |
| anti-D immunoglobulin | J06BB01 | 11.2.1 |
| aprepitant | A04AD12 | 17.2 |
| arsenic trioxide | L01XX27 | 8.2.1 |
| artemether | P01BE02 | 6.5.3.1 |
| artemether and lumefantrine | P01BF01 | 6.5.3.1 |
| artenimol and piperaquine | P01BF05 | 6.5.3.1 |
| artesunate | P01BE03 | 6.5.3.1 |
| artesunate and amodiaquine | P01BF03 | 6.5.3.1 |

| Medicine or item as in EML | ATC code | Section |
|---|---|---|
| artesunate and mefloquine | P01BF02 | 6.5.3.1 |
| artesunate and pyronaridine | P01BF06 | 6.5.3.1 |
| ascorbic acid | A11GA01 | 27 |
| asparaginase | L01XX02 | 8.2.1 |
| atazanavir | J05AE08 | 6.4.2.3 |
| atazanavir + ritonavir | J05AR23 | 6.4.2.3 |
| atracurium | M03AC04 | 20 |
| atropine | A03BA01 | 1.3; 4.2 |
| atropine | S01FA01 | 21.5 |
| azathioprine | L04AX01 | 8.1; 29.2 |
| azithromycin | J01FA10 | 6.2.2; 21.1 |
| | | |
| bacterial and viral vaccines, combined* | J07CA | 19.3 |
| barium sulfate with suspending agents* | V08BA01 | 14.2 |
| beclometasone | R03BA01 | 25.1 |
| bedaquiline | J04AK05 | 6.2.5 |
| bendamustine | L01AA09 | 8.2.1 |
| benzathine benzylpenicillin | J01CE08 | 6.2.1 |
| benznidazole | P01CA02 | 6.5.5.2 |
| benzoyl peroxide | D10AE01 | 13.4 |
| benzyl benzoate | P03AX01 | 13.5 |
| benzylpenicillin | J01CE01 | 6.2.1 |
| betamethasone | D07AC01 | 13.3 |
| bevacizumab | L01XC07 | 21.6 |
| bicalutamide | L02BB03 | 8.2.4 |
| biperiden | N04AA02 | 9 |
| bisoprolol | C07AB07 | 12.1; 12.2; 12.3; 12.4 |
| bleomycin | L01DC01 | 8.2.1 |
| bortezomib | L01XX32 | 8.2.2 |
| budesonide | R03BA02 | 25.1 |
| budesonide | R01AD05 | 28 |
| budesonide and formoterol | R03AK07 | 25.1 |
| bupivacaine | N01BB01 | 1.2 |
| | | |
| caffeine citrate | N06BC01 | 22.6 |
| calcium folinate | V03AF03 | 8.2.1 |
| calcium gluconate | A12AA03 | 4.2; 27 |
| capecitabine | L01BC06 | 8.2.1 |
| carbamazepine | N03AF01 | 5; 24.2.2 |
| carbamide* | D02AE01 | 13.4 |

| Medicine or item as in EML | ATC code | Section |
|---|---|---|
| carbetocin | H01BB03 | 22.3 |
| carbimazole* | H03BB01 | 18.7 |
| carbohydrates* | B05BA03 | 26.2 |
| carboplatin | L01XA02 | 8.2.1 |
| cefalexin | J01DB01 | 6.2.1 |
| cefazolin | J01DB04 | 6.2.1 |
| cefixime | J01DD08 | 6.2.2 |
| cefotaxime | J01DD01 | 6.2.2 |
| ceftazidime | J01DD02 | 6.2.2 |
| ceftazidime and beta-lactamase inhibitor* | J01DD52 | 6.2.3 |
| ceftriaxone | J01DD04 | 6.2.2 |
| cefuroxime | J01DC02 | 6.2.2 |
| chlorambucil | L01AA02 | 8.2.1 |
| chloramphenicol | J01BA01 | 6.2.1 |
| chlorhexidine | D08AC02 | 15.1; 22.6 |
| chloroquine | P01BA01 | 6.5.3.1; 6.5.3.2; 29.2 |
| chloroxylenol | D08AE05 | 15.2 |
| chlorpromazine | N05AA01 | 24.1 |
| cholera vaccines* | J07AE | 19.3 |
| ciclosporin | L04AD01 | 8.1 |
| ciprofloxacin | J01MA02 | 6.2.2 |
| ciprofloxacin | S02AA15 | 28 |
| cisplatin | L01XA01 | 8.2.1 |
| clarithromycin | J01FA09 | 6.2.2 |
| clindamycin | J01FF01 | 6.2.1 |
| clofazimine | J04BA01 | 6.2.4; 6.2.5 |
| clomifene | G03GB02 | 22.2 |
| clomipramine | N06AA04 | 24.4 |
| clopidogrel | B01AC04 | 12.5.1 |
| clotrimazole | G01AF02 | 6.3 |
| cloxacillin | J01CF02 | 6.2.1 |
| clozapine | N05AH02 | 24.1 |
| coagulation factor IX, II, VII and X in combination* | B02BD01 | 11.2.2 |
| coagulation factor VIII* | B02BD02 | 11.2.2 |
| codeine | R05DA04 | 2.2 |
| colecalciferol | A11CC05 | 27 |
| colistin | J01XB01 | 6.2.3 |
| Combinations of drugs for treatment of tuberculosis* | J04AM | 6.2.5 |

