Isoniazid + pyrazinamide + rifampicin

Section: 6. Anti-infective medicines > 6.2. Antibacterials > 6.2.5. Antituberculosis medicines

EMLc | ATC codes: J04AM05

Indication	Tuberculosis ICD11 code: 1B1Z
INN	Isoniazid + pyrazinamide + rifampicin
Medicine type	Chemical agent
List type	Core
Additional notes	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.
Formulations	**Oral > Solid > dispersible tablet:** 50 mg + 150 mg + 75 mg (EMLc)
EML status history	First added in 1997 (TRS 882) Changed in 2007 (TRS 950) Changed in 2009 (TRS 958) Changed in 2017 (TRS 1006) Changed in 2019 (TRS 1021) Changed in 2021 (TRS 1035)
Sex	All
Age	Children (1 month - 12 years)
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Isoniazid + pyrazinamide + rifampicin
DrugBank	Isoniazid, Pyrazinamide, Rifampicin

Expert Committee recommendation

The Expert Committee recommended the deletion of the following formulations from the EML and/or EMLc as requested in the application, noting that they are not the most appropriate formulations for the treatment of tuberculosis, which is in line with recommendations in the current WHO tuberculosis treatment guidelines. • Amikacin: powder for injection: 100 mg, 500 mg and 1 mg (as sulfate) in vial • Amoxicillin + clavulanic acid: oral liquid 125 mg + 31.25 mg/5 mL • Isoniazid tablet (scored): 50 mg • Isoniazid + pyrazinamide + rifampicin tablet: 75 mg + 400 mg + 150 mg • Linezolid: injection for intravenous administration: 2 mg/mL in 300 mL bag; tablet 400 mg • p-aminosalicylic acid tablet: 500 mg • Pyrazinamide tablet (scored): 150 mg The Committee recommended the inclusion of amikacin injection solution 250 mg/mL, noting that injection solutions are preferred over powder for injection formulations as they do not require reconstitution for administration. To better meet the dosing needs of paediatric patients, the Committee also recommended the addition of a 100 mg/2 mL strength of amikacin injection solution. The Committee recommended that formulation strengths rather than strengths ranges for ethambutol and isoniazid tablets be specified, as requested, to facilitate rational selection and provide better

clarity for countries in making national selection decisions. The Committee recognized that dispersible tablet formulations are the preferred child-friendly formulations and provide flexible dosing options. However, because of concerns about limited uptake and availability of dispersible-tablet formulations of ethambutol, ethionamide, isoniazid and pyrazinamide in some countries, the Committee did not recommend the deletion of the oral liquid formulations of ethambutol, isoniazid and pyrazinamide, nor the 125 mg tablet formulation of ethionamide at this time. To allow countries time to transition to the adoption of the preferred, listed dispersible-tablet formulations, the Committee advised that these formulations will be deleted from the Model Lists without further consideration in 2023, unless an application is received to support their retention.

Background

The WHO Global Tuberculosis department, and the Stop TB Partnership's Global Drug Facility carried out a comprehensive review of the 2019 Model Lists to examine the availability and appropriateness of the tuberculosis medicines and formulations listed, in the context of the latest available WHO recommendations on tuberculosis and procurement patterns. Formulations for deletion • Ethambutol: oral liquid 25 mg/mL (EMLc) • Isoniazid: oral liquid 50 mg/5 mL (EMLc); tablet (scored) 50 mg (EML and EMLc) • Pyrazinamide: oral liquid 30 mg/mL (EMLc); tablet (scored) 150 mg (EML and EMLc) • Isoniazid + pyrazinamide + rifampicin: tablet 75 mg + 400 mg + 150 mg (EML) • Amikacin: powder for injection 100 mg, 500 mg, 1 g in vial (EML and EMLc) • Amoxicillin + clavulanic acid: oral liquid 125 mg + 31.25 mg/5 mL (EMLc) • Ethionamide: tablet 125 mg (EML and EMLc) • Linezolid: injection for intravenous administration: 2 mg/mL in 300 mL bag; tablet 400 mg (EML and EMLc) • p-aminosalicylic acid: tablet 500 mg (EML and EMLc) Formulations for addition • Amikacin: injection 250 mg (as sulfate)/mL in 2 mL vial Removal of strength ranges • Ethambutol: tablet 100 mg to 400 mg (EML) • Isoniazid: tablet 100 mg to 300 mg (EML and EMLc)

