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THE USE OF ESSENTIAL DRUGS

Eighth report of the
WHO Expert Committee

(including the revised Model List of Essential Drugs)

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1. Introduction

The WHO Expert Committee on the Use of Essential Drugs met in Geneva from 1 to 5 December 1997. The meeting was opened on behalf of the Director-General by Mr D. Aitken, Assistant Director-General, who emphasized that the concept of essential drugs was fundamental both to WHO's revised drug strategy (*1*), as endorsed by the World Health Assembly in resolution WHA39.27 in 1986 (*2*), and to the development of national drug policies. Regular updating of WHO's Model List of Essential Drugs sustained the momentum of the revised drug strategy and was a basic element of the validated information required by most of WHO's Member States for optimal rationalization of drug procurement and supply. Mr Aitken also emphasized the importance of the emergence of resistance to antimicrobials that, in many cases, is dangerously eroding their effectiveness. This is leading to a situation whereby it will be increasingly difficult to combat serious infections.

The Committee decided to prepare its report as a self-contained document and to incorporate into it those parts of the previous report (*3*) that required no modification or merely bringing up to date. The tenth Model List of Essential Drugs will be found in section 15 of this report, and explanations of the changes in section 16.

In a report (*4*) to the Twenty-eighth World Health Assembly in 1975, the Director-General reviewed the main drug problems facing the developing countries and outlined possible new drug policies. The Director-General also referred to the experience gained in some countries where schemes of basic or essential drugs had been implemented. Such schemes were intended to extend the accessibility and rational use of the most necessary drugs to populations whose basic health needs could not be met by the existing supply system. The Director-General pointed out that the selection of these essential drugs would depend on the health needs and on the structure and development of the health services of each country. Lists of essential drugs should be drawn up locally, and periodically updated, with the advice of experts in public health, medicine, pharmacology, pharmacy and drug management. He also considered that adequate information on the properties, indications and use of the drugs listed should be provided. By resolution WHA28.66 (*5*), the Health Assembly requested the Director-General to implement the proposals contained in his report and, in particular, to advise Member States on the selection and procurement, at reasonable cost, of essential drugs of established quality corresponding to their national health needs.

Following wide consultation, an initial Model List of Essential Drugs was included in the first report of the Expert Committee on the Selection of Essential Drugs (*6*). This has subsequently been revised and updated in eight further reports (*3*, *7–13*).

In undertaking a further review of the list at its present meeting, the Expert Committee was guided throughout by the following statement contained in the previous reports:

> Because of the great differences between countries, the preparation of a drug list of uniform, general applicability is not feasible or possible. Therefore, each country has the direct responsibility of evaluating and adopting a list of essential drugs, according to its own policy in the field of health.
>
> The list of essential drugs based on the guidelines put forward in this report is a model which can furnish a basis for countries to identify their own priorities and to make their own selection.

The Committee reviewed the evolution of the Model List of Essential Drugs during the past 20 years and confirmed the definition of essential drugs as those that satisfy the health care needs of the majority of the population; they should therefore be available at all times in adequate amounts and in the appropriate dosage forms. Model lists have proved to be invaluable in reducing costs and meeting the health needs of populations through more rational use of drugs and wider access to drugs of acceptable quality. The Committee considered model lists as informational and educational tools for health professionals and consumers. Since concern about health care costs is now a priority even in developed countries, model lists are of greater importance than ever for the development of treatment guidelines, national formularies, information for patients and the general public, and other measures to improve drug use. The Committee emphasized that model lists should be seen in the context of comprehensive national drug formularies which address not only drug use but also strategies for drug procurement and supply, drug financing, drug donations, research priorities for drug use and drugs needed for specific diseases.

2. Guidelines for establishing a national programme for essential drugs

In order to ensure that an essential drugs programme is adequately instituted at national level, several steps are recommended:

1. A national drug regulatory authority should be established along the lines recommended in the guiding principles for small national

drug regulatory authorities presented in Annex 1 of the fifth report of the Expert Committee (*12*). The authority should interact with other interested bodies, including organizations responsible for drug procurement in the public and private sectors and the committee referred to in item 2.

2. A national drug and therapeutics committee of health care professionals should be appointed to give technical advice to the national programme. The committee should include individuals competent in the fields of medicine, clinical pharmacology, pharmacy and clinical microbiology, as well as other appropriate health care workers. Where individuals with adequate training are not available within the country, cooperation from WHO could be sought until such individuals can be trained. The first task of the committee should be to recommend a list of essential drugs for the national programme. The committee should remain a part of the national programme for essential drugs, continually advising on matters of technical importance.
3. The international nonproprietary (generic) names for drugs or pharmaceutical substances (*14*) should be used whenever available, and prescribers should be provided with a cross-index of nonproprietary and proprietary names.
4. Concise, accurate and comprehensive drug information should be prepared to accompany the list of essential drugs, in the form of a prescriber's formulary to serve as a pocket guide to rational drug use. More detailed information about drugs should be made available at drug and poison information centres, pharmacies and all educational institutes concerned with training health professionals.
5. The quality of all products, including stability and bioavailability, should be assured through a product registration process, with additional laboratory testing where appropriate for imported products. Assurance of quality can also be obtained through the use of WHO's Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (section 5.1) and is particularly important where resources for regulation of medicines are severely limited.
6. Competent health authorities should decide on the level of expertise required to prescribe individual drugs or a group of drugs in a therapeutic category. Consideration should be given, in particular, to the competence of the personnel to make a correct diagnosis. In some instances, while individuals with advanced training are necessary to prescribe initial therapy, individuals with less training could be responsible for maintenance therapy.
7. The success of the essential drugs programme is dependent upon the efficient administration of supply, storage and distribution at

every point from the manufacturer to the end-user. Government intervention may be necessary to ensure the availability of some drugs in the formulations listed, and special arrangements may need to be instituted for the storage and distribution of drugs that have a short shelf-life or require refrigeration.

8. Efficient management of stocks is necessary to eliminate waste and to ensure continuity of supplies. Procurement policy should be based upon detailed records of turnover. In many instances, drug utilization studies will contribute to a better understanding of true requirements.
9. Research, both clinical and pharmaceutical, is sometimes required to settle the choice of a particular drug product under local conditions. Facilities and trained personnel for such research must be provided. Clinical trials of pharmaceutical products should follow the WHO Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products presented in Annex 3 of the sixth report of the Expert Committee (*13*).

3. Criteria for the selection of essential drugs

The choice of essential drugs depends on many factors, such as the pattern of prevalent diseases; the treatment facilities; the training and experience of the available personnel; the financial resources; and genetic, demographic and environmental factors.

Because of differing views on the definition of an essential drug in terms of what is meant by the "health care needs of the majority" of the population, the model list has been gradually expanded since its introduction. Some drugs are included that are essential only if a therapeutic programme is planned to address the diseases for which these drugs are used. For example, the cytotoxic drugs (section 8.2 of the model list) are essential only if a comprehensive cancer treatment programme is planned. Such a programme requires adequate hospital, diagnostic and clinical laboratory facilities for its implementation. In contrast, the drugs used in palliative care (section 8.4) are always essential, even when a comprehensive cancer treatment programme does not exist.

The selection of essential drugs must always be evidence-based. Only those drugs should be selected for which sound and adequate data on efficacy and safety are available from clinical studies and for which evidence of performance in general use in a variety of medical settings has been obtained.

Each selected drug must be available in a form in which adequate quality, including bioavailability, can be assured; its stability under the anticipated conditions of storage and use must be established.

Where two or more drugs appear to be similar in the above respects, the choice between them should be made on the basis of a careful evaluation of their relative efficacy, safety, quality, price and availability.

In cost comparisons between drugs, the cost of the total treatment, and not only the unit cost of the drug, must be considered. The cost/benefit ratio is a major consideration in the choice of some drugs for the list. In some cases the choice may also be influenced by other factors, such as comparative pharmacokinetic properties, or by local considerations such as the availability of facilities for manufacture or storage.

Most essential drugs should be formulated as single compounds. Fixed-ratio combination products are acceptable only when the dosage of each ingredient meets the requirements of a defined population group and when the combination has a proven advantage over single compounds administered separately in therapeutic effect, safety or compliance.

4. Guidelines for the selection of pharmaceutical dosage forms

The purpose of selecting dosage forms and strengths for the drugs in the model list is to provide guidance to countries wishing to standardize or minimize the number of preparations in their own drug lists. As a general rule, pharmaceutical forms are selected on the basis of their general utility and their wide availability internationally. In many instances, a choice of preparations is provided, particularly in relation to solid dosage forms. Tablets are usually less expensive than capsules, but, while cost should be taken into account, the selection should also be based on a consideration of pharmacokinetics, bioavailability, stability under ambient climatic conditions, availability of excipients, and established local preference.

In a few instances where there is no uniformity of tablet strength, for example acetylsalicylic acid and paracetamol, a dosage range is provided from within which suitable tablet strengths should be selected on the basis of local availability and need. When precise dosage is not mandatory, the use of scored tablets is recommended as a simple method of making dosage more flexible if so required and, in some

instances, to provide a convenient paediatric dose. Specific paediatric dosages and formulations are included in the list only when indicated by special circumstances. In many instances, dosage is specified in terms of a selected salt or ester, but in others — for example chloroquine — it is calculated, in accordance with common practice, in terms of the active moiety.

For certain drugs with short half-lives that are rapidly metabolized, such as carbamazepine, calcium-channel blockers and theophylline, conventional-release dosage forms must often be taken three or four times a day to maintain drug levels in the required narrow range. Sustained-release dosage forms can reduce the frequency of drug administration, thereby improving compliance and, often, the therapeutic effectiveness of the drug by maintaining a more constant drug level than can be obtained using traditional dosage forms. Because the preparation of sustained-release products is difficult and requires special expertise, a proposal to include such a product in a national list of essential drugs should be justified by adequate documentation.

5. Quality assurance

Priority should be given to ensuring that the available drugs have been made according to good manufacturing practices (*15*, Annex 1) and are of generally recognized quality. This requires knowledge of and confidence in the origin of the product. The risks of procuring drugs from anonymous sources cannot be overstressed. It is recommended that drugs are purchased directly from known manufacturers, their duly accredited agents or recognized international agencies known to apply high standards in selecting their suppliers.

Quality assurance of drugs, as embodied in product development, good manufacturing practice and subsequent monitoring of quality throughout the distribution chain to utilization, is a crucial element in any essential drugs programme. All aspects of these procedures have been dealt with at length in the twenty-sixth to thirty-fifth reports of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (*15–24*).

5.1 WHO's Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce

The Committee emphasized the importance of WHO's Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, particularly in countries with inadequate laboratory facilities for drug analysis which may be unable to carry out the

process of quality control. This scheme has been available since 1975 as a means of exchanging information between regulatory authorities in importing and exporting countries. Its purposes are:

1. To provide assurance that a given product has been authorized to be placed on the market in the exporting country, and, if not, to explain why authorization has been withheld, or has not been requested.
2. To provide assurance that the plant in which the product is manufactured is subject to inspections at suitable intervals and conforms to the requirements for good practices in the manufacture and quality control of drugs, as recommended by WHO.
3. To provide for exchange of information on the implementation of inspections and controls by the authorities in the exporting country. In the case of serious quality defects inquiries may also be made.

The certification scheme has been revised to provide for a more comprehensive exchange of information between governments (*23*, Annex 10, *25*). Drug substances as well as finished dosage forms intended for administration to humans or to animals have been included within the scheme.

It is important that the certification scheme is followed when certificates are issued and that they are clearly identified as conforming to the format recommended by WHO, since they may differ from other certificates issued by countries. *This, however, does not mean that WHO issues certificates. These are issued by the competent authority in the exporting country.* Importing countries are also urged to use the scheme and request certificates from the exporting countries in the format recommended by WHO.

5.2 Bioavailability

Poor bioavailability of a pharmaceutical product can result in treatment failure just as readily as can a deficiency of active ingredients. The bioavailability of essential drugs should therefore continue to receive consideration since it is a key factor in the efficacy of multisource products. Guidelines on registration requirements to establish interchangeability of multisource (generic) pharmaceutical products were adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its thirty-fourth meeting, and are included in its report (*23*, Annex 9).

5.3 *The international pharmacopoeia*

The Committee appreciates that the development of the Model List of Essential Drugs has provided a natural focus for the third edition of

The international pharmacopoeia (*26*), thus enhancing its potential value to developing countries. Essential drugs are accorded priority and all quality specifications are supported by classical methods of testing and analysis. A plan for a small quality-control laboratory in which most of these tests can be performed has been available since 1984 (*19*). Since quality assurance of essential drugs is so important, the Committee recommends to national governments the setting up of such laboratories and the adoption of *The international pharmacopoeia* by those now lacking the means to confirm independently the quality of the supplies they procure. Where national capacity is lacking, a regional effort involving several countries may be useful. In this context, attention is also drawn to the WHO publications *Basic tests for pharmaceutical substances* and *Basic tests for drugs: pharmaceutical substances, medicinal plant materials and dosage forms* (*27*, *28*), which enable the identity of drug substances to be verified and gross degradation to be excluded when laboratory facilities for full pharmacopoeial analyses are not available.

The Committee emphasizes the need to extend the coverage of *The international pharmacopoeia* to include not only essential drug substances, but also the dosage forms (*29*) specified in the Model List of Essential Drugs, together with additional information on bioavailability, stability and recommended packaging and storage conditions.

The Committee noted that there were several drugs included in the model list for which no pharmacopoeial monographs exist at present. These include asparaginase, doxazosin, methylthioninium chloride (methylene blue) and permethrin.

