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(including the 13 Model List of Essential Medicines)

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Geneva, 31 March–3 April 2003

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The World Health Organization was established in 1948 as a specialized agency of the United Nations serving as the directing and coordinating authority for international health matters and public health. One of WHO's constitutional functions is to provide objective and reliable information and advice in the field of human health, a responsibility that it fulfils in part through its extensive programme of publications.

The Organization seeks through its publications to support national health strategies and address the most pressing public health concerns of populations around the world. To respond to the needs of Member States at all levels of development, WHO publishes practical manuals, handbooks and training material for specific categories of health workers; internationally applicable guidelines and standards; reviews and analyses of health policies, programmes and research; and state-of-the-art consensus reports that offer technical advice and recommendations for decision-makers. These books are closely tied to the Organization's priority activities, encompassing disease prevention and control, the development of equitable health systems based on primary health care, and health promotion for individuals and communities. Progress towards better health for all also demands the global dissemination and exchange of information that draws on the knowledge and experience of all WHO's Member countries and the collaboration of world leaders in public health and the biomedical sciences.

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1. Introduction

The WHO Expert Committee on the Selection and Use of Essential Medicines met in Geneva from 31 March to 3 April 2003. The meeting was opened on behalf of the Director-General by Dr J.D. Quick, Director, Department of Essential Drugs and Medicines Policy, WHO, who expressed appreciation for the rapid dissemination during 2002 of the report of the previous meeting and the first edition of the *WHO model formulary* (*1*). In referring to the recent twenty-fifth anniversary of the essential medicines concept, Dr Quick stressed that despite widespread acceptance of the global relevance of the concept, many challenges still remain, especially with regard to ensuring equitable access to essential medicines.

The WHO Secretariat requested and received agreement from the Committee to hold an open session as part of its meeting (see section 2). The purpose of the open session is to allow all stakeholders to participate in the discussions and to comment on issues relating to the WHO Model List of Essential Medicines (the Model List). Furthermore, for Expert Committee members it provides an opportunity to receive, at first-hand, additional information and opinions on matters under consideration. Participants were assured that the discussions and considerations of the open session would be reflected in the report of the meeting. A summary of the Committee's meeting report would be submitted to the WHO Executive Board in January 2004, together with a statement on the public health implications of its recommendations.

The Committee decided to maintain the reporting format adopted at its previous meeting whereby the updated version of the Model List, including explanatory notes and supporting background information relating to the use and development of the Model List, is presented as an annex to the meeting report (Annex 1). Similarly, a list of items on the Model List ordered by their corresponding Anatomical Therapeutic Chemical (ATC) classification code number(s) is again attached as annex (Annex 2).

2. Open session

The session was opened by Dr A. Asamoa-Baah, Executive Director, Health Technology and Pharmaceuticals, WHO, who informed participants that WHO is justly proud of the success of the essential medicines concept, as evidenced by its recent twenty-fifth anniversary. He stressed that careful selection of essential medicines for the

Model List remains at the heart of the programme, given that the Model List provides not only the moral basis for national drug policies but also a technical basis for the procurement, quality assurance and promotion of the rational use of medicines. The future success of the essential medicines programme depends on the credibility of the work of its Expert Committee, which, in turn, depends very much on the implementation of the new procedures for updating and disseminating the Model List, outlined at the previous meeting of the Committee (*2*). Dr Asamoa-Baah reminded participants that all comments made during the open session would be noted and taken into account by the Committee when formulating their final recommendations in subsequent private sessions.

As part of the open session, participants were briefed about various activities relating to the Model List (see section 3). Presentations outlining the simplified or "fast-track" deletion procedure adopted for selected items on the Model List (see section 5.1) and the results of various review exercises that had been undertaken since the previous meeting — including a review of the definition of "core" and "complementary" list medicines (see section 5.2) and a review of the use of the square box symbol (see section 5.3) — were also made. Comments made during the open session on these matters were noted and are reported under the appropriate sections of the meeting report.

A number of issues not on the agenda were raised and debated during the open session. The International Federation of Pharmaceutical Manufacturing Associations (IFPMA) made a statement of concern about the lack of transparency in the Committee's decision-making process, which it felt was, in part, related to the way in which members of the Committee are selected. It was suggested that potential conflicts of interest should be publicized and applied to all members of the Committee, including special advisors. The breadth of expertise should also be expanded. It was also suggested that technical advice from industry had not been effectively sought during the preparation period for the present meeting and thus industry's expertise had effectively been excluded from the Committee's deliberations. The IFPMA welcomed WHO's efforts to promote the provision of quality drugs through its new pre-qualification system, but cautioned against the promotion of untested fixed-dose regimens, for example, selected combinations of antiretroviral medicines that may actually harm some patients.

A representative of the United States Mission expressed satisfaction with the principle of the open session, and requested that it be estab-

lished as a permanent part of the procedure. He also stressed the need for the Committee to have permanent access to expertise in drug regulation and quality assurance.

In the ensuing discussion, the Committee cited the case of tuberculosis, where the advice of WHO had led to full standardization in the dosage of fixed-dose combination medicines, now followed by most manufacturers; it is anticipated that the WHO clinical guidelines for the treatment of HIV/AIDS with antiretroviral therapy will serve the same purpose. The Committee commented on the lack of technical contributions from pharmaceutical companies despite having posted information about the formal applications for changes to the Model List, together with details of relevant systematic reviews, on the WHO web site well in advance of the meeting. Finally, with regard to the matter of potential conflicts of interest by members of the Committee, the Secretary explained the standard procedure for declarations of interest, which is rigorously applied. Dr Asamoa-Baah added that the credibility of the Committee is, to a large extent, derived from the scientific basis and transparency of its recommendations.

3. Update on current activities

3.1 Dissemination of the previous report of the Expert Committee (including the 12th Model List)

Following approval by its members on Friday 19 April 2002, the report of the meeting of Expert Committee was approved for publication by the Director-General and posted on the WHO web site on Monday 22 April, just ten working hours after the meeting had closed. The rapid dissemination of the meeting report, together with the revised version of Model List and the summary of recommendations was widely appreciated, especially in view of the important recommendations the Committee had made on the selection of essential medicines for the treatment of HIV/AIDS and malaria.

Within weeks of the meeting, the 12th Model List (including the introductory text and explanatory notes) had been translated into Arabic, Chinese, French, Russian and Spanish and posted on the WHO web site. These web pages in the six official languages of WHO were also disseminated in large numbers as hard copy. During the remainder of 2002, the full report was edited for formal publication in the WHO Technical Report Series. However, the amount of work involved in separating the Model List into core and complementary lists and introducing the ATC classification for all items on the Model List meant that the meeting report was not published in final form

until early 2003. In January 2003, a summary of the Committee's report and a statement on its public health implications were submitted to the WHO Executive Board. The 12th Model List was also incorporated into the WHO Essential Medicines Library (see section 3.7).