| Medicine or item as in EML | ATC code | Section |
|---|---|---|
| cyclizine | R06AE3 | 2.3 |
| cyclophosphamide | L01AA01 | 8.2.1 |
| cycloserine | J04AB01 | 6.2.5 |
| cytarabine | L01BC01 | 8.2.1 |
| | | |
| dabigatran etexilate* | B01AE07 | 10.2 |
| dacarbazine | L01AX04 | 8.2.1 |
| daclatasvir | J05AX14 | 6.4.4.2.1 |
| dactinomycin | L01DA01 | 8.2.1 |
| dapsone | J04BA02 | 6.2.4 |
| darbepoetin alfa | B03XA02 | 10.1 |
| darunavir | J05AE10 | 6.4.2.3 |
| dasabuvir | J05AX16 | 6.4.4.2.2 |
| dasatinib | L01XE06 | 8.2.2 |
| daunorubicin | L01DB02 | 8.2.1 |
| deferoxamine | V03AC01 | 4.2; 10.3 |
| delamanid | J04AK06 | 6.2.5 |
| desmopressin | H01BA02 | 10.2 |
| dexamethasone | H02AB02 | 2.3; 3; 8.2.4; 17.2; 22.5 |
| dextran* | B05AA05 | 11.3 |
| diatrizoic acid* | V08AA01 | 14.2 |
| diazepam | N05BA01 | 2.3; 5; 24.3 |
| diazoxide | V03AH01 | 18.6 |
| diethylcarbamazine | P02CB02 | 6.1.2 |
| digoxin | C01AA05 | 12.2; 12.4 |
| diloxanide | P01AC01 | 6.5.1 |
| dimercaprol | V03AB09 | 4.2 |
| diphtheria antitoxin | J06AA01 | 19.2 |
| diphtheria toxoid* | J07AF01 | 19.3 |
| docetaxel | L01CD02 | 8.2.1 |
| docusate sodium | A06AA02 | 2.3 |
| dolutegravir | J05AX12 | 6.4.2.4 |
| dolutegravir + lamivudine + tenofovir | TBA | 6.4.2 |
| dopamine | C01CA04 | 12.4 |
| doxorubicin | L01DB01 | 8.2.1 |
| doxycycline | J01AA02 | 6.2.1; 6.5.3.1; 6.5.3.2 |
| | | |
| edetates* | V03AB03 | 4.2 |
| efavirenz (EFV or EFZ) | J05AG03 | 6.4.2.2 |