5.4 Counterfeit drugs

Concern has been expressed about the export, import and smuggling of falsely labelled, spurious, counterfeited or substandard pharmaceutical preparations. Some products contain little or no active ingredient and may even contain a different active substance from that on the label. A second workshop on counterfeit drugs cosponsored by WHO and the International Federation of Pharmaceutical Manufacturers Associations was held in 1997 (*30*), which emphasized the need for a comprehensive strategy to detect and deter the manufacture and distribution of counterfeited and substandard medicines. In response to this recommendation, WHO has established a database for reports of counterfeited drugs and developed methodologies for determining the prevalence of both counterfeited and substandard products. The Committee strongly endorsed these activities and recommended that they be continued by WHO and its Member States.

6. Reserve anti-infective agents and monitoring of resistance

The increasing prevalence of strains of common pathogenic bacteria resistant to widely available, relatively cheap antimicrobials included in the model list is, in many cases, dangerously eroding their effectiveness.

6.1 Need for surveillance of resistance

Many schemes have been initiated for laboratory-based monitoring of resistance to antimicrobials but there is a need for international coordination. It has already been emphasized that reference laboratories need to be established in developing as well as developed countries in order to monitor the resistance of important bacterial pathogens (*31*, *32*). Knowledge of prevailing susceptibility patterns is vital to the selection and use of antimicrobials and to the development of appropriate prescribing policies. Without these data the health of seriously ill patients could be jeopardized. Knowledge of susceptibility patterns should come from proper laboratory investigations. Research directed towards improving the link between the results of laboratory testing and prescribing policies is needed. Decisions on drug use should be taken on the basis of standardized therapeutic efficacy testing.

The exchange of information on patterns of antimicrobial susceptibility of important bacterial pathogens via the WHONET[1] and other sources of data should assist in the selection of the most appropriate antimicrobial agent. The WHONET includes information relating to agents in the WHO model list. Such information should be collected for bacterial and fungal pathogens, as well as for protozoal infections including malaria.

Educational workshops should be held at the national level to improve awareness of the problem of resistance to antimicrobials and national drug policies should include a policy on antimicrobial resistance.

Much of the existing data on antimicrobial resistance comes from patients in hospital. Hospitals suffer from localized epidemics with multi-resistant bacteria and marked differences are seen, even within the same city. Hospitals should appoint a committee to guide the

[1] For further information, contact the Division of Emerging and other Communicable Diseases Surveillance and Control, World Health Organization, 1211 Geneva 27, Switzerland.

selection and use of antimicrobials on the basis of laboratory findings. Data should be collected on *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Enterobacterium* spp. Information about community-acquired infections is usually more difficult to obtain. Data should be collected on *Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli* and *Salmonella* and *Shigella* spp. A limited range of antimicrobials are important for different organisms. For *Streptococcus pneumoniae*, for example, information on resistance to benzylpenicillin, cefalosporins, trimethoprim + sulfamethoxazole, erythromycin and chloramphenicol has the highest priority. Antimicrobial resistance in *Mycobacterium tuberculosis* and *Neisseria gonorrhoeae* is also important.

Accurate data on resistance to antimicrobials are essential for the formulation of treatment protocols for empirical treatment of community-acquired infections. The treatment of such infections is carried out without bacterial cultures in the great majority of cases. The prevalence of resistance varies greatly from one locality to another and information on local patterns of antimicrobial susceptibility is necessary to guide treatment policies. The level of resistance at which treatment protocols should be changed will vary, depending on several factors including the mortality of the infections. Purulent meningitis should be treated with cefalosporins rather than penicillins, even when the prevalence of penicillin resistance is low (say 4–5%).

6.2 Reserve antimicrobials

It is becoming increasingly common for important pathogens to emerge in a country or locality that are shown, on susceptibility testing, to have developed resistance to all normally appropriate essential drugs. In these circumstances a reserve antimicrobial is needed. A reserve antimicrobial is an antimicrobial that is useful for a wide range of infections but, because of the need to reduce the risk of development of resistance and because of its relatively high cost, it would be inappropriate to recommend its unrestricted use.

The concept of reserve antimicrobials is of practical relevance only when information is available on the prevailing susceptibilities of important bacterial pathogens. Within this context the β-lactam drugs, the fluoroquinolones and vancomycin are most important.

Resistance to β-lactam antimicrobials is generally due to the production of β-lactamases in staphylococci, enterobacteria, *Haemophilus* spp., gonococci and *Pseudomonas* spp. In several of these organisms and in others such as pneumococci and enterococci, other non-enzymic mechanisms are also involved. Many new β-lactam anti-

microbials have appeared and are included in the model list as reserve antimicrobials. In order to preserve the activity of these antimicrobials it is recommended that these agents are used only where rates of resistance to all normally appropriate essential drugs are high or for specific indications, as listed below.

The β-lactamase inhibitor amoxicillin + clavulanic acid is active against many of the enzymes produced by enterobacteria and also against *Bacteroides* spp. A specific indication for its use is in polymicrobial infections related to surgical conditions of the intestinal tract and female genital tract. Amoxicillin remains active against many common bacteria such as β-haemolytic streptococci and a high proportion of *Haemophilus influenzae* strains in many countries. The levels of penicillin resistance in *Streptococcus pneumoniae* do not at this time justify replacement of the use of penicillins in the treatment of respiratory tract infections.

Many parenteral cefalosporins active against Gram-negative bacteria are now available and are widely used for the treatment of infection. The model list now includes ceftriaxone as a reserve antimicrobial for the treatment of meningitis due to *Streptococcus pneumoniae* in areas where penicillin resistance is found. It has been listed as an example of a therapeutic group because the results of clinical trials indicate that cefotaxime is equally effective and may be preferred in some hospitals or treatment centres. The Committee notes that several other cefalosporins such as cefuroxime are widely used for chemoprophylaxis in surgery and for the treatment of respiratory infections. These cefalosporins are not as effective as ceftriaxone or cefotaxime in pneumococcal meningitis. However, they may be used as alternatives for chemoprophylaxis or for treatment of respiratory infections in areas of penicillin resistance. Chemoprophylaxis should be limited to the minimum number of doses needed to ensure efficacy, usually one or two. Ceftriaxone and cefotaxime should not be used for chemoprophylaxis.

Ceftazidime is included in the list because it is the most active cefalosporin against *Pseudomonas aeruginosa*. It is suggested that it should be used when the prevalence of resistance to gentamicin is high.

Imipenem + cilastatin is a broad-spectrum β-lactam antimicrobial included as a reserve agent for the treatment of *Acinetobacter* spp. infection and *Pseudomonas* spp. resistant to all normally appropriate antimicrobials. Such resistant organisms are usually only found in tertiary care hospitals and in particular in intensive care units where antimicrobial usage is high.

Ciprofloxacin is a member of the fluoroquinolone family of antimicrobials. Although this is now listed as an essential drug, the comparative costs of alternative broad-spectrum products will be an important determinant of selection. Ciprofloxacin and certain other fluoroquinolones may still be considered of value as reserve agents. Their use may need to be restricted to the following circumstances:

- For typhoid fever and other systemic salmonella infections where there are strains of *Salmonella* resistant to chloramphenicol, amoxicillin and trimethoprim + sulfamethoxazole.
- For severe shigellosis where *Shigella* spp. strains exist that are resistant to ampicillin, chloramphenicol, trimethoprim + sulfamethoxazole, tetracyclines and nalidixic acid.
- For gonorrhoea and chancroid, as alternatives to cefalosporins, when oral administration is appropriate.
- For hospital-acquired infections due to Gram-negative bacilli, including *Escherichia coli*, *Klebsiella* spp. and *Pseudomonas aeruginosa*, that are resistant to essential drugs such as amoxicillin, chloramphenicol and gentamicin.

Meticillin-resistant *Staphylococcus aureus* strains are usually resistant to all β-lactam antimicrobials and also to unrelated drugs such as erythromycin, clindamycin, chloramphenicol, the tetracyclines and the aminoglycosides. The only effective reserve drug for infections due to these multiresistant organisms is vancomycin, which is expensive and must be administered intravenously.

In some countries, strains of *Plasmodium falciparum* have developed resistance to all of the antimalarial drugs except for artemisinin and its derivatives. For patients with falciparum malaria resistant to chloroquine, sulfadoxine + pyrimethamine, mefloquine or quinine with tetracycline, the use of artemisinin and its derivatives appears essential. In order to limit the development of resistance to these drugs and keep them effective for as long as possible, their use should be restricted to areas in which multidrug-resistant falciparum malaria exists. In such countries artemisinin and its derivatives should be used for the treatment of uncomplicated infections resistant to all other antimalarials, or for severe falciparum malaria where quinine is ineffective.

The need for the discovery and development of new anti-infective drugs, especially for those diseases mainly prevalent in developing countries, continues to be of high priority. The research-based pharmaceutical industry should be encouraged to engage in this research.

7. Applications of the essential drugs concept

The concept of essential drugs has been endorsed unanimously by the World Health Assembly. It is intended to be flexible and adaptable to many different situations; exactly which drugs are regarded as essential remains a national responsibility.

The concept of essential drugs has been disseminated and promoted extensively at the country level by WHO's Action Programme on Essential Drugs, as well as by disease control programmes in WHO, international and nongovernmental organizations throughout the world and bilateral agencies. The wide applicability of the concept is now evident from experience gained in many countries. National lists of essential drugs may need to be stratified to reflect skills and requirements at different levels within the health care infrastructure. The model list now contains many medications which require a high degree of expertise to ensure safe and effective use. Adequate specialist skills and complementary resources are needed before the introduction of some classes of drugs. Examples of situations where specialist control of drug use is necessary are:

- The use of reserve antimicrobials for multiresistant bacteria.
- Establishing adequate regimens for treatment of tuberculosis and leprosy.
- The use of antineoplastic and immunosuppressive drugs.
- The use of antiretroviral drugs.
- The use of antimicrobial, antifungal and antiviral agents for the treatment of opportunistic infections in immunocompromised patients.

Typically, a very short list has been compiled for community health workers while the most comprehensive lists have been reserved for large urban and regional hospitals. Many countries have also successfully applied the concept to teaching hospitals and facilities providing specialized care. The concept has also been applied in the development of national formularies (section 13).

The model list has been adopted by numerous international and bilateral agencies that now include drug supply and the rationalization of drug use in their health care programmes. Adoption of the list has resulted in greater international coordination in health care development, and it is also being used to evaluate whether drug donations are appropriate in a given situation.

A shorter, adapted list has proved to be of particular value in emergency situations. It is contained in an emergency health kit (*33*), designed to cover the basic needs of a population of 10000 for a period of about 3 months, which has been developed and updated by WHO, the Office of the United Nations High Commissioner for Refugees, UNICEF, *Médecins sans frontières*, the International Federation of Red Cross and Red Crescent Societies, the Christian Medical Commission and several other nongovernmental organizations. Many non-profit suppliers maintain a stock of kits containing most of the drugs on the list, which allows a rapid response to demand. In addition, the same interagency group has drawn up a slightly longer list of essential drugs for use in emergency situations, which has been included in a United Nations catalogue of items for emergency relief (*34*).

The concept of essential drugs has also been applied to the integrated management of childhood illness (*35*), which the Committee considered an important aspect of WHO's work.

8. Essential drugs and primary health care

The selection of drugs for primary health care must be determined nationally since the training and responsibilities of the personnel charged to administer this care vary considerably. Highly trained workers are able to use a wide range of drugs, while workers with limited training should use only those drugs appropriate to their diagnostic skills, knowledge and experience. For this reason, a shorter adapted list of essential drugs is often adequate for primary health care. Decisions about which specific drugs should be made available in this shorter list can be made only when all relevant local factors have been taken into account. The following considerations will influence the compilation of such drug lists.

8.1 Existing systems of medicine

The establishment of primary health care services in developing countries should not result in abrupt disruption of prevailing cultural patterns in rural communities. The work of traditional healers, for example, should be adapted and supplemented so as to ensure that innovation is successfully integrated into existing systems of care.

8.2 The national health infrastructure

The type of primary health care service that a country requires is dependent upon the proximity and nature of the first referral facili-

ties. It is still not unusual in some countries for the nearest permanently staffed health post to be a day's travelling time or more from isolated villages in its catchment area.

8.3 The pattern of endemic disease

The prevalence of major endemic diseases may vary from region to region within a country. Careful planning and, in some cases, epidemiological surveys are required to ensure that the most effective drugs are provided and to obtain full benefit from limited resources.

8.4 Supplies

Continuity of essential drug supplies and information must be assured. It is especially important that drugs be distributed and stored correctly. For example, the cold chain must be maintained for drugs requiring this type of care, such as insulin and vaccines.

8.5 Medicinal drug promotion

Medicinal drug promotion and marketing activities can strongly influence prescribing practices. Methods of evaluating new drugs based on their comparative safety, efficacy, availability and cost should form part of the training of primary health care workers. In addition, the WHO ethical criteria for medicinal drug promotion (*36*) should continue to be widely distributed and followed. This is particularly important for drugs used to treat infections so that inappropriate use is minimized, thereby limiting both the development of resistance to new antimicrobial drugs and unwarranted expense.

9. Drug donations

Guidelines for drug donations have been developed by WHO, the Office of the United Nations High Commissioner for Refugees, UNICEF, the International Committee of the Red Cross, the International Federation of Red Cross and Red Crescent Societies, *Médecins sans frontières* and the World Council of Churches (*37*). The Committee encouraged the widespread use of these guidelines.