It was noted that changes in the name of the Expert Committee since its inception in 1977 had given rise to some confusion over the numbering of the various Committees and their corresponding meeting reports. For the sake of clarity, it was decided that the practice of numbering the meetings of the Committee should be abandoned in favour of referring simply to the number of the Model List.

3.2 The twenty-fifth anniversary of the WHO Model List of Essential Medicines

On 21 October 2002, exactly 25 years since the first Expert Committee approved the first WHO Model List of Essential Drugs (*3*), a technical seminar was held in Geneva to celebrate the achievements of the global application of the concept of essential medicines. Regional anniversary seminars were held on the same day in Cambodia and Brazil. The text of the presentations given at these events, including an important speech by the Director-General, is available on CD-ROM (*4*); alternatively these can be accessed through the Internet at the WHO web site[1].

3.3 The *WHO model formulary*

In order to make the *WHO model formulary* compatible with the Model List, entries for the antiretroviral medicines and the other additions to the 12th Model List were prepared immediately after the 2002 meeting of the Expert Committee in time for the release of the first edition of the *WHO model formulary* at the Annual Congress of the International Pharmaceutical Federation held in Nice, France, in September 2002. The publication was generally very well received. All 7000 printed copies were rapidly disseminated, either by free distribution or through commercial channels, necessitating a second printing in November 2002. A searchable version can be accessed via the WHO web site[1] and a CD-ROM version, for use by national and institutional committees, is nearing completion (*5*). Agreement has been reached with the Royal Pharmaceutical Society of Great Britain for editing and printing future editions of the *WHO model formulary*.

[1] http://www.who.int/medicines.

3.4 Review of the New Emergency Health Kit

All of the 55 essential medicines that are listed in the New Emergency Health Kit (*6*) are included in the list of 88 medicines recommended for emergency relief by the United Nations (*7*), all of which, in turn, are on the Model List. Following consultation with the partners involved in its development, it was decided that the New Emergency Health Kit is in need of updating, especially with regard to the antimalarial medicines, emergency contraception and injection materials. A review meeting will be convened by WHO in Spring 2004 to address these issues.

3.5 Review of essential medicines for reproductive health

It was noted that a draft interagency list of essential medicines for reproductive health and a Core List of Essential Medicines for Reproductive Health drawn up by the United Nations Population Fund (UNFPA) are not fully consistent with the Model List. For instance, 22 items on the draft interagency list and 6 medicines on the UNFPA list do not appear on the Model List. Work is under way to analyse these discrepancies; the analysis will take into account the relevant clinical guidelines and the evidence that supports the selection of items on the other two lists. This information will be used to streamline the three different lists and will become part of the WHO Essential Medicines Library.

3.6 Report of an ad hoc Advisory Committee on priority vaccines

The Committee was informed of the work of an ad hoc Advisory Committee on priority vaccines convened as a result of a recommendation made by the Strategic Advisory Group of Experts (SAGE) in 2002 to "establish an expert advisory committee with worldwide representation to develop a mechanism for prioritisation of vaccines for a model essential vaccine list for immunisation programmes".

The Advisory Committee recommended the establishment of national lists of essential vaccines and suggested that the construction of such lists would be facilitated by the creation of a Global Model List of Essential Vaccines as well as an evidence-based library of essential vaccines. In addition, the Advisory Committee considered that, as there are fundamental differences between medicines and vaccines, an evidence-based Global Model List of Essential Vaccines should be separate from the Model List of Essential Medicines. It was also proposed that, once a list of essential vaccines had been established, vaccines should be taken off the Model List, although the two lists should refer to each other. Whereas the traditional children's vaccines

would be included in the new list automatically, all other vaccines should be subjected to evaluation by an Expert Committee before inclusion. It was anticipated that a procedure similar to that used for updating the Model List of Essential Medicines could be followed.

The Advisory Committee also considered that while the creation of a Global Model List of Essential Vaccines would be of great value, the emphasis should remain on the development of national and/or regional lists based on the information provided in an essential vaccines library. The Advisory Committee therefore recommended that criteria for prioritizing vaccines for inclusion in national lists be developed. A draft list of such criteria has been prepared, and will be subjected to external review and tested before use. The recommendations of the Advisory Committee will be presented to SAGE in July 2003.

3.7 The WHO Essential Medicines Library

Work on the WHO Essential Medicines Library is continuing. In its current format, it contains searchable versions of the 12th Model List and the *WHO model formulary*, and links to the Management Services for Health (MSH) International Drug Price Indicator Guide and the web site of the WHO Collaborating Centre on Drug Statistics Methodology, Oslo, Norway. A central "Medicine link page" (giving the International Nonproprietary Name (INN), dosage(s), ATC classification code number(s) and justification for inclusion) has been prepared for each item in the Model List and links to key indications, disease summaries, systematic reviews and WHO clinical guidelines. These will supplement the links to the Model List, the *WHO model formulary* and the INN web site, and to external web sites such as that containing details of the ATC classification system. It is expected that the developmental version will be available for public access during the course of 2003.

3.8 Promoting rational use of essential medicines

3.8.1 *Update on activities to contain antimicrobial resistance*

Antimicrobial resistance occurs when a strain of a micro-organism is able to multiply in the presence of antimicrobial medicine concentrations that are higher than in the concentrations in humans receiving therapeutic doses. The development of resistance is a natural biological phenomenon and has followed the introduction into clinical practice of every antimicrobial agent. Increases in antimicrobial use have been associated with increases in rates of resistance, so much so that irrational overuse of antimicrobials is generally assumed to be a major

contributing factor to the escalating global problem of antimicrobial resistance. Currently, antimicrobials are being overused in all world regions and at all levels of the health care system, in amounts that are perhaps as much as double those that are clinically indicated. Resistance rates vary locally depending upon local antimicrobial use.

The World Health Assembly has recognized antimicrobial resistance as a serious public health problem and in 1998, with resolution WHA51.17, urged Member States to develop measures to encourage appropriate and cost-effective use of antimicrobials (*8*). Nevertheless, the problem of antimicrobial resistance, including multidrug resistance, has since continued to grow while the rate at which new antimicrobials are introduced has decreased. WHO's Global Strategy for the containment of Antimicrobial Resistance addressed this challenge by providing a framework of interventions aimed at slowing the emergence and reducing the spread of antimicrobial resistant microorganisms (*9*). More than 60 interventions were identified and prioritized on the basis of invited expert opinion and peer review. An adequately funded multi-sectoral task force and reference laboratory for conducting surveillance of both antimicrobial resistance and use were, however, considered fundamental to any national containment programme.