| Medicine or item as in EML | ATC code | Section |
|---|---|---|
| efavirenz + emtricitabine + tenofovir disoproxil | J05AR06 | 6.4.2 |
| efavirenz + lamivudine + tenofovir disoproxil | J05AR11 | 6.4.2 |
| eflornithine | P01CX03 | 6.5.5.1 |
| electrolytes with carbohydrates* | B05BB02 | 26.2 |
| electrolytes* | B05BB01 | 26.2 |
| emtricitabine + tenofovir disoproxil | J05AR03 | 6.4.2 |
| enalapril | C09AA02 | 12.3; 12.4 |
| encephalitis, Japanese, inactivated, whole virus* | J07BA02 | 19.3 |
| encephalitis, tick-borne, inactivated, whole virus* | J07BA01 | 19.3 |
| enoxaparin | B01AB05 | 10.2 |
| entecavir | J05AF10 | 6.4.4.1.1 |
| ephedrine | C01CA26 | 1.2 |
| epinephrine | S01EA01 | 21.5 |
| epinephrine (adrenaline) | C01CA24 | 3; 12.2; 25.1 |
| ergocalciferol | A11CC01 | 27 |
| ergometrine | G02AB03 | 22.3 |
| erlotinib | L01XE03 | 8.2.2 |
| erythromycin | S01AA17 | 21.1 |
| erythropoietin* | B03SA01 | 10.1 |
| ethambutol | J04AK02 | 6.2.5 |
| ethanol | D08AX08 | 15.1; 15.2 |
| ethionamide | J04AD03 | 6.2.5 |
| ethosuximide | N03AD01 | 5 |
| etonorgestrel | G03AC08 | 22.1.5 |
| etoposide | L01CB01 | 8.2.1 |
| fentanyl | N02AB03 | 2.2 |
| fexinidazole | P01CA03 | 6.5.5.1 |
| filgrastim | L03AA02 | 8.2.3 |
| fluconazole | J02AC01 | 6.3 |
| flucytosine | J02AX01 | 6.3 |
| fludarabine | L01BB05 | 8.2.1 |
| fludrocortisone | H02AA02 | 18.1 |
| fluorescein | S01JA01 | 14.1 |
| fluorouracil | L01BC02 | 8.2.1; 13.4 |
| fluoxetine | N06AB03 | 2.3; 24.2.1 |
| fluphenazine | N05AB02 | 24.1 |

| Medicine or item as in EML | ATC code | Section |
|---|---|---|
| folic acid | B03BB01 | 10.1 |
| fomepizole | V03AB34 | 4.2 |
| fosfomycin | J01XX01 | 6.2.3 |
| fresh frozen plasma* | B05AX03 | 11.1 |
| furosemide | C03CA01 | 12.4; 16 |
| | | |
| gemcitabine | L01BC05 | 8.2.1 |
| gentamicin | J01GB03 | 6.2.1 |
| gentamicin | S01AA11 | 21.1 |
| glecaprevir + pibrentasvir | J05AP57 | 6.4.4.2.1 |
| gliclazide | A10BB09 | 18.5.2 |
| glucagon | H04AA01 | 18.6 |
| glucose* | B05BA03 | 26.2 |
| glyceryl trinitrate | C01DA02 | 12.1 |
| griseofulvin | D01BA01 | 6.3 |
| | | |
| haloperidol | N05AD01 | 2.3; 24.1 |
| halothane | N01AB01 | 1.1.1 |
| hemophilus influenzae B, purified antigen conjugated* | J07AG01 | 19.3 |
| heparin* | B01AB01 | 10.2 |
| hepatitis A vaccine | J07BC02 | 19.3 |
| hepatitis B vaccine | J07BC01 | 19.3 |
| hydrazaline | C02DB02 | 12.3 |
| hydrochlorothiazide | C03AA03 | 12.3; 12.4; 16 |
| hydrocortisone | A07EA02 | 17.3 |
| hydrocortisone | D07AA02 | 13.3 |
| hydrocortisone | H02AB09 | 3; 8.2.4; 18.1 |
| hydroxocobalamin | B03BA03 | 10.1 |
| hydroxycarbamide | L01XX05 | 8.2.1; 10.3 |
| hydroxychloroquine | P01BA02 | 29.2 |
| hyoscine butylbromide* | A03BB01 | 2.3 |
| hyoscine hydrobromide* | A04AD01 | 2.3 |
| | | |
| ibuprofen | M01AE01 | 2.1; 7.1; 22.6 |
| ifosfamide | L01AA06 | 8.2.1 |
| imatinib | L01XE01 | 8.2.2 |
| immunoglobulins, normal human, for extravascular admin* | J06BA01 | 11.2.1 |
| immunoglobulins, normal human, for intravascular admin* | J06BA02 | 11.2.1 |