10. Post-registration drug studies

Clinical studies for the development of new drugs take place, for the most part, in major medical centres in developed countries, with extensive facilities and highly trained staff. The patients entering the

clinical trials in these centres will usually have received full medical evaluations.

Certain groups of patients such as pregnant women, young children, old people and ethnic groups will usually have been excluded from the trials. For this reason, the patients receiving the new drug prior to registration will not represent the full range of patients who will receive the drug after registration. In addition, the genetic and environmental factors influencing populations in other parts of the world may differ from those that characterize the populations in which the drug was studied and may cause differences in population dose–response relationships.

Little is known about the clinical consequences of different prescribing patterns between countries or between regions within a country. There are few systematic and comprehensive data on the use of drugs after they have been marketed but it is recognized that they are often not used to their full potential or in accordance with generally accepted criteria. Moreover, data on overdose effects and uncommon or longer-term adverse effects are usually not available at the time of registration. It is important, whenever feasible, to quantify these risks in order to identify the safest available products and to remove from the market those that are unacceptably dangerous. Such information is essential for rational drug selection.

Other information that can be obtained when a drug is used in practice relates to unanticipated uses discovered when the drug is given to patients with both the accepted indication and another illness. Furthermore, when used in practice, a drug may fail to produce the benefit that was expected on the basis of the pre-registration studies. This may be because the results of the pre-registration clinical trials cannot be applied to the entire population of patients with the indication for the drug or because the dosage form being used contains less than the labelled amount of the drug or contains the labelled amount, but not in a bioavailable form. These latter factors could result from poor manufacturing practices or from counterfeiting of legitimate dosage forms.

In order to obtain all the information needed for rational use of essential drugs, post-registration drug surveillance or surveys are needed.

Depending on their purpose and the facilities available, drug surveys can be carried out at various levels. Their value is enhanced by using standard procedures (common drug classification systems and units of measurement) in different regions and countries. These procedures

should be used to provide data on all relevant drugs in a particular therapeutic class, paying attention to both cost and quantities prescribed, and taking differences in therapeutic practice into consideration.

The main purpose of drug surveys is to quantify present usage and estimate future demands. Studies can be designed simply to quantify the drug inventory only or to evaluate drug use. Data can also be used: (a) to measure the effects of informational and regulatory measures, price policy, etc.; (b) to define areas for further investigation of the absolute and relative efficacy and safety of drug therapy; (c) to aid in the determination of benefit/risk ratios and cost-effectiveness; and (d) when properly interpreted, to indicate the overuse, underuse or misuse of individual drugs or therapeutic classes of drugs.

Many drug regulatory authorities have recognized the value of post-marketing surveillance and the need for sustained international surveillance schemes. For many years the WHO Collaborating Centre on International Drug Monitoring has collated the reports of national monitoring schemes based on spontaneous notification by health professionals. Originally the programme included only countries with highly evolved regulatory agencies, where its main use was for generating signals of possible adverse drug reactions and for confirming cases. Currently the Collaborating Centre is attracting many developing countries which are in the process of establishing national drug policies. WHO is collaborating closely with the Council for International Organizations of Medical Sciences to promote epidemiologically based methods of monitoring.

The ability of most developing countries to carry out studies using such methods is limited by cost and the need for skills in pharmacoepidemiology. Nevertheless, when concern arises over the safety of a drug used exclusively for a tropical disease, the need for post-marketing surveillance is as great as in any other situation. Such a matter is already being addressed by WHO in the instance of the use of ivermectin in community-based mass treatment programmes for onchocerciasis. Such surveillance may also require the establishment of special reporting facilities and small follow-up studies of people exposed to specific drugs may be necessary.

If the detection of longer-term adverse sequelae to drug use is to become more efficient, reliable methods of linking prescribing information to hospital records will need to be more widely introduced. This, in turn, will require a means of assuring the confidentiality of personal information. Until these methods are developed, the application of epidemiological principles to the assessment of

drug-induced effects will remain difficult to explore. WHO possesses the appropriate consultative capacity to promote debate of the issues, to promote the most suitable methods, and to monitor the results of their application.

These principles apply not only to the detection and assessment of adverse drug effects but to all other indicators of drug performance. In particular, access to microbiological reference laboratories is essential for the rational use of the expensive reserve antimicrobials.

The opportunities to advance therapeutics through post-registration drug studies will be only partially utilized until all health care professionals accept their responsibility to report on the effects of drugs in actual use.

11. Research and development

If the establishment of a list of essential drugs is to succeed in improving health and in reducing drug costs in developing countries, use of the list should be either preceded by, or developed together with, adequate supply and distribution systems and procurement procedures. To hasten the self-reliance of countries, research and development should be undertaken in the following broad areas.

11.1 Pharmaceutical aspects

1. Development of local or regional capability in quality assurance in order to ensure that drug quality is maintained.
2. Development of procurement procedures to take advantage of the benefits of purchasing large quantities of drugs.
3. Development of facilities for processing and packaging simple dosage forms, and ensuring the quality of the product.
4. Development of an efficient countrywide distribution system with suitably trained personnel.

11.2 Clinical and epidemiological aspects

1. Development of facilities and expertise to carry out clinical trials according to the guidelines presented in Annex 3 of the sixth report of the Committee (*13*) in order to assess, where necessary:
   — the relative efficacy and safety of new candidate compounds for inclusion in an essential drugs list;
   — the benefits and safety of traditional medicines, including medicinal plants;

— the effects of genetic and environmental differences among populations on pharmacokinetic, pharmacodynamic and therapeutic parameters.

2. Development of expertise to carry out drug utilization studies and to assess therapeutic practice.

11.3 Educational aspects

1. Development of training programmes in policy formulation, quality control, pharmaceutical information systems, and drug procurement, production, storage and distribution procedures.
2. Development of educational and training programmes for prescribers and other health care professionals.
3. Development of appropriate public education and information programmes in diagnosis and self-medication for conditions for which early recognition of symptoms and prompt self-medication are crucial.
4. Development of package inserts as an aid to consumer education.

12. Nomenclature

The need to identify each pharmaceutical substance by a unique, globally recognized generic name is of critical importance in facilitating communication as well as in the labelling and advertising of medicinal products in international commerce.

This is the objective of the WHO programme on the selection of international nonproprietary names (INNs), whose activities have led to the publication of names for roughly 6900 new pharmaceutical products since 1950. Its role is to coordinate and harmonize the activities of existing national drug nomenclature commissions, which now follow a common set of conventions for devising generic names. Officially assigned generic names now rarely differ from the INNs, and some countries have disestablished their national commissions and automatically accept all recommended INNs.

The procedure for selecting INNs allows manufacturers to contest names that are either identical or similar to their licensed trade marks. In contrast, trade-mark applications are disallowed, in accordance with the present procedure, only when they are identical to an INN. A case for increased protection of INNs is now apparent as a result of competitive promotion of products no longer protected by patents. Rather than marketing these products under the generic name, many companies apply for a trade mark derived from an INN and, in particular, including the INN common stem. This practice endangers

the principle that INNs are public property; it can frustrate the rational selection of further INNs for related substances, and it will ultimately compromise the safety of patients by promoting confusion in drug nomenclature.

On the basis of the Committee's previous recommendations concerning trade marks derived from INNs, a resolution on nonproprietary names for pharmaceuticals (WHA46.19) was adopted by the World Health Assembly in 1993 (*38*). The resolution requested Member States:

(1) to enact rules or regulations, as necessary, to ensure that international nonproprietary names (or the equivalent nationally approved generic names) used in the labelling and advertising of pharmaceutical products are always displayed prominently;
(2) to encourage manufacturers to rely on their corporate name and the international nonproprietary names, rather than on trade marks, to promote and market multisource products introduced after expiry of a patent;
(3) to develop policy guidelines on the use and protection of international nonproprietary names, and to discourage the use of names derived from them, and particularly names including established stems, as trade marks.

The resolution called upon the Director-General to intensify his consultations with governments and representatives of the pharmaceutical industry on ways of minimizing the problems arising from drug nomenclatures that may create confusion and jeopardize the safety of patients.

While INNs are widely used in reference books and journals, they are not always identified as such, or even accorded preference, particularly in the case of older substances that may have several different generic names. Editors are urged to give preference to INNs in reference works, journals and data banks and to allow the use of a code for a new substance (pending the assignment of an INN) rather than an unofficial name.

13. Drug information and educational activities

For the safe, effective and prudent use of essential drugs, relevant and reliable drug information should be available. In order to provide this, a series of publications entitled *WHO model prescribing information* is being prepared. The first five titles in this series, *Drugs used in*

anaesthesia (*39*), *Drugs used in parasitic diseases*, second ed. (*40*), *Drugs used in mycobacterial diseases* (*41*), *Drugs used in sexually transmitted diseases and HIV infection* (*42*) and *Drugs used in skin diseases* (*43*) have already been published. Further titles are in preparation. The Committee supports with great enthusiasm the provision of model prescribing information and considers that the documents published to date are clear, useful and well written.

At its previous meeting, the Committee had urged that a Model Formulary should be developed to complement the Model List of Essential Drugs. The purpose of such a formulary, which could be updated periodically, would be to provide general information and information on prototype drugs in the Model List of Essential Drugs according to the specifications as shown in the sample drug information sheet overleaf. This information could then be adapted by countries according to their own needs and would be a key element in rational drug use. The formulary was not intended to restrict the concept of essential drugs. The Committee was informed of progress in the development of this formulary.

Health care professionals should receive education about the use of drugs not only during their initial professional training but throughout their professional careers. The more highly trained individuals should assume a responsibility to educate those with less training. Pharmacists and other health care workers responsible for dispensing drugs should accept every opportunity to inform consumers about the rational use of these products, including those for self-medication, at the time they are dispensed.

The Committee recommended that comprehensive educational programmes for health care professionals include:

— accurate and understandable drug information and information on all aspects of medical care in which they are involved;
— information about patterns of disease in the community, especially prevailing sensitivity patterns, to aid in the selection of antimicrobial drugs;
— diagnostic and therapeutic guidelines for conditions recognized as important.

Governments, universities and professional associations have a major responsibility to collaborate on improving undergraduate, postgraduate and continuing education in clinical pharmacology, therapeutics and drug information issues.

Appropriate drug information that is well presented is cost-effective in that it ensures that drugs are used properly and decreases

inappropriate drug use; drug information activities should be financed from the national budget for the provision of drugs.

Drug information sheets

The following is an example of a format for supplying information to prescribers to facilitate the safe and effective use of drugs. The content should be adjusted to the needs, knowledge and responsibilities of the prescriber.

1. INN of each active substance.
2. Pharmacological data: a brief description of pharmacological properties and mechanism of action.
3. Clinical information:
   (a) Indications: whenever appropriate, simple diagnostic criteria should be provided.
   (b) Dosage regimen and relevant pharmacokinetic data:
      — average and range for adults and children;
      — dosing interval;
      — average duration of treatment;
      — special situations, e.g. renal, hepatic, cardiac or nutritional insufficiencies that require either an increased or a reduced dosage.
   (c) Contraindications.
   (d) Precautions and warnings (reference to pregnancy, lactation, etc.).
   (e) Adverse effects (quantify by category, if possible).
   (f) Drug interactions (include only if clinically relevant; drugs used for self-medication should be included).
   (g) Overdosage:
      — brief clinical description of symptoms;
      — non-drug treatment and supportive therapy;
      — specific antidotes.
4. Pharmaceutical information:
   (a) Dosage forms.
   (b) Strength of dosage form.
   (c) Excipients.
   (d) Storage conditions and shelf-life (expiry date).
   (e) Pack sizes.
   (f) Description of the product and package.
   (g) Legal category (narcotic or other controlled drug, prescription or non-prescription).
   (h) Name and address of manufacturer(s) and importer(s).

The Committee also recognized the need to develop appropriate drug information sheets for consumers.

14. Selection and updating of lists of essential drugs

An essential drug list must be flexible enough to accommodate, as necessary, new drugs, new information on established drugs and changes in the status of internationally controlled substances. Experience with the original model list and the subsequent revisions, as well as with regional and national lists of essential drugs, has confirmed the need for regular review and updating. Revision is necessary not only because of advances in drug therapy but also in order to meet the needs of practice in the light of experience. Frequent and extensive changes are clearly undesirable since they result in disruption of channels of procurement and distribution and may have implications for the training of health personnel. For this reason a number of drugs have been retained on the model list that have been largely superseded in countries where there is a more extensive range of new medicaments but that are still used widely and successfully elsewhere. In revising and updating the model list, the Committee was guided in its deliberations by the following statements which appeared in the first report:

1. The extent to which countries implement schemes or establish lists of essential drugs is a national policy decision of each country.
2. As far as health services in developing countries are concerned, the organized procurement and use of essential drugs have many advantages in terms of economy and effectiveness. However, the concept of "essential drug lists" must accommodate a variety of local situations if the lists are ever to meet the real health needs of the majority of the population.
3. There are convincing justifications for WHO to propose "model" or "guiding" lists of essential drugs as a contribution to solving the problems of Member States whose health needs far exceed their resources and who may find it difficult to initiate such an endeavour on their own.
4. Such "model" or "guiding" lists should be understood as a tentative identification of a "common core" of basic needs which has universal relevance and applicability. In certain situations, there is a need to make available additional drugs essential for rare diseases. The further local needs move away from the core, the more the health authorities or specific sectors of the health services will have to adjust the lists. However, any list proposed by WHO should set out to indicate priorities in drug needs, with the full understanding that exclusion does not imply rejection. A list of

essential drugs does not imply that no other drugs are useful, but simply that in a given situation these drugs are the most needed for the health care of the majority of the population and, therefore, should be available at all times in adequate amounts and in the proper dosage forms.