The interventions that were deemed to be the most important are:

— patient education on preventing infection (e.g. immunization, use of bednets) and reducing transmission (e.g. hand washing, food hygiene);
— education on antimicrobial use, antimicrobial resistance containment, disease prevention and infection control;
— targeted undergraduate and postgraduate education for all health workers and veterinary practitioners on accurate diagnosis and management of common infections;
— development, updating and use of clinical guidelines and treatment algorithms;
— establishment of infection control programmes in hospitals;
— good quality diagnostic laboratories;
— limitation of availability of antimicrobials to prescription-only;
— granting marketing authorization only to antimicrobials which meet international standards of quality, safety and efficacy.

Very few countries currently have national antimicrobial resistance containment programmes in place. Furthermore, many countries do not base their choice of antimicrobials for an essential medicines list or standard treatment guidelines on epidemiologically sound antimicrobial resistance data, even though this has been shown to be

crucial to ensuring best patient outcome and efficient use of antimicrobials. Nevertheless, reductions in antimicrobial resistance have been observed in a few countries that have succeeded in significantly reducing antimicrobial consumption and improving infection control.

Containing antimicrobial resistance and ensuring that patients are treated with the most effective antimicrobial requires the linked surveillance of antimicrobial resistance and consumption. WHO is currently supporting pilot projects to develop a new model and methodology for the linked surveillance of antimicrobial resistance and consumption and the local containment of antimicrobial resistance in developing countries. However, much more political and financial commitment will be necessary in the future.

3.8.2 *Guidelines for drugs and therapeutic committees*

Drugs and therapeutics committees (DTCs) — sometimes called pharmacy and therapeutics committees — are designated to ensure the safe and effective use of medicines in the facility or area under their jurisdiction. Such committees are well established in most industrialized countries as a successful way of promoting a more rational, cost-effective use of medicines in hospitals. WHO promotes the establishment of DTCs through its international training courses (which are run in collaboration with MSH), the preparation of a manual on DTCs and various other research projects.

The main responsibilities of a DTC are:

— developing, adapting or adopting clinical guidelines for the health institution or health facilities under its jurisdiction;
— selecting cost-effective and safe medicines (hospital/health facilities' drug formulary);
— implementing and evaluating strategies to improve medicine use (including drug use evaluations, and liaison with antibiotic and infection control committees);
— providing ongoing staff education (training and printed materials);
— controlling access to staff by the pharmaceutical industry and its promotional activities;
— monitoring and taking action to prevent adverse drug reactions and medication errors;
— providing advice about other drug management issues, such as quality and expenditure.

Governments should encourage all hospitals to set up a DTC (e.g. by making it an accreditation requirement to various professional societies) with a membership that represents all the major specialities and

the administration. DTC members should be independent and declare any conflict of interest. A senior doctor would usually be the chairperson and the chief pharmacist, the secretary. Factors critical to success include: clear objectives, a firm mandate, support from the senior hospital management, transparency, wide representation, technical competence, a multidisciplinary approach and sufficient resources to implement the DTC's decisions.

The WHO manual on establishing and running a DTC will be issued in 2003 (*10*); international 2-week training courses are ongoing in Asia and Africa.

3.8.3 *WHO database on rational drug use studies*

In 1985, WHO defined rational use of medicines as requiring that "patients receive medications appropriate to their clinical needs, in doses that meet their own requirements, for an adequate period of time, and at the lowest cost to them and their community" (*11*). Since then, the International Network for the Rational Use of Drugs (INRUD) has been formed and much work has been undertaken by WHO, INRUD and other organizations in order to develop and use indicators for monitoring medicine use and to initiate intervention studies to promote rational use.

The impact of these efforts is, however, not very well known. WHO is currently developing a database on the rational use of medicines, the main objective of which is to provide a general overview of existing drug use patterns in primary health care settings in developing countries over time, and to study the impact of different types of interventions on improving the use of medicines. This type of information is vital for developing a global multifaceted strategy for the promotion of rational use of medicines and for assisting regions and countries seeking to prioritize their own activities in this area.

Work has already started on identifying relevant published and unpublished studies from both INRUD and WHO sources, and entering the pertinent data (e.g. prescriber and facility type, disease pattern, methodology, outcome indicators) into the database. The data will be analysed by country and region, and over time (1990–2003), and then used to assess the impact of different kinds of interventions to promote the rational use of medicines. The database has been designed so as to be compatible with other WHO databases; this will allow future analysis of the impact of health systems and policies on the rational use of medicines.

At the time of the present meeting, 1160 articles from the INRUD bibliography covering the period 1997–2001 had been screened, and

from these, 92 data records extracted and entered into the database. A preliminary analysis of the data will be presented at the International Conference on Improving Use of Medicines (ICIUM) in 2004 and is intended as an advocacy tool for promoting rational use of medicines in the developing world. Future work includes entering data for earlier years and a systematic analysis of the full data set. There are also plans to expand the scope of the database to include such information as hospital-based drug use, self-medication, patients' adherence to treatment and diagnostic accuracy. The database will be made available to interested researchers and policy makers through the Internet.

4. Changes made in revising the Model List

Proposals for amendments to the Model List, including applications for additions and deletions, received by the Committee for consideration at its present meeting are summarized below.

4.1 Applications for additions

4.1.1 *Amodiaquine*

The Committee reviewed the re-application for the inclusion of amodiaquine, an antimalarial, having deferred a decision regarding this medicine at its previous meeting (*2*). Amodiaquine has been on the Model List since 1977 (*3*), was removed in 1979 (*12*), reinstated in 1982 (*13*) and removed again in 1988 (*14*) in view of safety concerns in prophylactic use. In 2002, the Committee reviewed an application for its inclusion for therapeutic use. At that time, the Committee concluded that as amodiaquine had been removed twice for safety reasons, a careful review of the safety information was needed before any decision about its future inclusion could be taken. The Committee had also noted with concern the results of a trial of amodiaquine in children that appeared to show a high rate of neutropenia (*2*).

The Committee noted the information supplied with the re-application, which included a systematic review of adverse events (prepared by the Cochrane Infectious Diseases Group) and a review of the effects of amodiaquine treatment on white blood cell and neutrophil counts (presented by Roll Back Malaria, WHO). The Committee agreed that antimalarial drug treatment with amodiaquine (either alone or in combination with sulfadoxine + pyrimethamine or artesunate), chloroquine and sulfadoxine + pyrimethamine may be associated with a decline in the total white cell

and neutrophil counts. Although both counts remained within the normal range in the majority of cases, a small proportion of patients were found to have developed neutropenia when assessed during follow-up. The clinical significance of this finding is, however, unknown. Other publications reviewed by the Committee suggest that peripheral neutropenia is a part of the natural course of malaria itself (*15*, *16*).