Benefits

In 2019, the Expert Committee recommended the addition of several new formulations for tuberculosis medicines for use in children be added to the core list of the EMLc, including ethambutol and isoniazid 100 mg dispersible tablet formulations. The Committee acknowledged that quality-assured dispersible tablet formulations are preferred to oral liquid formulations and recommended that the oral liquid formulations of isoniazid and ethambutol be considered for removal from the Model Lists in 2021 (1). Thus, ethambutol, isoniazid and pyrazinamide oral liquid formulations are proposed for deletion. Ethambutol, isoniazid and pyrazinamide dispersible tablet formulations have been available from the Global Drug Facility since January 2018, March 2019 and March 2018, respectively. All are available from at least one WHO-prequalified supplier. The single-pill combination of isoniazid + pyrazinamide + rifampicin is proposed for deletion from the EML as no quality-assured supplier of this formulation has been identified. Ethambutol-containing single-pill combinations with isoniazid, pyrazinamide and rifampicin are listed and remain a suitable option with a lower pill burden for treatment of adults with drug-susceptible tuberculosis (2). Amikacin is included in the recommendations for longer regimens to treat multidrug-resistant tuberculosis, classified in Group C (to be used to complete the regimen when medicines from Groups A and B cannot be used). Amikacin is not included in recommendations for shorter regimens for treatment of drug-resistant tuberculosis (3). Amikacin powder for injection formulations 100 mg, 500 mg and 1 g are proposed for deletion, because of the unavailability of quality-assured formulations (1 g), the low efficiency in dose delivery (100 mg), and the fact that these formulations (all) require reconstitution before administration and are less preferred to liquid injection formulations. The application proposed to replace the current formulations of amikacin with a 250 mg/mL in 2 mL vial liquid injection formulation, noting that this formulation is already included on the Model Lists as an Access group antibiotic, and is available from the Global Drug Facility. Linezolid 400 mg tablet is proposed for deletion because of unavailability of quality-assured formulations. Linezolid intravenous injection 2 mg/mL is proposed for deletion because of WHO's recommendations for use of all-oral regimens to treat drug-resistant tuberculosis (3). The oral formulations of linezolid currently listed are suitable for treatment for both adults and children. Ethionamide 125 mg tablet is proposed for deletion given the availability of a preferred dispersible tablet formulation of the same strength, which is included on the Model Lists. The dispersible tablet formulation is available from the Global Drug Facility, and is available from WHO prequalified

suppliers. Amoxicillin + clavulanic oral liquid (125 mg + 31.25 mg/5 mL) is proposed for deletion to consolidate the market for this medicine around the 250 mg + 62.5 mg/5mL strength formulation. This higher strength formulation is included in WHO's recommended dosing schemes (4) and enables appropriate dosing of children across age groups and it uses smaller volumes for administration than the formulation proposed for deletion. The application also proposes changes to the listing for isoniazid and ethambutol tablets, to replace strength ranges with specific strength formulations. In the case of ethambutol, 100 mg and 400 mg strength formulations deliver appropriate dosing for adults and children with tuberculosis. No quality-assured formulation within the strength range of 100 mg to 400 mg that could deliver added value to patient dosing is currently available on the market. In the case of isoniazid, 100 mg and 300 mg strength formulations are suitable to achieve appropriate dosing for adults and children. A 200 mg strength tablet formulation is available and approved in Germany; however, this formulation does not deliver added value in terms of facilitating dosing for adults or children.

WHO guidelines

The proposed changes are in alignment with recommendations in current WHO guidelines for the treatment of drug-susceptible and drug-resistant tuberculosis.

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2019 (including the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2019 (WHO Technical Report Series, No. 1021; https://apps.who.int/iris/handle/10665/330668, accessed 19 August 2021).
2. Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/handle/10665/255052, accessed 19 August 2021).
3. WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/332397, accessed 19 August 2021).
4. WHO operational handbook on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/332398, accessed 19 August 2021).