5. The selection of essential drugs is a continuing process, which should take into account changing priorities for public health action and epidemiological conditions, as well as progress in pharmacological and pharmaceutical knowledge. It should be accompanied by a concomitant effort to supply information and give education and training to health personnel in the proper use of the drugs.

Applications for the addition of drugs to the model list will always receive full consideration by WHO. An application form can be found in Annex 1.

15. Model List of Essential Drugs (tenth list)

Explanatory notes[1]

Many drugs included in the list are preceded by a square symbol (□) to indicate that they represent an *example of a therapeutic group* and that various drugs could serve as alternatives. It is imperative that this is understood when drugs are selected at national level, since choice is then influenced by the comparative cost and availability of equivalent products. Examples of acceptable substitutions include:

- □ Codeine: other drugs for the symptomatic treatment of diarrhoea in adults, such as loperamide.
- □ Hydrochlorothiazide: any other thiazide-type diuretic currently in broad clinical use.
- □ Hydralazine: any other peripheral vasodilator having an antihypertensive effect.
- □ Senna: any mild stimulant laxative (either synthetic or of plant origin).
- □ Sulfadiazine: any other short-acting, systemically active sulfonamide unlikely to cause crystalluria.

Numbers in parentheses following the drug names indicate:

[1] The numbers preceding the drug sections and subsections in the model list have, in general, been allocated in accordance with English alphabetical order; they have no formal significance.

(1) Drugs subject to international control under: (a) the Single Convention on Narcotic Drugs, 1961 (*44*); (b) the Convention on Psychotropic Substances, 1971 (*45*); or (c) the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, 1988 (*46*).
(2) Specific expertise, diagnostic precision, individualization of dosage or special equipment required for proper use.
(3) Greater potency or efficacy.
(4) In renal insufficiency, contraindicated or dosage adjustments necessary.
(5) To improve compliance.
(6) Special pharmacokinetic properties.
(7) Adverse effects diminish benefit/risk ratio.
(8) Limited indications or narrow spectrum of activity.
(9) For epidural anaesthesia.
(10) Sustained-release preparations are available. A proposal to include such a product in a national list of essential drugs should be supported by adequate documentation.
(11) Monitoring of therapeutic drug concentrations (in plasma) can be used to improve safety and efficacy.

Letters in parentheses after the drug names indicate the reasons for the inclusion of *complementary drugs*:

(A) When drugs in the main list cannot be made available.
(B) When drugs in the main list are known to be ineffective or inappropriate for a given individual.
(C) For use in rare disorders or in exceptional circumstances.

Certain pharmacological effects have many therapeutic uses. Drugs with these effects could be listed in many different therapeutic categories in the model list. However, the inclusion of such drugs in more than one therapeutic category has been limited to circumstances that the Committee wished to emphasize. Drugs in the model list are therefore not necessarily listed in each of the therapeutic categories in which they are of value. Information on therapeutic use is available in the *WHO model prescribing information* publications (*39–43*) and several other WHO publications (*47–49*). In addition, essential drugs could be categorized by whether their use is to treat a life-threatening illness, to minimize or prevent a disability, or to improve the quality of life. This system is not used here, however, since the Committee considered all of these uses to be essential for proper therapeutics. It is necessary for individual countries to specify which drugs have priority in their country.

Drug	*Route of administration, dosage forms and strengths*[a]
1. Anaesthetics	
1.1 *General anaesthetics and oxygen*	
ether, anaesthetic (1c, 2)	inhalation
halothane (2)	inhalation
ketamine (2)	injection, 50 mg (as hydrochloride)/ml in 10-ml vial
nitrous oxide (2)	inhalation
oxygen	inhalation (medicinal gas)
□ thiopental (2)	powder for injection, 0.5 g, 1.0 g (sodium salt) in ampoule
1.2 *Local anaesthetics*	
□ bupivacaine (2, 9)	injection, 0.25%, 0.5% (hydrochloride) in vial
	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
	injection, 1%, 2% (hydrochloride) + epinephrine 1:200 000 in vial
	injection for spinal anaesthesia, 5% (hydrochloride) in 2-ml ampoule to be mixed with 7.5% glucose solution
	topical forms, 2–4% (hydrochloride)
	dental cartridge, 2% (hydrochloride) + epinephrine 1:80 000
Complementary drug	
ephedrine[b] (C)	injection, 30 mg (hydrochloride)/ml in 1-ml ampoule
1.3 *Preoperative medication and sedation for short-term procedures*	
atropine	injection, 1 mg (sulfate) 1-ml ampoule
chloral hydrate	syrup, 200 mg/5 ml

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

[b] For use in spinal anaesthesia during delivery, to prevent hypotension.

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
1. Anaesthetics (*continued*)	
1.3 *Preoperative medication and sedation for short-term procedures* (*continued*)	
□ diazepam (1b)	injection, 5 mg/ml in 2-ml ampoule
	tablet, 5 mg
□ morphine (1a)	injection, 10 mg (sulfate or hydrochloride) in 1-ml ampoule
□ promethazine	elixir or syrup, 5 mg (hydrochloride)/5 ml
2. Analgesics, antipyretics, nonsteroidal anti-inflammatory drugs, drugs used to treat gout and disease-modifying agents used in rheumatic disorders	
2.1 *Non-opioid analgesics and nonsteroidal anti-inflammatory drugs*	
acetylsalicylic acid	tablet, 100–500 mg
	suppository, 50–150 mg
□ ibuprofen	tablet, 200 mg, 400 mg
paracetamol	tablet, 100–500 mg
	suppository, 100 mg
	syrup, 125 mg/5 ml
2.2 *Opioid analgesics*	
□ codeine (1a)	tablet, 30 mg (phosphate)
□ morphine (1a)	injection, 10 mg (sulfate or hydrochloride) in 1-ml ampoule
	oral solution, 10 mg (hydrochloride or sulfate)/5 ml
	tablet, 10 mg (sulfate)
Complementary drug	
□ pethidine (A) (1a, 4)	injection, 50 mg (hydrochloride) in 1-ml ampoule
	tablet, 50 mg, 100 mg (hydrochloride)

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
2. Analgesics, antipyretics, nonsteroidal anti-inflammatory drugs, drugs used to treat gout and disease-modifying agents used in rheumatic disorders (*continued*)	
2.3 *Drugs used to treat gout*	
allopurinol (4)	tablet, 100 mg
colchicine (7)	tablet, 500 µg
2.4 *Disease-modifying agents used in rheumatic disorders*	
azathioprine (2)	tablet, 50 mg
chloroquine (2)	tablet, 100 mg, 150 mg (as phosphate or sulfate)
cyclophosphamide (2)	tablet, 25 mg
methotrexate (2)	tablet, 2.5 mg (as sodium salt)
penicillamine (2)	capsule or tablet, 250 mg
sulfasalazine (2)	tablet, 500 mg
3. Antiallergics and drugs used in anaphylaxis	
□ chlorphenamine	tablet, 4 mg (hydrogen maleate)
	injection, 10 mg (hydrogen maleate) in 1-ml ampoule
□ dexamethasone	tablet, 500 µg, 4 mg
	injection, 4 mg dexamethasone phosphate (as disodium salt) in 1-ml ampoule
epinephrine	injection, 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule
hydrocortisone	powder for injection, 100 mg (as sodium succinate) in vial
□ prednisolone	tablet, 5 mg
4. Antidotes and other substances used in poisonings	
4.1 *Non-specific*	
□ charcoal, activated	powder
ipecacuanha	syrup, containing 0.14% ipecacuanha alkaloids calculated as emetine

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
4. Antidotes and other substances used in poisonings (*continued*)	
4.2 *Specific*	
atropine	injection, 1 mg (sulfate) in 1-ml ampoule
calcium gluconate (2, 8)	injection, 100 mg/ml in 10-ml ampoule
deferoxamine	powder for injection, 500 mg (mesilate) in vial
dimercaprol (2)	injection in oil, 50 mg/ml in 2-ml ampoule
□ DL-methionine	tablet, 250 mg
methylthioninium chloride (methylene blue)	injection, 10 mg/ml in 10-ml ampoule
naloxone	injection, 400 µg (hydrochloride) in 1-ml ampoule
penicillamine (2)	capsule or tablet, 250 mg
potassium ferric hexacyanoferrate (II)·$2H_2O$ (Prussian blue)	powder for oral administration
sodium calcium edetate (2)	injection, 200 mg/ml in 5-ml ampoule
sodium nitrite	injection, 30 mg/ml in 10-ml ampoule
sodium thiosulfate	injection, 250 mg/ml in 50-ml ampoule
5. Anticonvulsants/antiepileptics	
carbamazepine (10, 11)	scored tablet, 100 mg, 200 mg
□ diazepam (1b)	injection, 5 mg/ml in 2-ml ampoule (intravenous or rectal)
ethosuximide	capsule, 250 mg
	syrup, 250 mg/5 ml
phenobarbital (1b, 11)	tablet, 15–100 mg
	elixir, 15 mg/5 ml
phenytoin (7, 11)	capsule or tablet, 25 mg, 50 mg, 100 mg (sodium salt)
	injection, 50 mg (sodium salt)/ml in 5-ml vial

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
5. Anticonvulsants/antiepileptics (*continued*)	
valproic acid (7, 11)	enteric coated tablet, 200mg, 500mg (sodium salt)
Complementary drugs	
□ clonazepam (B) (1b)	scored tablet, 500µg
magnesium sulfate (C)	injection, 500mg/ml in 2-ml ampoule, 500 mg/ml in 10-ml ampoule
6. Anti-infective drugs	
6.1 *Anthelminthics*	
6.1.1 *Intestinal anthelminthics*	
albendazole	chewable tablet, 400mg
levamisole	tablet, 50mg, 150mg (as hydrochloride)
□ mebendazole	chewable tablet, 100mg, 500mg
niclosamide	chewable tablet, 500mg
praziquantel	tablet, 150mg, 600mg
pyrantel	chewable tablet, 250mg (as embonate)
	oral suspension, 50mg (as embonate)/ml
6.1.2 *Antifilarials*	
diethylcarbamazine	tablet, 50mg, 100mg (dihydrogen citrate)
ivermectin	scored tablet, 3mg, 6mg
Complementary drug	
suramin sodium (B) (2, 7)	powder for injection, 1g in vial
6.1.3 *Antischistosomals and other antitrematode drugs*	
praziquantel	tablet, 600mg
triclabendazole	tablet, 250mg
Complementary drug	
oxamniquine (C) (8)	capsule, 250mg
	syrup, 250mg/5ml

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
6. Anti-infective drugs (*continued*)	
6.2 *Antibacterials*	
6.2.1 *β-Lactam drugs*	
□ amoxicillin	capsule or tablet, 250 mg, 500 mg (anhydrous)
	powder for oral suspension, 125 mg (anhydrous)/5 ml
ampicillin	powder for injection, 500 mg, 1 g (as sodium salt) in vial
benzathine benzylpenicillin	powder for injection, 1.44 g benzylpenicillin (= 2.4 million IU) in 5-ml vial
benzylpenicillin	powder for injection, 600 mg (= 1 million IU), 3 g (= 5 million IU) (sodium or potassium salt) in vial
□ cloxacillin	capsule, 500 mg, 1 g (as sodium salt)
	powder for oral solution, 125 mg (as sodium salt)/5 ml
	powder for injection, 500 mg (as sodium salt) in vial
phenoxymethylpenicillin	tablet, 250 mg (as potassium salt)
	powder for oral suspension, 250 mg (as potassium salt)/5 ml
procaine benzylpenicillin	powder for injection, 1 g (= 1 million IU), 3 g (= 3 million IU) in vial
Restricted indications	
□ amoxicillin + □ clavulanic acid	tablet, 500 mg + 125 mg
ceftazidime	powder for injection, 250 mg (as pentahydrate) in vial
□ ceftriaxone	powder for injection, 250 mg (as sodium salt) in vial

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
6. Anti-infective drugs (*continued*)	
6.2 *Antibacterials* (*continued*)	
6.2.1 *β-Lactam drugs* (*continued*)	
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
6.2.2 *Other antibacterials*	
□ chloramphenicol (7)	capsule, 250 mg
	oral suspension, 150 mg (as palmitate)/5 ml
	powder for injection, 1 g (sodium succinate) in vial
□ ciprofloxacin	tablet, 250 mg (as hydrochloride)
□ doxycycline (5, 6)	capsule or tablet, 100 mg (hydrochloride)
□ erythromycin	capsule or tablet, 250 mg (as stearate or ethyl succinate)
	powder for oral suspension, 125 mg (as stearate or ethyl succinate)
	powder for injection, 500 mg (as lactobionate) in vial
□ gentamicin (2, 4, 7, 11)	injection, 10 mg, 40 mg (as sulfate)/ml in 2-ml vial
□ metronidazole	tablet, 200–500 mg
	injection, 500 mg in 100-ml vial
	suppository, 500 mg, 1 g
	oral suspension, 200 mg (as benzoate)/5 ml
nalidixic acid (8)	tablet, 250 mg, 500 mg
nitrofurantoin (4, 8)	tablet, 100 mg
spectinomycin (8)	powder for injection, 2 g (as hydrochloride) in vial