The Committee concluded that the above findings generally support the conclusions of the systematic review of adverse events submitted by the Cochrane Infectious Diseases Group namely that, relative to other commonly used antimalarial drugs, therapeutic use of amodiaquine does not appear to be associated with an increased risk of neutropenia. The Committee therefore recommended that amodiaquine (as tablets, 153 mg, 200 mg (base)) be added to the Model List as a core list medicine, with the following footnote:

> Amodiaquine should preferably be used as part of combination therapy.

and that the following text be added at the beginning of the relevant section of the Model List, i.e. section 6.5.3(a):

> Medicines for the treatment of *P. falciparum* malaria cases should be used in combination.

The Committee also recommended that amodiquine's place in curative treatment be further defined by WHO guidelines and expressed an interest in reviewing the results of more clinical trials on the comparative efficacy and safety of fixed-dose combinations in the treatment of malaria.

4.1.2 *Azithromycin*

The Committee reviewed two applications for the addition of azithromycin to the Model List. One application was submitted by Médecins sans Frontières (MSF), Brussels, Belgium, for inclusion as an individual core list medicine for the treatment of chlamydial infection and trachoma; the second application was made by the Department of Reproductive Health and Research, WHO, for inclusion as an individual core list medicine for the treatment of genital chlamydia. The MSF application was reviewed and supported by the Department of Reproductive Health and Research, WHO.

The Committee noted that azithromycin, a macrolide antibiotic, has antimicrobial activity against a wide variety of microbes. Its effectiveness against *Chlamydia trachomatis* genital infection with a single dose has been demonstrated in studies cited in the applications. Cited studies also show that azithromycin is safe for use in both growing

adolescents and in pregnancy, both contraindications for tetracycline, the main alternative. The Committee acknowledged that the safety of this medicine in these sectors of the population, combined with the advantages offered by a single-dose curative regimen, support the selection of azithromycin for the treatment of this particular disease.

The MSF application also cited studies that indicate that oral azithromycin is as effective in treating trachoma as antibiotic ointments. The Committee recognized the advantage of a single oral dose treatment of an infection, especially when it is directly observed, over a prolonged course of prescribed medication.

The Committee thus recommended that azithromycin (as capsules, 250 mg, 500 mg and as a oral suspension, 200 mg/5 ml) be added to the Model List as a core list medicine (in section 6.2.2), for the single dose treatment of genital *C. trachomatis* infection and of trachoma only. This recommendation was made in view of the effectiveness and safety of azithromycin as documented in the applications, and because of its ease of use relative to the principal alternatives (i.e. doxycycline twice daily for a week, or tetracycline ophthalmic ointment for 6 weeks). The Committee recommended that the entry be annotated with the following footnote:

> Only listed for single dose treatment of genital *C. trachomatis* and of trachoma.

4.1.3 *Ibuprofen (paediatric formulation)*

The Committee reviewed an application submitted by Boots Healthcare International, Nottingham, England, for the inclusion of a paediatric formulation of ibuprofen in the Model List[1]. Comments on the application were received from the Department of Child and Adolescent Health, WHO, the United Nations Children's Fund (UNICEF) and the Cochrane Pain Research Group, Oxford, England.

The Committee noted that the application proposes the use of ibuprofen suspension and suppositories in children younger than 12 years and makes reference to evidence relating to the antipyretic effect of ibuprofen. Ibuprofen is used in the management of mild to moderate pain and inflammation; the latter property is, however, generally considered to be the weaker of the two. In its assessment of the application, the Committee paid particular attention to evidence on the efficacy and effectiveness of ibuprofen as an antipyretic agent.

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[1] Details of the full application (including comments received) are available via the Internet from the WHO web site (http://www.who.int/medicines).

The Committee agreed that the application was incomplete in that important information regarding efficacy, safety and cost of ibuprofen in relation to its antipyretic effect was missing. In the opinion of the Committee, the application did not constitute a systematic review; confounding variables such as age, bacterial infection, positive culture and antimicrobial therapy prior to taking the antipyretic were not always taken into account.

The Committee considered that there was insufficient evidence to conclude that ibuprofen provides a superior antipyretic effect to paracetamol. Data on the comparative safety and cost-effectiveness of ibuprofen and paracetamol were also lacking. On these grounds, the Committee recommended that the application for the addition of a pediatric form of ibuprofen be rejected, although it would consider a re-application provided it was submitted in the required format and supplied the missing information as mentioned above.

In considering the use of paracetamol in adults, the Committee recommended the addition of the following footnote to the entry for paracetamol in section 2.1 (Non-opioid analgesics and antipyretics and non-steroidal anti-inflammatory medicines) of the Model List:

> Not recommended for anti-inflammatory use due to lack of proven benefit to that effect.

4.1.4 *Insulin semilente*

The Committee reviewed an application submitted by the Patient Association for the Preservation of Natural Animal Insulin Switzerland, Bern, Switzerland, the Insulin Forum Switzerland, Bern, Switzerland, the Insulin Dependent Diabetes Trust International, Northampton, England, and the Swiss Tropical Institute, Swiss Centre for International Health, Basel, Switzerland, for the inclusion of intermediate amorphous (100%) porcine insulin suspension (insulin "semilente"). Comments on the application were received from The Diabetes Programme, Division of Noncommunicable Diseases and Mental Health, WHO.

The Committee noted that the Model List currently includes an intermediate-acting and a short-acting (soluble) insulin, but that neither the origin (i.e. human or animal) nor the type (i.e. zinc suspension or isophane insulin) are specified. Arguments for the inclusion of the intermediate-acting "semilente" form were summarized as follows:

— it has more favourable pharmacokinetic properties than other intermediate-acting insulins and the incidence of both nocturnal hypoglycaemia and early morning hyperglycaemia is lower;

— it is the only prompt intermediate-acting insulin with added zinc ions and not bound to fish protamine;
— human insulins were introduced without any proof of superiority over animal insulins;
— some patients present loss of hypoglycaemia warning symptoms after transfer to human insulin;
— animal insulins are cheaper than the corresponding human insulins.

The Committee agreed that a number of points regarding the introduction of human insulins merit attention:

— human insulins were introduced without any proof that they are less immunogenic than animal insulins;
— the number of patients participating in randomized trials has been limited (2156 in the recent Cochrane Review (*17*)) and the mean duration of such trials short (5.8 months);
— the frequency of insulin resistance has not been assessed.

Furthermore, the transfer to human insulins has been associated with a higher risk of severe hypoglycaemia in some studies; however, this finding is not universal. According to the Cochrane Review, the frequency of hypoglycaemic episodes is similar with both types of insulins (*17*).

In the light of the conclusion of the 2003 Cochrane Review, namely that there are no clinically relevant differences between animal and human insulins (*17*), the Committee concluded that the choice between the two types of insulin should be made on the basis of cost. Noting that intermediate-acting insulin was already on the Model List, the Committee further concluded that insufficient evidence had been presented to justify a decision to single out a species-specific insulin.