| Medicine or item as in EML | ATC code | Section |
|---|---|---|
| influenza vaccine | J07BB | 19.3 |
| insulin (human)* | A10AB01 | 18.5.1 |
| insulin (human)* | A10AC01 | 18.5.1 |
| Iodine therapy* | H03CA | 18.7; 27 |
| iodine* | D08AG03 | 6.3 |
| iohexol | V08AB02 | 14.2 |
| iotroxic acid* | V08AC02 | 14.2 |
| ipratropium bromide | R03BB01 | 25.1 |
| irinotecan | L01XX19 | 8.2.1 |
| Iron in combination with folic acid* | B03AD | 10.1 |
| Iron preparations* | B03A | 10.1 |
| isoflurane | N01AB06 | 1.1.1 |
| isoniazid | J04AC01 | 6.2.5 |
| isoniazid, sulfamethoxazole, trimethoprim and pyridoxine* | J04AM08 | 6.4.2.5 |
| isopropanol* | D08AX05 | 15.2 |
| isosorbide dinitrate | C01DA08 | 12.1 |
| Isotonic solutions* | B05DA | 23 |
| itraconazole | J02AC02 | 6.3 |
| ivermectin | P02CF01 | 6.1.1; 6.1.2; 6.6 |
| ketamine | N01AX03 | 1.1.2 |
| lactulose | A06AD11 | 2.3 |
| lamivudine (3TC) | J05AF05 | 6.4.2.1 |
| lamivudine + nevirapine + zidovudine | J05AR05 | 6.4.2 |
| lamivudine + zidovudine (ZDV or AZT) | J05AR01 | 6.4.2 |
| lamotrigine | N03AX09 | 5 |
| latanoprost | S01EE01 | 21.4 |
| ledipasvir + sofosbuvir | J05AX65 | 6.4.4.2.2 |
| lenalidomide | L04AX04 | 8.2.3 |
| leuprorelin | L02AE02 | 8.2.4 |
| levamisole | P02CE01 | 6.1.1 |
| levodopa and decarboxylase inhibitor* | N04BA02 | 9 |
| levofloxacin | J01MA12 | 6.2.5 |
| levonorgestrel | G03AC03 | 22.1.1; 22.1.5 |
| levonorgestrel | G03AD01 | 22.1.1 |
| levonorgestrel and ethinylestradiol | G03AA07 | 22.1.1 |
| levothyroxine sodium* | H03AA01 | 18.7 |
| lidocaine | C01BB01 | 12.2 |

| Medicine or item as in EML | ATC code | Section |
|---|---|---|
| lidocaine | N01BB02 | 1.2 |
| lidocaine, combinations* | N01BB52 | 1.2 |
| linezolid | J01XX08 | 6.2.3; 6.2.5 |
| lisinopril and amodipine | C09BB03 | 12.3 |
| lisinopril and diuretics* | C09BA03 | 12.3 |
| lithium* | N05AN01 | 24.2.2 |
| loperamide | A07DA03 | 2.3 |
| lopinavir + ritonavir (LPV/r)* | J05AR10 | 6.4.2.3 |
| loratadine | R06AX13 | 3 |
| lorazepam | N05BA06 | 5 |
| losartan | C09CA01 | 12.3; 12.4 |
| Lung surfactants | R07AA | 22.6 |
| magnesium sulfate | B05XA05 | 5 |
| mannitol | B05BC01 | 16 |
| measles vaccine, live attenuated* | J07BD01 | 19.3 |
| mebendazole | P02CA01 | 6.1.1 |
| medicinal charcoal* | A07BA01 | 4.1 |
| medroxyprogesterone and estrogen* | G03AA08 | 22.1.2 |
| medroxyprogesterone* | G03AC06 | 18.4; 22.1.2 |
| mefloquine | P01BC02 | 6.5.3.1; 6.5.3.2 |
| meglumine antimoniate | P01CB01 | 6.5.2 |
| melarsoprol | P01CD01 | 6.5.5.1 |
| melphalan | L01AA03 | 8.2.1 |
| meningococcal vaccines* | J07AH | 19.3 |
| mercaptopurine | L01BB02 | 8.2.1 |
| meropenem | J01DH02 | 6.2.2; 6.2.5 |
| meropenem + vaborbactam | J01DH52 | 6.2.3 |
| mesna | V03AF01 | 8.2.5 |
| metformin | A10BA02 | 18.5.2 |
| methadone | N07BC02 | 2.2; 24.5 |
| methotrexate | L01BA01 | 8.2.1; 29.2 |
| methoxy polyethylene glycol-epoetin beta | B03AX03 | 10.1 |
| methyldopa (levorotatory)* | C02AB01 | 12.3 |
| methylprednisolone | H02AB04 | 8.2.4 |
| methylthioninium chloride (methylene blue) | V03AB17 | 4.2 |
| metoclopramide | A03FA01 | 2.3; 17.2 |
| metronidazole | J01XD01 | 6.2.1 |
| metronidazole | P01AB01 | 6.5.1 |
| miconazole | D01AC02 | 13.1 |