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
6. Anti-infective drugs (*continued*)	
6.2 *Antibacterials* (*continued*)	
6.2.2 *Other antibacterials* (*continued*)	
□ sulfadiazine (4)	tablet, 500 mg
	injection, 250 mg (sodium salt) in 4-ml ampoule
□ sulfamethoxazole + trimethoprim (4)	tablet, 100 mg + 20 mg, 400 mg + 80 mg
	oral suspension, 200 mg + 40 mg/5 ml
	injection, 80 mg + 16 mg/ml in 5-ml ampoule, 80 mg + 16 mg/ml in 10-ml ampoule
trimethoprim (8)	tablet, 100 mg, 200 mg
	injection, 20 mg/ml in 5-ml ampoule
Complementary drugs	
chloramphenicol (C)	oily suspension, 0.5 g (as sodium succinate)/ml in 2-ml ampoule
clindamycin (B) (8)	capsule, 150 mg
	injection, 150 mg (as phosphate)/ml
Restricted indications	
vancomycin	powder for injection, 250 mg (as hydrochloride) in vial
6.2.3 *Antileprosy drugs*	
clofazimine	capsule, 50 mg, 100 mg
dapsone	tablet, 25 mg, 50 mg, 100 mg
rifampicin	capsule or tablet, 150 mg, 300 mg
6.2.4 *Antituberculosis drugs*	
ethambutol (4)	tablet, 100–400 mg (hydrochloride)
isoniazid	tablet, 100–300 mg
isoniazid + ethambutol (5)	tablet, 150 mg + 400 mg
pyrazinamide	tablet, 400 mg

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
6. Anti-infective drugs (*continued*)	
6.2 *Antibacterials* (*continued*)	
6.2.4 *Antituberculosis drugs* (*continued*)	
rifampicin	capsule or tablet, 150mg, 300mg
rifampicin + isoniazid (5)	tablet, 150mg + 75mg, 300mg + 150mg, 150mg + 150mg[b]
rifampicin + isoniazid + pyrazinamide (5)	tablet, 150mg + 75mg + 400mg, 150mg + 150mg + 500mg[b]
streptomycin (4)	powder for injection, 1g (as sulfate) in vial
Complementary drug	
thioacetazone + isoniazid (A) (5, 7)	tablet, 50mg + 100mg, 150mg + 300mg
6.3 *Antifungal drugs*	
amphotericin B (4)	powder for injection, 50mg in vial
griseofulvin (7)	capsule or tablet, 125mg, 250mg
□ ketoconazole (2)	tablet, 200mg
	oral suspension, 100mg/5ml
nystatin	tablet, 100000IU, 500000IU
	lozenge, 100000IU
	pessary, 100000IU
Complementary drugs	
flucytosine (B) (4, 8)	capsule, 250mg
	infusion, 2.5g in 250ml
potassium iodide (A)	saturated solution
6.4 *Antiviral drugs*	
6.4.1 *Antiherpes drugs*	
aciclovir (8)	tablet, 200mg
	powder for injection, 250mg (as sodium salt) in vial

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

[b] For intermittent use three times weekly.

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
6. Anti-infective drugs (*continued*)	
6.4 *Antiviral drugs* (*continued*)	
6.4.2 *Antiretroviral drugs*	
zidovudine (8)	capsule, 100 mg
	tablet, 250 mg
	injection, 10 mg/ml in 20-ml vial
	oral solution, 50 mg/5 ml

Drugs for the treatment of human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS) include nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors. The prototype drug, zidovudine, has been shown to reduce or prevent maternal transmission of HIV infection. *This is the only indication for which it is included here.* Single drug use with zidovudine, except in pregnancy, is now regarded as obsolete, because of the development of resistance. Triple therapy is beyond the budgets of most national drug programmes and therefore HIV/AIDS treatment policies must be decided at the country or institutional level.

6.5 *Antiprotozoal drugs*	
6.5.1 *Antiamoebic and antigiardiasis drugs*	
□ diloxanide	tablet, 500 mg (furoate)
□ metronidazole	tablet, 200–500 mg
	injection, 500 mg in 100-ml vial
	oral suspension, 200 mg (as benzoate)/5 ml
6.5.2 *Antileishmaniasis drugs*	
□ meglumine antimoniate	injection, 30%, equivalent to approx. 8.5% antimony, in 5-ml ampoule
pentamidine (5)	powder for injection, 200 mg, 300 mg (isetionate) in vial
Complementary drug	
amphotericin B (B) (4)	powder for injection, 50 mg in vial

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
6. Anti-infective drugs (*continued*)	
6.5 *Antiprotozoal drugs* (*continued*)	
6.5.3 *Antimalarial drugs*	
(a) For curative treatment	
□ chloroquine	tablet, 100mg, 150mg (as phosphate or sulfate)
	syrup, 50mg (as phosphate or sulfate)/5ml
	injection, 40mg (as hydrochloride, phosphate or sulfate)/ml in 5-ml ampoule
primaquine	tablet, 7.5mg, 15mg (as diphosphate)
□ quinine	tablet, 300mg (as bisulfate or sulfate)
	injection, 300mg (as dihydrochloride)/ml in 2-ml ampoule
Complementary drugs	
□ doxycycline (B)[b]	capsule or tablet, 100mg (hydrochloride)
mefloquine (B)	tablet, 250mg (as hydrochloride)
□ sulfadoxine + pyrimethamine (B)	tablet, 500mg + 25mg
Restricted indications	
artemether	injection, 80mg/ml in 1-ml ampoule
(b) For prophylaxis	
chloroquine	tablet, 150mg (as phosphate or sulfate)
	syrup, 50mg (as phosphate or sulfate)/5ml
mefloquine	tablet, 250mg (as hydrochloride)
proguanil[c]	tablet, 100mg (hydrochloride)
6.5.4 *Antipneumocystosis and antitoxoplasmosis drugs*	
pentamidine (2)	tablet, 200mg, 300mg

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

[b] For use only in combination with quinine.

[c] For use only in combination with chloroquine.

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
6. Anti-infective drugs (*continued*)	
6.5 *Antiprotozoal drugs* (*continued*)	
6.5.4 *Antipneumocystosis and antitoxoplasmosis drugs* (*continued*)	
pyrimethamine	tablet, 25 mg
sulfamethoxazole + trimethoprim	injection, 80 mg + 16 mg/ml in 5-ml ampoule, 80 mg + 16 mg/ml in 10-ml ampoule
6.5.5 *Antitrypanosomal drugs*	
(a) African trypanosomiasis	
melarsoprol (2)	injection, 3.6% solution
pentamidine (2)	powder for injection, 200 mg, 300 mg (isetionate) in vial
suramin sodium	powder for injection, 1 g in vial
Complementary drug	
eflornithine (C)	injection, 200 mg (hydrochloride)/ml in 100-ml bottles
(b) American trypanosomiasis	
benznidazole (7)	tablet, 100 mg
nifurtimox (2, 8)	tablet, 30 mg, 120 mg, 250 mg
6.6 *Insect repellents*	
diethyltoluamide	topical solution, 50%, 75%
7. Antimigraine drugs	
7.1 *For treatment of acute attack*	
acetylsalicylic acid	tablet, 300–500 mg
ergotamine (1c, 7)	tablet, 1 mg (tartrate)
paracetamol	tablet, 300–500 mg
7.2 *For prophylaxis*	
□ propranolol	tablet, 20 mg, 40 ml (hydrochloride)

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
8. Antineoplastic and immunosuppressive drugs and drugs used in palliative care	
8.1 *Immunosuppressive drugs*	
□ azathioprine (2)	tablet, 50 mg
	powder for injection, 100 mg (as sodium salt) in vial
ciclosporin (2)[b]	capsule, 25 mg
	concentrate for injection, 50 mg/ml in 1-ml ampoule
8.2 *Cytotoxic drugs*	
asparaginase (2)	powder for injection, 10 000 IU in vial
bleomycin (2)	powder for injection, 15 mg (as sulfate) in vial
calcium folinate (2)	tablet, 15 mg
	injection, 3 mg/ml in 10-ml ampoule
chlormethine (2)	powder for injection, 10 mg (hydrochloride) in vial
cisplatin (2)	powder for injection, 10 mg, 50 mg in vial
cyclophosphamide (2)	tablet, 25 mg
	powder for injection, 500 mg in vial
cytarabine (2)	powder for injection, 100 mg in vial
dacarbazine (2)	powder for injection, 100 mg in vial
dactinomycin (2)	powder for injection, 500 µg in vial
□ doxorubicin (2)	powder for injection, 10 mg, 50 mg (hydrochloride) in vial
etoposide (2)	capsule, 100 mg
	injection, 20 mg/ml in 5-ml ampoule
fluorouracil (2)	injection, 50 mg/ml in 5-ml ampoule
levamisole (2)	tablet, 50 mg (as hydrochloride)
mercaptopurine (2)	tablet, 50 mg

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

[b] For organ transplantation.

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
8. Antineoplastic and immunosuppressive drugs and drugs used in palliative care (*continued*)	
8.2 *Cytotoxic drugs* (*continued*)	
methotrexate (2)	tablet, 2.5 mg (as sodium salt)
	powder for injection, 50 mg (as sodium salt) in vial
procarbazine	capsule, 50 mg (as hydrochloride)
vinblastine (2)	powder for injection, 10 mg (sulfate) in vial
vincristine (2)	powder for injection, 1 mg, 5 mg (sulfate) in vial
8.3 *Hormones and antihormones*	
□ prednisolone	tablet, 5 mg
	powder for injection, 20 mg, 25 mg (as sodium phosphate or sodium succinate) in vial
tamoxifen	tablet, 10 mg, 20 mg (as citrate)
8.4 *Drugs used in palliative care*	
The Committee recommended that all the drugs mentioned in the WHO publication *Cancer pain relief: with a guide to opioid availability*, second ed. (*50*) be considered essential. The drugs are included in the relevant sections of the model list, according to their therapeutic use, e.g. analgesics.	
9. Antiparkinsonism drugs	
□ biperiden	tablet, 2 mg (hydrochloride)
	injection, 5 mg (lactate) in 1-ml ampoule
levodopa + □ carbidopa (5, 6)	tablet, 100 mg + 10 mg, 250 mg + 25 mg
10. Drugs affecting the blood	
10.1 *Antianaemia drugs*	
ferrous salt	tablet, equivalent to 60 mg iron
	oral solution, equivalent to 25 mg iron (as sulfate)/ml

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
10. Drugs affecting the blood (*continued*)	
10.1 *Antianaemia drugs* (*continued*)	
ferrous salt + folic acid[b]	tablet, equivalent to 60 mg iron + 400 µg folic acid
folic acid (2)	tablet, 1 mg, 5 mg
	injection, 1 mg (as sodium salt) in 1-ml ampoule
hydroxocobalamin (2)	injection, 1 mg in 1-ml ampoule
Complementary drug	
□ iron dextran (B) (5)	injection, equivalent to 50 mg iron/ml in 2-ml ampoule
10.2 *Drugs affecting coagulation*	
desmopressin (8)	injection, 4 µg (acetate)/ml in 1-ml ampoule
	nasal spray, 10 µg (acetate)/metered dose
heparin sodium	injection, 1000 IU/ml, 5000 IU/ml, 20 000 IU/ml in 1-ml ampoule
phytomenadione	injection, 10 mg/ml in 5-ml ampoule
	tablet, 10 mg
protamine sulfate	injection, 10 mg/ml in 5-ml ampoule
□ warfarin (2, 6)	tablet, 1 mg, 2 mg, 5 mg (sodium salt)
11. Blood products and plasma substitutes	
11.1 *Plasma substitutes*	
□ dextran 70	injectable solution, 6%
□ polygeline	injectable solution, 3.5%
11.2 *Plasma fractions for specific uses*[c]	
□ albumin, human (2, 8)	injectable solution, 5%, 25%

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

[b] Nutritional supplement for use during pregnancy.

[c] All plasma fractions should comply with the Requirements for the Collection, Processing and Quality Control of Blood, Blood Components and Plasma Derivatives (Revised 1992). *WHO Expert Committee on Biological Standardization. Forty-third report* (WHO Technical Report Series, No. 840, 1994, Annex 2).

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
11. Blood products and plasma substitutes (*continued*)	
11.2 *Plasma fractions for specific uses*[c] (*continued*)	
Complementary drugs	
□ factor VIII concentrate (C) (2, 8)	dried
□ factor IX complex (coagulation factors II, VII, IX, X) concentrate (C) (2, 8)	dried
12. Cardiovascular drugs	
12.1 *Antianginal drugs*	
□ atenolol	tablet, 50 mg, 100 mg
glyceryl trinitrate	tablet (sublingual), 500 µg
□ isosorbide dinitrate	tablet (sublingual), 5 mg
□ verapamil (10)	tablet, 40 mg, 80 mg (hydrochloride)
12.2 *Antiarrhythmic drugs*	
□ atenolol	tablet, 50 mg, 100 mg
digoxin (4, 11)	tablet, 62.5 µg, 250 µg
	oral solution, 50 µg/ml
	injection, 250 µg/ml in 2-ml ampoule
lidocaine	injection, 20 mg (hydrochloride)/ml in 5-ml ampoule
verapamil (8, 10)	tablet, 40 mg, 80 mg (hydrochloride)
	injection, 2.5 mg (hydrochloride)/ml in 2-ml ampoule
Complementary drugs	
epinephrine (C)	injection, 1 mg (as hydrochloride)/ml in ampoule
isoprenaline (C)	injection, 20 µg (hydrochloride)/ml in ampoule

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

[c] See footnote c on page 40.