4.1.5 *Miconazole nitrate buccal tablets*

The Committee reviewed the re-application, submitted through Family and Community Health, WHO, to include miconazole nitrate buccal tablets for the treatment of oropharyngeal and oesophageal candidiasis in the Model List[1]. The application to add miconazole nitrate buccal tablets was first considered by the Committee at its previous meeting. At that time, the Committee had been concerned about the lack of comparative data on the efficacy and safety of miconazole nitrate buccal tablets and nystatin lozenges and, thus, on

[1] Details of the full application (including comments received) are available via the Internet from the WHO web site (*http://www.who.int/medicines*).

the grounds of insufficient evidence of any additional benefit, had decided not to add miconazole nitrate buccal tablets to the Model List (*2*).

The Committee reviewed the new evidence provided with the re-application and concluded that the efficacy of miconazole nitrate buccal tablets is no worse than that of ketoconazole given systemically and nystatin used locally. The Committee also noted that adverse effects were rarely reported on an estimated 552 381 patient exposure worldwide. Assuming therapeutic equivalence, the appropriate economic evaluation would be a cost-minimization analysis, comparing treatment with miconazole nitrate buccal tablets, ketoconazole tablets and nystatin lozenges. On this basis, the total cost for 100 patients was similar for the miconazole nitrate- and ketoconazole-based medications, and lower that that for the nystatin-based preparation. In a secondary analysis, cumulative costs at week 3 were approximately one-third less for patients treated with miconazole nitrate buccal tablets when compared with ketoconazole- and nystatin-treated patients.

The Committee considered that the comparison of the effectiveness of miconazole nitrate formulations and nystatin formulations was inadequate; that comparative safety data for miconazole nitrate buccal tablets and nystatin lozenges were lacking; and that evidence for clinical benefits arising from a possibly improved adherence to treatment had not been provided. Furthermore, the application was not specifically supported by Family and Community Health. The Committee therefore recommended that the application to add miconazole nitrate buccal tablets to the Model List be rejected.

4.1.6 *Misoprostol*

The Committee reviewed an application from the Department of Obstetrics and Gynaecology, Medical School, Makarere University, Kampala, Uganda, to include misoprostol for obstetric and gynaecological indications.

The Committee noted that misoprostol, a synthetic prostaglandin E1 analogue, is only approved for the prevention and treatment of non-steroidal anti-inflammatory drug (NSAID)-associated peptic ulcers; a 25 µg vaginal tablet has, however, been registered for hospital use in Brazil (*18*). Nevertheless, misoprostol has been extensively studied and is widely used for a number of obstetric and gynaecological indications, such as pre-induction cervical ripening (3rd trimester), labour induction (3rd trimester, especially at low Bishop scores), evacuation of the uterus after pregnancy failure or for various

other medical reasons (2nd trimester) and primary postpartum haemorrhage. It has been shown to be an effective myometrial stimulant of the pregnant uterus, even at the beginning of pregnancy. Thus, it is also an effective abortive agent. Concern about the widespread use of misoprostol as a self-medication has justified its non-approval for marketing in various countries, mainly where abortion is considered illegal. For instance, the use of misoprostol for obstetric indications is not approved by the United States Food and Drug Administration (USFDA).

In view of the limited registration for obstetric and gynaecological indications, the Committee decided that the application to add misoprostol to the Model List could not be considered at this meeting. However, if more widespread registration were to be achieved, a full application — supported by a review of available data on efficacy and safety — would be considered.

4.1.7 *Valaciclovir*

The Committee reviewed an application from the Department of Reproductive Health and Research, WHO, for the inclusion of valaciclovir as a better example within a therapeutic group than aciclovir (currently listed in section 6.4.1 Antiherpes medicines) on the grounds of superior bioavailability and a simpler treatment regimen (valaciclovir can be administered as twice daily doses rather than as 4–6 doses per day as required with aciclovir). In the case of sexually transmitted infections (STIs), compliance is a key issue in ensuring the effectiveness of treatments. Successful treatment is important for reducing the transmission of HIV and for promoting the credibility and acceptance of the syndromic approach to treatment.

The Committee noted the comprehensive review of studies on the comparative efficacy and safety of valaciclovir and aciclovir that was provided as part of the application. The studies compared the two medicines as treatments for the first clinical episode of genital herpes, as treatments for recurrent infections or as suppressive therapy, and presented the dosage regimen for each indication.

The Committee recognized that none of the randomized controlled trials and studies of comparative effectiveness revealed significant differences between the two medicines and that both valaciclovir and aciclovir are effective when compared with a placebo. However, none of the trials reported adherence to treatment or patient preferences as an outcome measure. The Committee also noted that the treatment regimens for some of the indications involved twice-daily dosing for both medicines.

Given the assessment of comparative clinical performance and the lack of evidence of any benefit from better adherence to treatment, the appropriate economic evaluation would be a cost-minimization analysis. On this basis, the cost per course (i.e. 5 days treatment) with aciclovir is in the range US$ 1.46–31.69 whereas the cost per course (i.e. of 5 days treatment) with valaciclovir is higher, at US$ 36.72. Such a cost differential could only be justified if other direct and indirect non-medicine costs (e.g. physician visits, hospitalization, adverse events, productivity losses) associated with use of aciclovir are substantially greater than those associated with treatment with valaciclovir. Based on the available clinical trial evidence, this is unlikely to be the case.

The Committee also noted the scarcity of published data on the cost-effectiveness of treatment of herpes simplex with valaciclovir and aciclovir in HIV-infected patients. According to the results of one trial (*19*), in which the cost-effectiveness of the two medicines for the treatment of herpes simplex virus were compared, relative to aciclovir, the use of valaciclovir reduced direct medical costs by an average of 17% (US$ 60.01) and indirect medical costs by an average of 25% (US$ 46.54). However, this particular analysis was based on a cost-consequence approach and was not a true cost-effectiveness analysis. Moreover, as the analysis was highly system specific, the Committee did not consider it necessarily applicable to other settings.

The Committee concluded that valaciclovir could only be considered cost-effective if its price were to be reduced sufficiently, or if evidence were to be presented that adherence to treatment and treatment outcomes are considerably better than those achieved with aciclovir. In the absence of such information, the Committee recommended that valaciclovir should not be added to the Model List, but that aciclovir should take a box symbol for this indication, with valaciclovir identified as one of the alternatives in the same pharmacological class.

4.2 Applications for deletions

4.2.1 *Ethinylestradiol + levonorgestrel tablets (50μg + 250μg, pack of four)*

The Committee considered a request submitted by the Department of Reproductive Health and Research, WHO, to delete the emergency contraceptive, ethinylestradiol + levonorgestrel (tablets, 50μg + 250μg (pack of four)) from the Model List. The Committee was informed that a levonorgestrel-only regimen is associated with significantly fewer side-effects (*20*, *21*) and, according to a large ran-

domized double-blind multinational study organized by the Special Programme of Research, Development and Research Training in Human Reproduction, WHO, more effective as an emergency contraceptive than the combination regimen based on ethinylestradiol + levonorgestrel (four-pill pack) (*22*). Since the publication of the results of the WHO multinational trial in 1998, the levonorgestrel-only regimen has been registered in over 90 countries and some manufacturers have taken the combined emergency contraceptive pill (four-pill pack) off the market.