| Medicine or item as in EML | ATC code | Section |
|---|---|---|
| midazolam | N05CD08 | 1.3; 2.3; 5 |
| mifepristone | G03XB01 | 22.3 |
| miltefosine | L01XX09 | 6.5.2 |
| misoprostol | G02AD06 | 22.3 |
| morphine | N02AA01 | 1.3; 2.2 |
| moxifloxacin | J01MA14 | 6.2.5 |
| multienzymes (lipase, protease, etc.)* | A09AA02 | 17 |
| multiple micronutrient powders | B03AE10 | 27 |
| mumps vaccine, live attenuated* | J07BE01 | 19.3 |
| mupirocin | D06AX09 | 13.2 |
| naloxone | V03AB15 | 4.2 |
| natamycin | S01AA10 | 21.1 |
| neostigmine | N07AA01 | 20 |
| nevirapine (NVP) | J05AG01 | 6.4.2.2 |
| niclosamide | P02DA01 | 6.1.1 |
| nicotinamide | A11HA01 | 27 |
| nicotine* | N07BA01 | 24.5 |
| nifedipine | C08CA05 | 22.4 |
| nifurtimox | P01CC01 | 6.5.5.1; 6.5.5.2 |
| nilotinib | L01XE08 | 8.2.2 |
| nitrofurantoin | J01XE01 | 6.2.1 |
| nitroprusside* | C02DD01 | 12.3 |
| nitrous oxide | N01AX13 | 1.1.1 |
| nivolumab | L01XC17 | 8.2.3 |
| norethisterone and ethinylestradiol | G03AA05 | 22.1.1 |
| norethisterone* | G03AC01 | 22.1.2 |
| nystatin | D01AA01 | 6.3 |
| ofloxacin | S01AE01 | 21.1 |
| ombitasvir + paritaprevir + ritonavir | J05AX66 | 6.4.4.2.2 |
| omeprazole | A02BC01 | 17.1 |
| ondansetron | A04AA01 | 2.3; 17.2 |
| oral rehydration salt formulations* | A07CA | 17.5.1; 26.1 |
| oseltamivir | J05AH02 | 6.4.3 |
| oxaliplatin | L01XA03 | 8.2.1 |
| oxamniquine | P02BA02 | 6.1.3 |
| oxygen | V03AN01 | 1.1.1; 1.4 |
| oxytocin | H01BB02 | 22.3 |
| p-aminosalicylic acid* | J04AA01 | 6.2.5 |
| paclitaxel | L01CD01 | 8.2.1 |