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
12. Cardiovascular drugs (*continued*)	
12.2 *Antiarrhythmic drugs* (*continued*)	
Complementary drugs (*continued*)	
□ procainamide (B)	injection, 100mg (hydrochloride)/ml in 10-ml ampoule
□ quinidine (A) (7)	tablet, 200mg (sulfate)
12.3 *Antihypertensive drugs*	
□ atenolol	tablet, 50mg, 100mg
□ captopril	scored tablet, 25mg
□ hydralazine	tablet, 25mg, 50mg (hydrochloride)
	powder for injection, 20mg (hydrochloride) in ampoule
□ hydrochlorothiazide	scored tablet, 25mg
methyldopa (7)	tablet, 250mg
□ nifedipine (10)	sustained-release formulations
	tablet, 10mg
□ reserpine	tablet, 100µg, 250µg
	injection, 1mg in 1-ml ampoule
Complementary drugs	
□ doxazosin (B)	tablet, 1mg, 2mg, 4mg (mesilate)
□ sodium nitroprusside (C) (2, 8)	powder for infusion, 50mg in ampoule
12.4 *Drugs used in heart failure*	
□ captopril	scored tablet, 25mg
digoxin (4, 11)	tablet, 62.5µg, 250µg
	oral solution, 50µg/ml
	injection, 250µg/ml in 2-ml ampoule
dopamine	injection, 40mg (hydrochloride)/ml in 5-ml vial
□ hydrochlorothiazide	tablet, 25mg, 50mg

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
12. Cardiovascular drugs (*continued*)	
12.5 *Antithrombotic drugs*	
acetylsalicylic acid	tablet, 100 mg
Complementary drug	
streptokinase (C)	powder for injection, 100 000 IU, 750 000 IU in vial
12.6 *Lipid-lowering agents*	

The Committee recognizes the value of lipid-lowering drugs in treating patients with hyperlipidaemia. However, there are many other risk factors for atherosclerosis and its complications, including tobacco smoking and inadequately controlled hypertension. Most hyperlipidaemias can be controlled by diet.

β-Hydroxy-β-methylglutaryl-coenzyme A (HMG CoA) reductase inhibitors, often referred to as "statins", are a family of potent and effective lipid-lowering drugs with a good tolerability profile. Several of these drugs have been shown to reduce the incidence of fatal and non-fatal mycardial infarction, stroke and mortality (all causes), as well as the need for coronary by-pass surgery. All remain very costly but may be cost-effective for secondary prevention of cardiovascular disease as well as for primary prevention in some very high-risk patients. Since no single drug has been shown to be significantly more effective or less expensive than others in the group, none is included in the model list; the choice of drug for use in patients at highest risk should be decided at the national level.

13. Dermatological drugs (topical)	
13.1 *Antifungal drugs*	
benzoic acid + salicylic acid	ointment or cream, 6% + 3%
□ miconazole	ointment or cream, 2% (nitrate)
sodium thiosulfate	solution, 15%
Complementary drug	
selenium sulfide (C)	detergent-based suspension, 2%
13.2 *Anti-infective drugs*	
□ methylrosanilinium chloride (gentian violet)	aqueous solution, 0.5%
	tincture, 0.5%

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
13. Dermatological drugs (topical) (*continued*)	
13.2 *Anti-infective drugs* (*continued*)	
neomycin + □bacitracin (7)	ointment, 5 mg neomycin sulfate + 500 IU bacitracin zinc/g
potassium permanganate	aqueous solution, 1:10 000
silver sulfadiazine	cream, 1%, in 500-g container
13.3 *Anti-inflammatory and antipruritic drugs*	
□betamethasone (3)	ointment or cream, 0.1% (as valerate)
□calamine lotion	lotion
□hydrocortisone	ointment or cream, 1% (acetate)
13.4 *Astringent drugs*	
aluminium diacetate	solution, 13% for dilution
13.5 *Drugs affecting skin differentiation and proliferation*	
benzoyl peroxide	lotion or cream, 5%
coal tar	solution, 5%
dithranol	ointment, 0.1–2%
fluorouracil	ointment, 5%
□podophyllum resin (7)	solution, 10–25%
salicylic acid	solution, 5%
urea	ointment or cream, 10%
13.6 *Scabicides and pediculicides*	
□benzyl benzoate	lotion, 25%
permethrin	cream, 5%
	lotion, 1%
13.7 *Ultraviolet-blocking agents*	
Complementary drug	
topical sun protection agent with activity against ultraviolet A and ultraviolet B (C)	cream, lotion or gel

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
14. Diagnostic agents	
14.1 *Ophthalmic drugs*	
fluorescein	eye drops, 1% (sodium salt)
□ tropicamide	eye drops, 0.5%
14.2 *Radiocontrast media*	
□ amidotrizoate	injection, 140–420 mg iodine (as sodium or meglumine salt)/ml in 20-ml ampoule
barium sulfate	aqueous suspension
□ iopanoic acid	tablet, 500 mg
□ propyliodone	oily suspension, 500–600 mg/ml in 20-ml ampoule[b]
Complementary drug	
□ meglumine iotroxate (C)	solution, 5–8 g iodine in 100–250 ml
15. Disinfectants and antiseptics	
15.1 *Antiseptics*	
□ chlorhexidine	solution, 5% (digluconate) for dilution
□ polyvidone iodine	solution, 10%
15.2 *Disinfectants*	
□ chlorine base compound	powder (0.1% available chlorine) for solution
□ chloroxylenol	solution, 4.8%
glutaral	solution, 2%
16. Diuretics	
□ amiloride (4, 7, 8)	tablet, 5 mg (hydrochloride)
□ furosemide	tablet, 40 mg
	injection, 10 mg/ml in 2-ml ampoule
□ hydrochlorothiazide	tablet, 25 mg, 50 mg
spironolactone (8)	tablet, 25 mg

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

[b] For administration only into the bronchial tree.

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
16. Diuretics (*continued*)	
Complementary drug	
□ mannitol (C)	injectable solution, 10%, 20%
17. Gastrointestinal drugs	
17.1 *Antacids and other antiulcer drugs*	
aluminium hydroxide	tablet, 500 mg
	oral suspension, 320 mg/5 ml
□ cimetidine	tablet, 200 mg
	injection, 200 mg in 2-ml ampoule
magnesium hydroxide	oral suspension, equivalent to 550 mg magnesium oxide/10 ml
17.2 *Antiemetic drugs*	
metoclopramide	tablet, 10 mg (hydrochloride)
	injection, 5 mg (hydrochloride)/ml in 2-ml ampoule
□ promethazine	tablet, 10 mg, 25 mg (hydrochloride)
	elixir or syrup, 5 mg (hydrochloride)/5 ml
	injection, 25 mg (hydrochloride)/ml in 2-ml ampoule
17.3 *Antihaemorrhoidal drugs*	
□ local anaesthetic, astringent and anti-inflammatory drug	ointment or suppository
17.4 *Anti-inflammatory drugs*	
hydrocortisone	suppository, 25 mg (acetate)
	retention enema
□ sulfasalazine (2)	tablet, 500 mg
	suppository, 500 mg
	retention enema

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
17. Gastrointestinal drugs (*continued*)	
17.5 ***Antispasmodic drugs***	
□ atropine	tablet, 1 mg (sulfate)
	injection, 1 mg (sulfate) in 1-ml ampoule
17.6 ***Laxatives***	
□ senna	tablet, 7.5 mg (sennosides) (or traditional dosage forms)
17.7 ***Drugs used in diarrhoea***	
17.7.1 Oral rehydration	
oral rehydration salts (for glucose–electrolyte solution	powder, 27.9 g/l
Components	*g/l*
sodium chloride	3.5
trisodium citrate dihydrate[b]	2.9
potassium chloride	1.5
glucose	20.0
17.7.2 Antidiarrhoeal (symptomatic) drugs	
□ codeine (1a)	tablet, 30 mg (phosphate)
18. Hormones, other endocrine drugs and contraceptives	
18.1 ***Adrenal hormones and synthetic substitutes***	
□ dexamethasone	tablet, 500 µg, 4 mg
	injection, 4 mg dexamethasone phosphate (as disodium salt) in 1-ml ampoule
hydrocortisone	powder for injection, 100 mg (as sodium succinate) in vial
□ prednisolone	tablet, 1 mg, 5 mg
Complementary drug	
fludrocortisone (C)	tablet, 100 µg (acetate)

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

[b] 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 only recommended when manufactured for immediate use.

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
18. Hormones, other endocrine drugs and contraceptives (*continued*)	
18.2 *Androgens*	
Complementary drug	
testosterone (C) (2)	injection, 200 mg (enantate) in 1-ml ampoule
18.3 *Contraceptives*	
18.3.1 Hormonal contraceptives	
□ ethinylestradiol + □levonorgestrel	tablet, 30 µg + 150 µg
□ ethinylestradiol + □norethisterone	tablet, 35 µg + 1.0 mg
Complementary drugs	
□ ethinylestradiol + □levonorgestrel (C)	50 µg + 250 µg (pack of four)
□ levonorgestrel (B)	tablet, 30 µg
medroxyprogesterone acetate (B) (7, 8)	depot injection, 150 mg in 1-ml vial
norethisterone enantate (B) (7, 8)	oily solution, 200 mg in 1-ml ampoule
18.3.2 Intrauterine devices	
copper-containing device	
18.3.3 Barrier methods	
condoms with or without spermicide (nonoxinol)	
diaphragms with spermicide (nonoxinol)	
18.4 *Estrogens*	
□ ethinylestradiol	tablet, 10 µg, 50 µg
18.5 *Insulins and other antidiabetic agents*	
□ glibenclamide	tablet, 2.5 mg, 5 mg
insulin injection (soluble)	injection, 40 IU/ml in 10-ml vial, 100 IU/ml in 10-ml vial

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
18. Hormones, other endocrine drugs and contraceptives (*continued*)	
18.5 *Insulins and other antidiabetic agents* (*continued*)	
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)
metformin	tablet, 500 mg (hydrochloride)
18.6 *Ovulation inducers*	
□ clomifene (2, 8)	tablet, 50 mg (citrate)
18.7 *Progestogens*	
norethisterone	tablet, 5 mg
Complementary drug	
medroxyprogesterone acetate (B)	tablet, 5 mg
18.8 *Thyroid hormones and antithyroid drugs*	
levothyroxine	tablet, 50 µg, 100 µg (sodium salt)
potassium iodide	tablet, 60 mg
□ propylthiouracil	tablet, 50 mg
19. Immunologicals	
19.1 *Diagnostic agents*	
tuberculin,[b] purified protein derivative (PPD)	injection
19.2 *Sera and immunoglobulins*[c]	
anti-D immunoglobulin (human)	injection, 250 µg in single-dose vial
antiscorpion sera	injection
□ antitetanus immunoglobulin (human)	injection, 500 IU in vial
antivenom sera	injection

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

[b] All tuberculins should comply with the Requirements for Tuberculins (Revised 1985). *WHO Expert Committee on Biological Standardization. Thirty-sixth report* (WHO Technical Report Series, No. 745, 1987, Annex 1).

[c] All plasma fractions should comply with the Requirements for the Collection, Processing and Quality Control of Blood, Blood Components and Plasma Derivatives (Revised 1992). *WHO Expert Committee on Biological Standardization. Forty-third report* (WHO Technical Report Series, No. 840, 1994, Annex 2).

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
19. Immunologicals (*continued*)	
19.2 *Sera and immunoglobulins*[b] (*continued*)	
diphtheria antitoxin	injection, 10000IU, 20000IU in vial
immunoglobulin, human normal (2)	injection (intramuscular)
immunoglobulin, human normal (2, 8)	injection (intravenous)
□ rabies immunoglobulin	injection, 150IU/ml in vial
19.3 *Vaccines*[c]	
19.3.1 For universal immunization	
BCG vaccine (dried)	injection
diphtheria–pertussis–tetanus vaccine	injection
diphtheria–tetanus vaccine	injection
hepatitis B vaccine	injection
measles–mumps–rubella vaccine	injection

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

[b] See footnote c on page 49.

[c] All vaccines should comply with the following Requirements for Biological Substances, as published in the reports of the WHO Expert Committee on Biological Standardization. Dried BCG vaccine (Revised 1985) (WHO Technical Report Series, No. 745, 1987) and Amendment 1987 (WHO Technical Report Series, No. 771, 1988); Diphtheria, Tetanus, Pertussis and Combined Vaccines (Revised 1989) (WHO Technical Report Series, No. 800, 1990); Measles, Mumps and Rubella Vaccines and Combined Vaccine (Live) (Revised 1992) (WHO Technical Report Series, No. 840, 1994) and Note (WHO Technical Report Series, No. 848, 1994); Poliomyelitis Vaccine (Oral) (Revised 1989) (WHO Technical Report Series, No. 800, 1990); Poliomyelitis Vaccine (Inactivated) (Revised 1981) (WHO Technical Report Series, No. 673, 1982) and Addendum 1985 (WHO Technical Report Series, No. 745, 1987); Hepatitis B Vaccine Prepared from Plasma (Revised 1994) (WHO Technical Report Series, No. 858, 1995); Influenza Vaccine (Inactivated) (Revised 1990) (WHO Technical Report Series, No. 814, 1991); Meningococcal Polysaccharide Vaccine (WHO Technical Report Series, No. 594, 1976) and Addendum 1980, incorporating Addendum 1976 and Addendum 1977 (WHO Technical Report Series, No. 658, 1981); Rabies Vaccine for Human Use (Revised 1980) (WHO Technical Report Series, No. 658, 1981) and Amendment 1992 (WHO Technical Report Series, No. 840, 1994); Rabies Vaccine (Inactivated) for Human Use Produced in Continuous Cell Lines (Revised 1986) (WHO Technical Report Series, No. 760, 1987) and Amendment 1992 (WHO Technical Report Series, No. 840, 1994); Typhoid Vaccine (Live, Attenuated, Ty 21a, Oral) (WHO Technical Report Series, No. 700, 1984); Vi Polysaccharide Typhoid Vaccine (WHO Technical Report Series, No. 840, 1994); Yellow Fever Vaccine (Revised 1995) (WHO Technical Report Series, No. 872, 1998).