The Committee was also informed about the results of a more recent randomized, double-blind trial which demonstrated that one dose of 1.5 mg levonorgestrel has the same efficacy, and without an increase in side-effects, as two 0.75 mg doses of levonorgestrel taken at an interval of 12 hours (*23*). In the light of this finding, one dose of 1.5 mg levonorgestrel is now the recommended regimen for emergency contraception. At the present time, commercial packs contain two tablets of 0.75 mg levonorgestrel, but it is likely that single tablets of 1.5 mg levonorgestrel will be available for this indication in the future.

The Committee noted that the Model List currently contains two dosage forms for emergency contraception, namely: ethinylestradiol + levonorgestrel tablet, 50 µg + 250 µg (pack of four) and levonorgestrel tablet, 750 µg (pack of two). The Committee considered that the application for the deletion of the former, that is the combination four-pill pack, is supported by a high level of clinical evidence of its inferiority relative to the levonorgestrel-only regimen, as summarized in the Cochrane Review (*21*). The Committee also acknowledged the better safety profile of the levonorgestrel-only regimen, confirmed statistically and clinically, and with fewer side effects. The relative risk of pregnancy (RR) for the levonorgestrel-only regimen compared with the four-pill combination was 0.80 with a 95% confidence interval (CI) of 0.74–0.86. Nausea (16.1% vs 46.5% and 23.1% vs 50.5%) and vomiting (2.7% vs 22.4% and 5.6% vs 18.8%) occurred less frequently with the levonorgestrel-only regimen ($P < 0.01$) (*22*).

The Committee also considered the results of the recent WHO multicentre randomized trial of the two levonorgestrel-only based regimens (i.e. a single dose of 1.5 mg as opposed to two doses of 0.75 mg taken 12 hours apart), involving 4071 women in 15 family-planning clinics in 10 countries, which has demonstrated a high and equal efficacy of both regimens if taken within 5 days of unprotected coitus. The pregnancy rates were 1.5% (or 20 out of 1356) in women assigned single-dose levonorgestrel and 1.8% (or 24 out of 1356) in those prescribed the two-dose levonorgestrel regimen (no statistical

difference, p = 0.83). The relative risk of pregnancy for single-dose levonorgestrel compared with two-dose levonorgestrel was 0.83 with 95% CI = 0.46–1.50 (*23*). The Committee concluded that there is good evidence in favour of the substitution of the two-dose regimen (0.75 mg 12 hours apart) with the single 1.5 mg dose of levonorgestrel; the use of a single dose simplifies the use of levonorgestrel for emergency contraception without an increase in side effects.

On the basis of the evidence before it, the Committee recommended that a 1.5 mg tablet be added as a new dosage form of levonorgestrel and that ethinylestradiol + levonorgestrel (tablet, 50 µg + 250 µg, pack of four) be deleted from the Model List.

4.2.2 *Nonoxynol*

The Committee considered an application submitted by the Department of Reproductive Health and Research, WHO, to delete nonoxynol as a condom-additive vaginal spermaticide and virucidal. In addition, a safety analysis was received from the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden, along with a copy of the USFDA proposed rule on the labelling of over-the-counter vaginal contraceptive drug products containing nonoxynol-9.

In the application, reference was made to a large multicountry study sponsored by WHO, the former Global Programme on AIDS (GPA) and the Joint United Nations Programme on HIV/AIDS (UNAIDS), results of which indicated that, contrary to expectation, there is a higher incidence of HIV infection in women using nonoxynol-9 than in women using a placebo gel. Prompted by this finding, the Department of Reproductive Health and Research, WHO, in partnership with the CONRAD Program, convened a technical consultation in October 2001 to review the implications of the new data on the use of nonoxynol-9 as a spermicide. All available evidence regarding the use of nonoxynol-9 as a contraceptive, its effectiveness in preventing infection with gonorrhoea or *Chlamydia trachomatis*, and its effectiveness in preventing HIV infection was summarized in the report of the consultation (*24*). The main conclusions reached are as follows:

— although nonoxynol-9 has been shown to increase the risk of HIV infection when used frequently by women at high risk of infection, it remains a contraceptive option for women at low risk;
— nonoxynol-9 offers no protection against STIs such as gonorrhoea or chlamydia;
— there is no evidence that condoms lubricated with nonoxynol-9 are any more effective in preventing pregnancy or infection than

condoms lubricated with silicone, and such condoms should no longer be promoted; however, it is better to use a nonoxynol-9 lubricated condom than no condom at all;
— nonoxynol-9 should not be used rectally.

In 2002, and subsequent to the consultation, the final results of the WHO/GPA/UNAIDS-sponsored study (the COL-1492 study) were published in the *Lancet* (*25*); a systematic review of the use of nonoxynol-9 for STI and HIV prevention was also published (*26*).

In light of the presented evidence, the Department of Reproductive Health and Research proposed that the specific mention of condoms lubricated with nonoxynol should be removed from the Model List, but that condoms themselves should be retained. The role of condoms in the prevention of pregnancy and HIV transmission is well proven; condoms are also the mainstay of HIV and STI prevention programmes. A silicone-oil lubricant is recommended in the joint WHO-UNAIDS publication *The Male Latex Condom* (*27*).

The Committee, on the basis of the evidence before it, recommended to maintain condoms on the Model List but to delete the mention of nonoxynol in view of the increased risk of transmitting HIV infection. As there is insufficient evidence to suggest an alternative spermicide to nonoxynol, the Committee recommended that the reference to spermicides be deleted as well.

The Committee acknowledged the continued need to offer diaphragms as part of the contraceptive mix in family planning, despite their moderate contraceptive effect, and thus recommended that they too should be maintained on the Model List. With regard to the use of nonoxynol with a diaphragm, the Committee noted that most observational studies are conducted with spermicide and that one randomized study reported a statistically non-significant additional beneficial effect of the spermicide in preventing pregnancy (*28*). The Committee therefore recommended the removal of the reference to spermicides, including nonoxynol, in the entry for diaphragms, in view of the lack of evidence of any additional benefit of spermicides and the strong suggestion of the potential of nonoxynol to increase the risk of transmission of HIV infection.

4.3 Applications for addition of information

4.3.1 *Anti-leprosy medicines*

The Committee reviewed a request submitted by the Department of Communicable Diseases Prevention, Control and Eradication, WHO, to modify the Model List so as to better reflect the fact that anti-

leprosy medicines should be used exclusively in combination (i.e. as multidrug therapy (MDT)) and be presented in colour-coded blister packs (i.e. MDT blister packs) in order to (i) prevent antimicrobial resistance, (ii) improve patient adherence to treatment and (iii) facilitate logistics and inventory control; and that MDT blister packs can be obtained free of charge through WHO.