| Medicine or item as in EML | ATC code | Section |
|---|---|---|
| paracetamol | N02BE01 | 2.1; 7.1 |
| paromomycin | A07AA06 | 6.5.2 |
| pegaspargase | L01XX24 | 8.2.1 |
| peginterferon alfa-2a* | L03AB11 | 6.4.4.2.3 |
| peginterferon alfa-2b* | L03AB10 | 6.4.4.2.3 |
| penicillamine | M01CC01 | 4.2; 29.2 |
| pentamidine isethionate* | P01CX01 | 6.5.4; 6.5.5.1 |
| permethrin | P03AC04 | 13.5 |
| pertussis vaccine | J07AJ01 | 19.3 |
| phenobarbital | N03AA02 | 5 |
| phenoxymethylpenicillin | J01CE02 | 6.2.1 |
| phenytoin | N03AB02 | 5 |
| phytomenadione | B02BA01 | 10.2 |
| pilocarpine | S01EB01 | 21.4 |
| piperacillin and enzyme inhibitor* | J01CR05 | 6.2.2 |
| plastic IUD with copper* | G02BA02 | 22.1.3 |
| plastic IUD with progestogen* | G02BA03 | 22.1.3 |
| platelet concentrates | B05A | 11.1 |
| plazomicin | TBA | 6.2.3 |
| pneumococcus, purified polysaccharides antigen* | J07AL01 | 19.3 |
| podophyllotoxin* | D06BB04 | 13.4 |
| poliomyelitis vaccine | J07BF | 19.3 |
| polymyxin B | J01XB02 | 6.2.3 |
| potassium chloride | B05XA01 | 26.1; 26.2 |
| potassium ferric hexacyanoferrate (II) ·2H2O (Prussian blue) | V03AB31 | 4.2 |
| potassium permanganate | D08AX06 | 13.2 |
| povidone-iodine* | D08AG02 | 15.1 |
| praziquantel | P02BA01 | 6.1.1; 6.1.3 |
| prednisolone | H02AB06 | 3; 8.2.4 |
| prednisolone | S01BA04 | 21.2 |
| primaquine | P01BA03 | 6.5.3.1 |
| procaine benzylpenicillin | J01CE09 | 6.2.1 |
| procarbazine | L01XB01 | 8.2.1 |
| proguanil | P01BB01 | 6.5.3.2 |
| propofol | N01AX10 | 1.1.2 |
| propranolol | C07AA05 | 7.2 |
| propylthiouracil | H03BA02 | 18.7 |
| prostaglandins* | C01EA | 22.6 |

| Medicine or item as in EML | ATC code | Section |
|---|---|---|
| protamine* | V03AB14 | 10.2 |
| pyrantel | P02CC01 | 6.1.1 |
| pyrazinamide | J04AK01 | 6.2.5 |
| pyridostigmine | N07AA02 | 20 |
| pyridoxine | A11HA02 | 27 |
| pyrimethamine | P01BD01 | 6.5.4 |
| pyrimethamine, combinations* | P01BD51 | 6.5.3.1; 6.5.3.2 |
| quinine | P01BC01 | 6.5.3.1 |
| | | |
| rabies immunoglobulin | J06BB05 | 11.2.1 |
| rabies vaccine | J07BG | 19.3 |
| raltegravir | J05AX08 | 6.4.2.4 |
| ranitidine | A02BA02 | 17.1 |
| realgar-Indigo naturalis formula | TBA | 8.2.1 |
| red blood cells* | B05AX01 | 11.1 |
| retinol | A11CA01 | 27 |
| ribavirin | J05AB04 | 6.4.3; 6.4.4.2.3 |
| riboflavin | A11HA04 | 27 |
| rifabutin | J04AB04 | 6.2.5 |
| rifampicin | J04AB02 | 6.2.4; 6.2.5 |
| rifampicin and isoniazid* | J04AM02 | 6.2.5 |
| rifampicin, pyrazinamide and isoniazid* | J04AM05 | 6.2.5 |
| rifampicin, pyrazinamide, ethambutol and isoniazid* | J04AM06 | 6.2.5 |
| rifapentine | J04AB05 | 6.2.5 |
| risperidone | N05AX08 | 24.1 |
| ritonavir (r) | J05AE03 | 6.4.2.3 |
| rituximab | L01XC02 | 8.2.2 |
| rota virus diarrhea vaccines* | J07BH | 19.3 |
| rubella vaccines | J07BJ | 19.3 |
| | | |
| salbutamol | R03CC02 | 25.1 |
| salicylic acid | D01AE12 | 13.4 |
| selenium sulfide | D01AE13 | 13.1 |
| senna glycosides* | A06AB06 | 2.3; 17.4 |
| silver sulfadiazine | D06BA01 | 13.2 |
| simvastatin | C10AA01 | 12.6 |
| snake venom antiserum* | J06AA03 | 19.2 |
| sodium bicarbonate* | B05XA02 | 26.2 |
| sodium chloride | B05XA03 | 26.2 |