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
19. Immunologicals (*continued*)	
19.3 *Vaccines*[b] (*continued*)	
19.3.1 For universal immunization (*continued*)	
measles vaccine	injection
poliomyelitis vaccine (inactivated)	injection
poliomyelitis vaccine (live attenuated)	oral solution
tetanus vaccine	injection
tetanus–diphtheria (Td) vaccine	injection
19.3.2 For specific groups of individuals	
influenza vaccine	injection
meningococcal vaccine	injection
rabies vaccine (inactivated) (prepared in cell culture)	injection
rubella vaccine	injection
typhoid vaccine	injection
yellow fever vaccine	injection
20. Muscle relaxants (peripherally acting) and cholinesterase inhibitors	
□ alcuronium (2)	injection, 5 mg (chloride)/ml in 2-ml ampoule
□ neostigmine	tablet, 15 mg (bromide)
	injection, 500 µg, 2.5 mg (metilsulfate) in 1-ml ampoule
pyridostigmine (2, 8)	tablet, 60 mg (bromide)
	injection, 1 mg (bromide) in 1-ml ampoule
suxamethonium (2)	injection, 50 mg (chloride)/ml in 2-ml ampoule
	powder for injection (chloride), in vial
Complementary drug	
vecuronium (C)	powder for injection, 10 mg (bromide) in vial

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

[b] See footnote c on page 50.

□ Example of a therapeutic group

Drug	*Route of administration, dosage forms and strengths*[a]
21. Ophthalmological preparations	
21.1 *Anti-infective agents*	
□ gentamicin	solution (eye drops), 0.3% (as sulfate)
□ idoxuridine	solution (eye drops), 0.1%
	eye ointment, 0.2%
silver nitrate	solution (eye drops), 1%
□ tetracycline	eye ointment, 1% (hydrochloride)
21.2 *Anti-inflammatory agents*	
□ prednisolone	solution (eye drops), 0.5% (sodium phosphate)
21.3 *Local anaesthetics*	
□ tetracaine	solution (eye drops), 0.5% (hydrochloride)
21.4 *Miotics and antiglaucoma drugs*	
acetazolamide	tablet, 250 mg
□ pilocarpine	solution (eye drops), 2%, 4% (hydrochloride or nitrate)
□ timolol	solution (eye drops), 0.25%, 0.5% (as maleate)
21.5 *Mydriatics*	
atropine	solution (eye drops), 0.1%, 0.5%, 1% (sulfate)
Complementary drug	
epinephrine (A)	solution (eye drops), 2% (as hydrochloride)
22. Oxytocics and antioxytocics	
22.1 *Oxytocics*	
□ ergometrine (1c)	tablet, 200 µg (hydrogen maleate)
	injection, 200 µg (hydrogen maleate) in 1-ml ampoule
oxytocin	injection, 10 IU in 1-ml ampoule

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
22. Oxytocics and antioxytocics (*continued*)	
22.2 ***Antioxytocics***	
□ salbutamol (2)	tablet, 4 mg (as sulfate)
	injection, 50 µg (as sulfate)/ml in 5-ml ampoule
23. Peritoneal dialysis solution	
intraperitoneal dialysis solution (of appropriate composition)	parenteral solution
24. Psychotherapeutic drugs	
24.1 ***Drugs used in psychotic disorders***	
□ chlorpromazine	tablet, 100 mg (hydrochloride)
	syrup, 25 mg (hydrochloride)/5 ml
	injection, 25 mg (hydrochloride)/ml in 2-ml ampoule
□ fluphenazine (5)	injection, 25 mg (decanoate or enantate) in 1-ml ampoule
□ haloperidol	tablet, 2 mg, 5 mg
	injection, 5 mg in 1-ml ampoule
24.2 ***Drugs used in mood disorders***	
24.2.1 Drugs used in depressive disorders	
□ amitriptyline	tablet, 25 mg (hydrochloride)
24.2.2 Drugs used in bipolar disorders	
carbamazepine (10, 11)	scored tablet, 100 mg, 200 mg
lithium carbonate (2, 4)	capsule or tablet, 300 mg
valproic acid (7, 11)	enteric coated tablet, 200 mg, 500 mg (sodium salt)
24.3 ***Drugs used in generalized anxiety and sleep disorders***	
□ diazepam (1b)	scored tablet, 2 mg, 5 mg
24.4 ***Drugs used in obsessive–compulsive disorders and panic attacks***	
clomipramine	capsules, 10 mg, 25 mg (hydrochloride)

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
25. Drugs acting on the respiratory tract	
25.1 *Antiasthmatic drugs*	
□ aminophylline (2)	injection, 25 mg/ml in 10-ml ampoule
□ beclometasone	inhalation (aerosol), 50 µg, 250 µg (dipropionate) per dose
□ epinephrine	injection, 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule
ipratropium bromide	inhalation (aerosol), 20 µg per dose
□ salbutamol	tablet, 2 mg, 4 mg (as sulfate)
	inhalation (aerosol), 100 µg (as sulfate) per dose
	syrup, 2 mg (as sulfate)/5 ml
	injection, 50 µg (as sulfate)/ml in 5-ml ampoule
	respirator solution for use in nebulizers, 5 mg (as sulfate)/ml
theophylline (10, 11)	tablet, 100 mg, 200 mg
Complementary drug	
□ cromoglicic acid (B)	inhalation (aerosol), 20 mg (sodium salt) per dose
25.2 *Antitussives*	
□ dextromethorphan	oral solution, 3.5 mg (bromide)/5 ml
26. Solutions correcting water, electrolyte and acid–base disturbances	
26.1 *Oral*	
oral rehydration salts (for glucose–electrolyte solution)	for composition see section 17.7.1 (p. 47)
potassium chloride	powder for solution
26.2 *Parenteral*	
glucose	injectable solution, 5% isotonic, 50% hypertonic

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
26. Solutions correcting water, electrolyte and acid–base disturbances (*continued*)	
26.2 *Parenteral* (*continued*)	
glucose with sodium chloride	injectable solution, 4% glucose, 0.18% sodium chloride (equivalent to Na^+ 30 mmol/l, Cl^- 30 mmol/l)
potassium chloride (2)	11.2% solution in 20-ml ampoule (equivalent to K^+ 1.5 mmol/ml, Cl^- 1.5 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, HCO_3^- 167 mmol/l)
	8.4% solution in 10-ml ampoule (equivalent to Na^+ 1 mol/l, HCO_3^- 1 mol/l)
□ compound solution of sodium lactate	injectable solution
26.3 *Miscellaneous*	
water for injection	2-ml, 5-ml, 10-ml ampoules
27. Vitamins and minerals	
ascorbic acid	tablet, 50 mg
□ ergocalciferol	capsule or tablet, 1.25 mg (50 000 IU)
	oral solution, 250 µg/ml (10 000 IU/ml)
iodine	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
	capsule, 200 mg
□ nicotinamide	tablet, 50 mg
pyridoxine	tablet, 25 mg (hydrochloride)

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
27. Vitamins and minerals (*continued*)	
□ retinol	sugar-coated tablet, 10000 IU (as palmitate) (5.5 mg)
	capsule, 200000 IU (as palmitate) (110 mg)
	oral oily solution, 100000 IU/ml in multidose dispenser (as palmitate)
	water-miscible injection, 100000 IU (as palmitate) (55 mg) in 2-ml ampoule
riboflavin	tablet, 5 mg
□ sodium fluoride	in any appropriate formulation
thiamine	tablet, 50 mg (hydrochloride)
Complementary drug	
calcium gluconate (C) (2, 8)	injection, 100 mg/ml in 10-ml ampoule

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

□ Example of a therapeutic group.

16. Considerations and changes made in revising the model list

Amendments to the individual entries in the list are detailed below.

Section 1. Anaesthetics

1.2 *Local anaesthetics*

Ephedrine is included as a complementary drug in this section because it is used to prevent hypotension in spinal anaesthesia during delivery.

Section 2. Analgesics, antipyretics, nonsteroidal anti-inflammatory drugs, drugs used to treat gout and disease-modifying agents used in rheumatic disorders

The name of this section is changed.

2.1 *Non-opioid analgesics and nonsteroidal anti-inflammatory drugs*

Allopurinol and colchicine are moved to section 2.3, for drugs used to treat gout.

There are many nonsteroidal anti-inflammatory drugs with a similar action. The Committee considered that the square symbol preceding ibuprofen could cover all these agents provided that both the 200-mg and 400-mg tablet forms are included. The Committee recognized that although ibuprofen caused fewer adverse effects than other nonsteroidal anti-inflammatory drugs, it could not be used for the treatment of all rheumatological diseases. The choice of nonsteroidal anti-inflammatory drugs would be a national decision.

2.2 *Opioid analgesics*

A toxic metabolite of pethidine, norpethidine, accumulates during therapy and can cause central nervous system excitation, including myoclonus and seizures. Morphine or alternative opioid analgesics, including hydromorphone and levorphanol, are preferred when they are available.

Following the recommendation of the Committee at its previous meeting (*3*), endorsed subsequently by the International Narcotics Control Board, an international consensus was established at the United Nations Commission on Narcotic Drugs in 1996 on the application of simplified control measures to permit the use of morphine in emergency situations. On the basis of this consensus, WHO has developed model guidelines on the simplified control procedures (*51*) and distributed them to national drug regulatory authorities.

2.3 *Drugs used to treat gout*

This new section is added to the list. It comprises allopurinol and colchicine.

2.4 *Disease-modifying agents used in rheumatic disorders*

This new section is added to the list. It comprises azathioprine, chloroquine, cyclophosphamide, methotrexate, penicillamine and sulfasalazine, with the number (2), since specific expertise and diagnostic precision are required.

Section 3. Antiallergics and drugs used in anaphylaxis

Chlorphenamine is listed as the prototype for the antihistamine H_1 antagonist class. This class includes drugs with less sedative action than the traditional antihistamines or with different therapeutic potencies. The selection of drugs in this class should be based on the intended therapeutic uses, the adverse reaction profile and the cost.

Section 4. Antidotes and other substances used in poisonings

4.2 *Specific*

Calcium gluconate is added to this section for the specific treatment of magnesium toxicity.

Section 5. Anticonvulsants/antiepileptics

The name of this section is changed.

The number (11) is added to carbamazepine, phenobarbital, phenytoin and valproic acid, to indicate the benefits of monitoring therapeutic drug concentrations.

Magnesium sulfate is moved to the complementary list with the letter (C). A 500mg/ml solution in a 10-ml ampoule is added for intramuscular injection.

The number (7) is added to phenytoin because of its significant adverse effects.

The square symbol preceding clonazepam is to accommodate clobazam, for the treatment of refractory epilepsy.

Section 6. Anti-infective drugs

6.1.1 *Intestinal anthelminthics*

The number (8) is removed from levamisole, since it is recognized to be one of the four first-line anthelminthic agents in many infections.

6.1.2 *Antifilarials*

For diethylcarbamazine, a 100-mg tablet is added.

For ivermectin, a 3-mg tablet is added.

6.1.3 *Antischistosomals and other antitrematode drugs*

The name of this section is changed to accommodate triclabendazole, which is added for the treatment of fascioliasis and paragonimiasis, since it is now registered in Egypt. This drug has been shown to be well tolerated and effective, and is being used in WHO programmes. The Committee noted, however, that the current preparation has so far been used in relatively few patients, although toxicity does not appear to be a problem.

Metrifonate (used for *Schistosoma haematobium*) is deleted from this section, since it is no longer available for the treatment of schistosomiasis and it is no longer used in control programmes because three doses are required at 2-week intervals.

Oxamniquine is transferred to the complementary list with the letter (C) and the number (8).

6.2.1 *β-Lactam drugs*

The name of this section is changed to accommodate cefalosporins.

The prevalence of penicillin-resistant pneumococci has risen in many areas. However, amoxicillin, ampicillin and benzylpenicillin and its repository formulations are still considered essential for the treatment of respiratory tract infections. Oral amoxicillin is preferred to oral ampicillin except in the treatment of shigellosis, for which the latter drug is still recommended.

The number (4) is deleted from amoxicillin and ampicillin, and a 1-g dosage form is added to amoxicillin and cloxacillin.

Restricted indications

Amoxicillin + clavulanic acid is added for the treatment of infections where the organisms are resistant to ampicillin due to β-lactamase. The square symbol is to accommodate other β-lactamase inhibitors, such as sulbactum.

The square symbol preceding ceftriaxone is to indicate that other parenteral cefalosporins may be considered, e.g. cefotaxime may be used for bacterial meningitis. Neither drug is recommended for chemoprophylaxis in surgery, where alternatives such as cefuroxime or cefazolin are more appropriate. The duration of therapy should be kept to a minimum.

Ceftazidime is retained for the treatment of *Pseudomonas* spp. infections resistant to aminoglycosides.

Imipenem + cilastatin is added to this section for the treatment of severe hospital infections with multiresistant *Pseudomonas* spp. and *Acinetobacter* spp.

6.2.2 *Other antibacterials*

For doxycycline, the hyclate salt is replaced by the hydrochloride salt.

The numbers (2) and (7) after gentamicin are retained in order to discourage its indiscriminate use. The number (11) is added. The dosage must always be calculated according to the weight and renal clearance of the patient.

The number (7) is deleted from nitrofurantoin.