To this end, the Committee recommended that the following text be inserted at the head of the appropriate section of the Model List (section 6.2.3 Antileprosy medicines):

> Medicines used in the treatment of leprosy should never be used except in combination (i.e. as multidrug therapy (MDT)). Combination therapy is essential to prevent the emergence of drug resistance. Colour-coded blister packs (MDT blister packs) containing standard two-medicine (paucibacillary leprosy) or three-medicine (multibacillary leprosy) combinations for adult and childhood leprosy should be used. MDT blister packs can be supplied free of charge through WHO.

The Committee also recommended that the same information be included in the WHO Essential Medicines Library and the *WHO model formulary*.

4.4 Other changes

4.4.1 *Oral rehydration salts*

The Committee reviewed an application submitted by the Department of Child and Adolescent Health, WHO, to change the formula of oral rehydration salts (ORS). The current formula, which provides a solution containing 90 mEq/l of sodium with an osmolarity of 311 mOsm/l, has proven effective, without apparent adverse effects, in worldwide use, and has contributed substantially to the dramatic global reduction in mortality from diarrhoeal disease.

The Committee was informed that, over the past 20 years, numerous studies have been undertaken with a view to developing an "improved" ORS formulation. The goal has been a product that is at least as safe and as effective as the standard ORS solution for preventing or treating dehydration from all types of diarrhoea but which would, in addition, reduce stool frequency or have other important clinical benefits. One approach that was adopted involved decreasing the osmolarity of the standard ORS solution to avoid possible adverse effects of hypertonicity on net fluid absorption. This was achieved by reducing the solution's glucose and salt (NaCl) concentrations.

Studies evaluating this approach were reviewed at a consultative technical meeting held in New York in July 2001; as a result, technical recommendations were made to WHO and UNICEF regarding the

efficacy and safety of a reduced-osmolarity ORS solution in children with acute non-cholera diarrhoea, and in adults and children with cholera (*29*). The studies showed that the efficacy of ORS treatment in children with acute non-cholera diarrhoea is improved by reducing the sodium concentration to 75 mEq/l, the glucose concentration to 75 mmol/l, and the total osmolarity to 245 mOsm/l. Compared with the established ORS solution, the need for unscheduled supplemental intravenous therapy is reduced by 33% (NNT = 20). In addition, a combined analysis of the studies reviewed at the New York meeting and other studies involving reduced-osmolarity ORS solutions of differing composition (osmolarity 210–268 mOsm/l, sodium 50–75 mEq/l), reported a reduction in stool output of about 20% and a decrease in the incidence of vomiting of about 30%. The 245 mOsm/l solution also appeared to be as safe, and at least as effective, as the standard ORS solution for use in children with cholera (*29*).

The application also mentioned the fact that the reduced-osmolarity ORS solution containing 75 mEq/l sodium, 75 mmol/l glucose (total osmolarity = 245 mOsm/l) has been shown to be as effective as standard ORS in treating adults with cholera, but is associated with an increased incidence of transient, asymptomatic hyponatraemia. Thus, the reduced osmolarity ORS may be used in place of the standard ORS solution for treating adults with cholera, but careful monitoring is advised for significant hyponatraemia.

In its discussions, the Committee noted that the new reduced-osmolarity ORS formulation has already been officially released by WHO and its partners during the United Nations General Assembly Special Session on Children that was held in New York, and that UNICEF, USAID and MSF are supporting this application. The Committee further noted that WHO and UNICEF have recently published criteria for acceptable ORS formulations (*29*). These criteria are summarized in Table 1.

The Committee concluded that the evidence supporting the superiority of the new reduced osmolarity ORS solution for the treatment of acute non-cholera diarrhoea in children was convincing, with a 5% absolute risk reduction (NNT = 20) in the need for unplanned intravenous infusions, and on this basis recommended that the formula for ORS in the Model List (section 17.7.1 Oral hydration) be changed to 75 mEq/l sodium (sodium chloride 2.6 g/l) and 75 mmol/l (13.5 g/l) glucose. The Committee also recommended the addition of the following footnote:

> In cases of cholera a higher concentration of sodium may be required.

Table 1
Recommended composition of oral rehydration salts[a]

Substance	Concentration
Total substances (including that contributed by glucose)	200–310 mmol/l
Individual substances	
Glucose	At least equal that of sodium, but not exceeding 111 mmol/l
Sodium	60–90 mEq/l
Potassium	15–25 mEq/l
Citrate	8–12 mmol/l
Chloride	50–80 mEq/l

[a] The listed criteria specify the desired characteristics of the solution after it has been prepared according to the instructions on the packet.
Source: reference *30*.

4.4.2 *Streptokinase*

The Committee reviewed an application submitted by Aventis Behring, GmbH, Marburg Germany, to remove the 100 000 IU dosage form of streptokinase from the Model List[1] (section 12.5 Antithrombotic medicines).

The Committee noted that the recommended standard dosage for streptokinase's main indication, the treatment of acute myocardial infarction, is 1.5 million IU. The Committee recommended that the dosage form for streptokinase be changed to: powder for injection, 1.5 million IU in vial and that the note, "For use in rare or exceptional circumstances." be removed since its value in treating acute myocardial infarction is now well established and its use is no longer reserved for exceptional situations.

5. Reviews of sections of the Model List

At the previous meeting of the Committee, a number of issues relating to the listing and presentation of medicines on the Model List, such as the use of the square box symbol, the classification of medicines as either core or complementary and the possibility of initiating a simplified procedure for deleting items, were identified as being in need of detailed consideration and/or re-evaluation (*2*). Thus during the period between the previous and present meetings, a series of

[1] Details of the full application (including comments received) are available via the Internet from the WHO web site (http://www.who.int/medicines).

reviews were undertaken by several small groups of international experts formed from the 2002 Expert Committee and the WHO Secretariat. The results of these reviews were reported at the present meeting for approval by the full Expert Committee. In addition, and following a recommendation to that effect made by the Committee at its previous meeting, the medicines for the treatment of hypertension (section 12.3 of the Model List) were subjected to a full review.

5.1 "Fast-track" procedure for deleting items from the Model List

At its previous meeting, the Expert Committee recognized that, for certain items on the Model List at least, a simplified or "fast-track" deletion procedure may be appropriate and recommended that such a procedure be developed (*2*). The rationale for this recommendation was that selected items on the Model List, for which no systematic reviews or sufficient evidence of efficacy and safety are available, were probably now obsolete, but the fact that they were probably obsolete (or not essential) did not justify the costly investment of a full systematic review.