| Medicine or item as in EML | ATC code | Section |
|---|---|---|
| sodium fluoride | A12CD01 | 27 |
| sodium nitrite | V03AB08 | 4.2 |
| sodium stibogluconate | P01CB02 | 6.5.2 |
| sofosbuvir | J05AX15 | 6.4.4.2.1 |
| sofosbuvir + velpatasvir | J05AX69 | 6.4.4.2.1 |
| Solvents and diluting agents, incl. irrigating solutions* | V07AB | 26.3 |
| spectinomycin | J01XX04 | 6.2.1 |
| spironolactone | C03DA01 | 12.4; 16 |
| streptokinase | B01AD01 | 12.5.2 |
| streptomycin | J01GA01 | 6.2.5 |
| sulfadiazine | J01EC02 | 6.5.4 |
| sulfamethoxazole + trimethoprim | J01EE01 | 6.2.1; 6.5.4 |
| sulfasalazine | A07EC01 | 17.3; 29.2 |
| suramin sodium | P01CX02 | 6.5.5.1 |
| suxamethonium | M03AB01 | 20 |
| tamoxifen | L02BA01 | 8.2.4 |
| tars* | D05AA | 13.4 |
| Technical disinfectants* | V07AV | 15.2 |
| telmisartan and amlodipine | C09DB04 | 12.3 |
| telmisartan and diuretics* | C09DA07 | 12.3 |
| tenofovir disoproxil fumarate | J05AF07 | 6.4.2.1; 6.4.4.1.1 |
| terbinafine | D01BA02 | 13.1 |
| testosterone | G03BA03 | 18.2 |
| tetanus immunoglobulin* | J06BB02 | 11.2.1 |
| tetanus toxoid* | J07AM01 | 19.3 |
| tetracaine | S01HA03 | 21.3 |
| tetracycline | S01AA09 | 21.1 |
| thalidomide | L04AX02 | 8.2.3 |
| thiamine | A11DA01 | 27 |
| thiosulfate* | V03AB06 | 4.2; 13.1 |
| timolol | S01ED01 | 21.4 |
| tioguanine | L01BB03 | 8.2.1 |
| tiotropium | R03BB04 | 25.1 |
| tranexamic acid | B02AA02 | 10.2; 22.5 |
| trastuzumab | L01XC03 | 8.2.2 |
| tretinoin* | L01XX14 | 8.2.2 |
| triclabendazole | P02BX04 | 6.1.3 |
| tropicamide | S01FA06 | 14.1 |

| Medicine or item as in EML | ATC code | Section |
|---|---|---|
| tuberculin, purified protein derivative (PPD) - BCG* | V04CF01 | 19.1 |
| tuberculosis, live attenuated* | J07AN01 | 19.3 |
| typhoid vaccine | J07AP | 19.3 |
| ulipristal | G03AD02 | 22.1.1 |
| vaginal ring with progestogen* | G02BB02 | 22.1.6 |
| valganciclovir | J05AB14 | 6.4.3 |
| valproic acid | N03AG01 | 5; 24.2.2 |
| vancomycin | J01XA01 | 6.2.2 |
| varicella zoster vaccines* | J07BK | 19.3 |
| vecuronium | M03AC03 | 20 |
| verapamil | C08DA01 | 12.1; 12.2 |
| vinblastine | L01CA01 | 8.2.1 |
| vincristine | L01CA02 | 8.2.1 |
| vinorelbine | L01CA04 | 8.2.1 |
| voriconazole | J02AC03 | 6.3 |
| warfarin | B01AA03 | 10.2 |
| Water for Injection | V07AB | 26.3 |
| whole blood* | B05A | 11.1 |
| xylometazoline | R01AA07 | 28 |
| yellow fever vaccines | J07BL | 19.3 |
| zidovudine (ZDV or AZT) | J05AF01 | 6.4.2.1 |
| Zinc products* | D02AB | 13.3 |
| zinc sulfate | A12CB01 | 17.5.2 |
| zoledronic acid | M05BA08 | 8.2.5 |

* Medicine or item name differs slightly from the name used.

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Annexes to the main report include the 2019 WHO Model List of Essential Medicines (21st edition) and the 2019 WHO Model List of Essential Medicines for Children (7th edition). In addition, all medicines on the Model Lists are presented according to their Anatomical Therapeutic Chemical (ATC) classification codes.

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