Sulfadimidine is replaced by sulfadiazine since this drug has been shown to be more effective for the treatment of toxoplasmosis when used in combination with pyrimethamine. Attention is drawn to the lower solubility of sulfadiazine compared to sulfadimidine and the need to ensure adequate hydration of the patient during its use.

For sulfamethoxazole + trimethoprim, two intravenous preparations are added for those unable to take oral therapy. An intravenous preparation of trimethoprim is added for similar reasons. The Committee again considered the difficulty of obtaining accurate information on the susceptibility of *Streptococcus pneumoniae* to sulfamethoxazole + trimethoprim. It was agreed that this drug remains an essential antibiotic for the treatment of respiratory infections.

Chloramphenicol oily suspension has been found to be helpful in situations of catastrophic epidemics of meningococcal meningitis during which the medical services are overwhelmed by the epidemic. For this reason, this product should be reserved for use in epidemics of meningococcal meningitis when the overwhelming scale of the epidemic precludes any other form of antibiotic therapy.

For clindamycin, a 150-mg capsule is added. The number (8) is added.

6.2.3 *Antileprosy drugs*

For dapsone, a 25-mg tablet is added, since it is used in leprosy programmes for children under 10 years.

6.2.4 *Antituberculosis drugs*

The number (5) is added to the combination products isoniazid + ethambutol, rifampicin + isoniazid and rifampicin + isoniazid + pyrazinamide in the main list and thioacetazone + isoniazid in the complementary list since they improve patient compliance.

It is essential that all combination tablets containing rifampicin are shown to have adequate bioavailability.

6.3 *Antifungal drugs*

Ketoconazole is retained as the prototype for the oral imidazole antifungal agents. Fluconazole and itraconazole have higher efficacy and lower hepatotoxicity than ketoconazole, but are more expensive. Fluconazole is the most effective oral agent for the treatment of cryptococcal meningitis. It is also active against most strains of *Candida* spp. but not *Aspergillus* spp. Itraconazole is primarily used for the treatment of aspergillosis, histoplasmosis and penicillosis in immunocompromised patients. It is also effective for maintenance therapy of cryptococcal infection after treatment with amphotericin B.

6.4 *Antiviral drugs*

This new section is added to the list.

6.4.1 *Antiherpes drugs*

Intravenous and oral preparations of aciclovir are included since they are used in disseminated herpes simplex and disseminated herpes zoster infections in immunocomprised patients and in herpesviral encephalitis. The number (8) is added.

6.4.2 *Antiretroviral drugs*

Zidovudine is included in the list for the prevention of transmission of maternal HIV infection to newborn infants. Monotherapy with zidovudine, except in pregnancy, is now regarded as obsolete, because of the development of resistance. Triple therapy with antiretrovirals is beyond the budgets of most national drug programmes and therefore AIDS treatment policies must be decided at the country or institutional level.

6.5.2 *Antileishmaniasis drugs*

Pentamidine powder for injection, 300mg (isetionate) in vial, is added.

6.5.3 ***Antimalarial drugs***

(a) For curative treatment

For doxycycline, the hyclate salt is replaced by the hydrochloride salt. It should be used only in combination with quinine.

(b) For prophylaxis

Proguanil should be used only in combination with chloroquine.

It should be noted that no antimalarial drug can guarantee 100% protection. Prophylaxis should be restricted to pregnant women, non-immune visitors to endemic areas, and special groups such as labour teams and military teams living in closed communities.

6.5.4 ***Antipneumocystis and antitoxoplasmosis drugs***

In view of the increasing number of immunocompromised patients (e.g. with cancer and AIDS) who are susceptible to infection with opportunistic pathogens, this new section is added for the treatment of *Toxoplasma gondii* and/or *Pneumocystis carinii* infections. Pentamidine, pyrimethamine and sulfamethoxazole + trimethoprim are included.

6.5.5 ***Antitrypanosomal drugs***

(a) African trypanosomiasis

Pentamidine powder for injection, 300mg (isetionate) in vial, is added.

Section 10. Drugs affecting the blood

10.1 ***Antianaemia drugs***

The folic acid content of the ferrous salt + folic acid combination tablets is increased from 250µg to 400µg since evidence has shown that the latter preparation is more effective in meeting the folate requirements of women of childbearing age, thereby reducing the incidence of neural tube defects.

Section 12. Cardiovascular drugs

12.2 ***Antiarrhythmic drugs***

The name of this section is changed. Digoxin is added to the main list with the numbers (4) and (11) to indicate the benefits of monitoring therapeutic drug concentrations.

Epinephrine injection, 1mg/ml, is added to the complementary list.

12.3 *Antihypertensive drugs*

Methyldopa is transferred to the main list. It refers to the L-isomer only.

There was prolonged discussion on the inclusion of nifedipine, 10-mg tablets, in the light of the recently published cardiac mortality data on long-term use of short-acting nifedipine for hypertension control. The 10-mg tablet is retained since it is effective in specific circumstances. Nifedipine sustained-release formulations are added with a square symbol to indicate that the choice of long-acting calcium-channel blocker is for the national drug and therapeutics committee. The 10-mg capsule is deleted.

Reserpine is transferred to the main list, since it is recognized as an inexpensive alternative for the treatment of hypertension.

Doxazosin and sodium nitroprusside are retained in the complementary list. The Committee recognized that doxazosin is also of value for the treatment of prostatic hypertrophy. A square symbol is added to indicate that the choice of α-adrenergic blocking agent is for the national drug and therapeutics committee.

12.4 *Drugs used in heart failure*

The title of this section is changed. It now contains all drugs useful in the treatment of heart failure, including captopril, digoxin, dopamine and hydrochlorothiazide.

Captopril remains as the prototype inhibitor of angiotensin-converting enzyme since it was not felt that any of the newer inhibitors of angiotensin-converting enzyme showed significant clinical advantages over this drug.

The number (11) is added to digoxin to indicate the benefits of monitoring therapeutic drug concentrations.

Digitoxin is deleted from the complementary list.

12.6 *Lipid-lowering agents*

This new section is added because the Committee recognizes the value of lipid-lowering drugs in treating patients with hyperlipidaemia (see page 43). The choice of drug is for the national drug and therapeutics committee.

Section 13. Dermatological drugs (topical)

13.2 *Anti-infective drugs*

Antibiotic preparations are widely used for skin infections, but raise problems related to toxicity and antimicrobial resistance. Neomycin +

bacitracin is retained in the main list but it is recognized that other antibiotics such as fusidic acid are also used as alternatives.

Neomycin is deleted from this section.

13.5 *Drugs affecting skin differentiation and proliferation*

The title of this section is changed.

13.6 *Scabicides and pediculicides*

A square symbol is added to benzyl benzoate to accommodate precipitated sulfur.

13.7 *Ultraviolet-blocking agents*

The benzophenones and zinc oxide in the complementary list are replaced by a broad-spectrum topical sun protection agent with activity against ultraviolet A and ultraviolet B. The agent consists of 3% octyl methoxycinnamate, 2% titanium dioxide and 2% butyl methoxydibenzoylmethane formulated in an arylate polymer or an oily base.

Section 15. Disinfectants and antiseptics

15.1 *Antiseptics*

Hydrogen peroxide is deleted from the list because of the tissue-damaging effects and delay in healing of lesions treated with this drug.

15.2 *Disinfectants*

Chlorine base compound, powder for solution, replaces calcium hypochlorite powder since it is more stable and practical, giving very satisfactory levels of chlorine, i.e. 0.1% of available chlorine. The square symbol preceding the drug is retained to indicate that various formulations can be used.

Chloroxylenol replaces the phenolic disinfectants. A square symbol is added to accommodate other phenolic disinfectants.

Section 16. Diuretics

Spironolactone is transferred to the main list with the number (8).

The square symbol preceding mannitol is retained to indicate that sorbitol could serve as an alternative.

Section 17. Gastrointestinal drugs

17.1 *Antacids and other antiulcer drugs*

The Committee recognizes the need to treat *Helicobacter pylori* infection. The drugs already on the list are considered to be adequate.

17.4 ***Anti-inflammatory drugs***

The square symbol preceding sulfasalazine is to accommodate mesalazine, for the treatment of patients who are allergic to sulfonamides. Retention enema formulations of sulfasalazine and hydrocortisone are added. For sulfasalazine, a 500-mg suppository is also added.

17.6 ***Laxatives***

The name of this section is changed.

Section 18. Hormones, other endocrine drugs and contraceptives

18.3.1 ***Hormonal contraceptives***

For ethinylestradiol + levonorgestrel, the 30-μg + 250-μg tablet is deleted since it is no longer widely available.

The letter (B) is added to levonorgestrel in the complementary list.

18.4 ***Estrogens***

The square symbol preceding ethinylestradiol is retained since conjugated estrogens may be more beneficial for hormone replacement therapy.

18.5 ***Insulins and other antidiabetic agents***

The 80 IU/ml soluble and intermediate-acting formulations of insulin are deleted since they are no longer used and standardization of the dosage of insulin is recommended.

Glibenclamide with a square symbol replaces tolbutamide as it is recognized to be more suitable as the prototype drug.

Metformin is added to this section to complete the range of oral antidiabetic drugs necessary in the management of diabetes.

Section 21. Ophthalmological preparations

21.1 ***Anti-infective agents***

The Committee was informed that clinical trials were being conducted by the WHO Alliance for Global Elimination of Trachoma to evaluate the efficacy of a single dose of systemic azithromycin for the treatment of trachoma. As no results are as yet available, however, tetracycline is retained as the drug of choice.

Section 24. Psychotherapeutic drugs

24.1 ***Drugs used in psychotic disorders***

The square symbol preceding chlorpromazine is retained to accommodate any non-depot phenothiazine preparation and that preceding

fluphenazine is retained to accommodate any neuroleptic depot preparation.

The square symbol preceding haloperidol is retained to indicate that any non-phenothiazine, non-depot preparation can be used in its place.

24.2 *Drugs used in mood disorders*

This section is now divided into two subsections.

24.2.1 *Drugs used in depressive disorders*

This new section comprises amitriptyline.

24.2.2 *Drugs used in bipolar disorders*

This new section comprises carbamazepine, lithium carbonate and valproic acid. The number (11) after carbamazepine and valproic acid is to indicate the benefits of monitoring therapeutic drug concentrations.

24.3 *Drugs used in generalized anxiety and sleep disorders*

The name of this section is changed.

Selective serotonin reuptake inhibitors

The Committee considered the selective serotonin reuptake inhibitors paroxetine and fluoxetine, but decided not to include them in the list at this time because of their extremely high cost, although they are associated with fewer side-effects than tricyclic antidepressants. The Committee also considered risperidone, but decided not to include it in the list since it is very expensive and has no significant advantages over haloperidol.

Section 25. Drugs acting on the respiratory tract

25.1 *Antiasthmatic drugs*

For beclometasone, a 250-μg formulation for inhalation is added.

Ipratropium bromide aerosol (for inhalation) is added.

The number (11) is added to theophylline to indicate the benefits of monitoring therapeutic drug concentrations.

25.2 *Antitussives*

Dextromethorphan, oral solution, replaces codeine since it is more widely available and less likely to lead to drug abuse.

17. Glossary of terms used in the report

In the course of its work, the Expert Committee used certain terms with the meanings given below:

Benefit/risk ratio	The ratio of benefit to risk in the use of a drug; a means of expressing a judgement concerning the role of the drug in the practice of medicine, based on efficacy and safety data along with consideration of misuse potential, severity and prognosis of the disease, etc. The concept may be applied to a single drug or in comparisons between two or more drugs used for the same condition.
Bioavailability	The rate and extent of absorption of a drug from a dosage form as determined by its concentration/time curve in the systemic circulation or by its excretion in urine.
Compliance	Faithful adherence by the patient to the prescriber's instructions.
Dosage form	The form of the completed pharmaceutical product, e.g. tablet, capsule, elixir, suppository.
Drug	Any substance in a pharmaceutical product that is used to modify or explore physiological systems or pathological states for the benefit of the recipient.
Drug formulation	The composition of a dosage form, including the characteristics of its raw materials and the operations required to process it.
Drug utilization	The marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences.
Efficacy	The ability of a drug to produce the purported effect as determined by scientific methods.
Excipient	Any component of a finished dosage form other than the claimed therapeutic ingredient or ingredients.

Pharmaceutical product	Synonymous with dosage form.
Pharmacokinetics	The study of the rate of drug action, particularly with respect to: — the variation of drug concentrations in tissues with time, and — the absorption, distribution, metabolism and excretion of drugs and metabolites.

18. Alphabetical list of essential drugs

Acknowledgement

The Committee wishes to record its appreciation of the contribution made by Dr J. Quick, Action Programme on Essential Drugs, WHO, Geneva, Switzerland.

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Annex 1

Application form for inclusion in the Model List of Essential Drugs[1]

Submitted by:

Name of responsible officer:

Address:

Contact person (if submitted by an organization):

Telephone No.: Fax No.:

We hereby request the World Health Organization to consider the following pharmaceutical product for inclusion in the WHO Model List of Essential Drugs

Signature _____ *Date* _____

Name of drug (INN and trade name):

Dosage form and strength:

Why is this drug being proposed for inclusion in the list?

Please state how it conforms to the criteria for inclusion as an essential drug:

Please provide evidence of efficacy (with references):

If a therapeutic class for this drug already exists in the list, please summarize the advantages of this product:

Describe the drug's pharmacokinetics:

List any contraindications, precautions and toxic effects:

Is this drug available as a generic product?

Please state any restrictions on the use of this drug. Should a note be included in the list regarding its use?

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[1] A summary (maximum 3 pages) of relevant background information should be attached, together with relevant literature to support the therapeutic use.