A consultation technique, which included the use of two questionnaires, was used to identify those medicines most in need of a full systematic review on the basis of doubtful safety and/or efficacy or which could be proposed for fast-track deletion. The first questionnaire comprised a list of medicines compiled from a number of sources; some were considered by the full Committee to be questionable in terms of safety and/or efficacy, some were identified by means of a survey that compared medicines on the Model List with a sample of 12 national essential medicine lists, and others were identified by the WHO Secretariat. Respondents were asked to indicate which items they thought should be deleted, which should be retained and which should be subjected to a systematic review. The second questionnaire was a simple list of the pharmacological section headings used in the Model List, with a request to rank those sections considered to be in need of revision. In addition, the other reviews — of core versus complementary listing (see section 5.2) and of the use of the square box symbol (see section 5.3) — led to several proposals for medicines for fast-track deletion or for full review; these proposals were subjected to peer review and also to review by the WHO Secretariat.

The first questionnaire was sent to a group of 81 individuals proposed by the Secretariat, consisting of Expert Panel members, members of a wider advisory group and relevant WHO staff, including regional advisers. In addition, a message was sent out via the e-drug electronic

discussion group on the Internet, which resulted in another 27 expressions of interest. In response to the total of 104 forms sent out, 28 (or 24%) completed forms were received from 20 countries.

On the basis of the questionnaire responses received, the Committee recommended to retain the following three medicines on the Model List:

— codeine for analgesic use (section 2.2 Opioid analgesics);
— pyrantel (section 6.1.1 Intestinal anthelminthics);
— verapamil tablets (section 12.1 Antianginal medicines).

The Committee also recommended, on the basis of the questionnaire responses and other arguments as detailed below, to delete, or to make changes to, the following medicines:

- *Chloral hydrate (section 1.3 Preoperative medication and sedation for short-term procedures)*. The Committee noted that chloral hydrate was included in only 2 of 25 national essential medicines lists. It further noted that this medicine is described in the 1996 WHO publication on cancer pain relief as the "drug of choice for painless procedures" (*30*), but concluded that there are many as effective and safe alternatives, such as promethazine syrup. The Committee thus recommended that chloral hydrate be deleted from the Model List.
- *Clomifene (section 18.6 Ovulation inducers)*. The Committee noted that subfertility is a common problem which can cause considerable distress, that there is a Cochrane Review (*31*) that demonstrates the effectiveness of clomifene (NNT = 2.74) but no WHO clinical guidelines on infertility treatment, and thirdly, that clomifene is listed on 20 of 25 national essential medicines lists. The Committee recommended that clomifene be retained on the Model List but moved to the complementary list (in view of the need for specialist care) and its square box symbol removed.
- *Dextromethorphan (section 25.2 Antitussive medicines)*. The Committee noted the conclusions of WHO clinical guidelines that state, "Given the conflicting nature of the evidence, no clear recommendation can be made in favour of its use." (*32*), and also those of a recent Cochrane Review which was unable to find good evidence in support of the use of over-the-counter medications against cough (*33*). The Committee concluded that there was insufficient evidence to support the listing of dextromethorphan (oral solution) as an essential medicine and recommended that the item be deleted.
- *Fludrocortisone (section 18.1 Adrenal hormones and synthetic substitutes)*. The Committee noted that although fludrocortisone is a

life-saving medicine in cases of adrenal insufficiency (which is considered to be a rare condition), it features in only 9 of 25 national essential medicines lists, is not listed in the MSH drug price indicator guide and is not currently being supplied by UNICEF and the International Dispensary Association (IDA). The Committee concluded that there is no need for this item to be on the Model List and recommended that it be deleted (see also section 5.3).

- *Folic acid, injection (section 10.1 Antianaemia medicines).* The Committee noted that there was no identified need for this presentation and therefore recommended that folic acid injections be deleted from the Model List.

- *Immunoglobulin, human normal (section 19.2 Sera and immunoglobulins).* The Committee noted that there is no need for this item in view of the availability of suitable vaccines, that there are no WHO clinical guidelines recommending its use, and that quality control of this blood product poses a problem. The Committee thus recommended that immunoglobulin, human normal be deleted.

- *Ipecacuanha (section 4.1 Non-specific antidotes and other substances used in poisonings).* The Committee noted the lack of need for an emetic in the treatment of poisoning due to the risk of aspiration pneumonia, and the absence of evidence on the efficacy and safety of ipecacuanha in the management of poisoning. The Committee further noted that ipecacuanha is not included in the International Programme for Chemical Safety (IPCS) INTOX databank and thus recommended that it be deleted from the Model List.

The Committee noted that selected medicines, such as fludrocortisone, were deleted from the Model List because, on reflection, the Committee considered the diseases for which they are needed are too rare for these items to meet the selection criteria, ". . . satisfy the priority health care needs of the population". The Committee fully recognized the essential and even life-saving nature of certain medicines for patients with rare but treatable diseases. While the treatment of such diseases, on reflection, falls outside its remit, the Committee nevertheless urged that effective treatments for serious uncommon diseases be made available whenever possible. At the national level, special arrangements for specific individuals may need to be made in this regard.

Finally, the Committee agreed that the sections of the Model List dealing with anaesthetics (section 1) and dermatological medicines (section 13) should be subject to a full systematic review before any

further deletions could be recommended in these medicine groups. Recommendations for deletions in section 12.3 of the Model List (Antihypertensive medicines) are covered separately (see pages 36–41).

5.2 Review of core versus complementary listing of medicines

The 12th Model List of Essential Medicines (revised April 2002) is presented as two separate lists: a "core" list and a "complementary" list, which are described as follows:

- The core list presents a list of minimum medicine needs for a basic health care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.
- The complementary list presents essential medicines for priority diseases which are efficacious, safe and cost-effective but not necessarily affordable, or for which specialized health care facilities or services may be needed.

At the meeting of the Committee in 2002, there was considerable debate about whether the system of two lists should be retained or whether they should be combined into a single list. This discussion was prompted in part by the observation that the existing criteria for core or complementary listing had become blurred and had been misapplied to those medicines that are for priority conditions but are thought to be expensive. Moreover, as the prices of pharmaceuticals are variable and changing, it did not seem reasonable to use "cost-effective but not necessarily affordable" as the main criterion for the placement of an item on the complementary list (*2*).

During the course of 2002, and in the wake of this debate, the designation of all medicines on the 12th Model List as "core" or "complementary" was reviewed according to the following general principles:

1. All essential medicines should be placed on the core list, unless there is a specific reason for them to be on the complementary list.
2. If there is uncertainty about the classification, the medicine should be put on the core list.

The following criteria were used for putting items on the complementary list:

- *Primary criterion*. Use of the medicine requires specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training.

- *Secondary criterion* (to be used only in cases of doubt). Consistently higher cost or less attractive cost-effectiveness in a variety of settings.

Seventy-nine (or 24%) of the total 325 medicines included in the 12th Model List are listed as complementary; some appear on both the core and the complementary list. For each of these medicines the indications and specifications for use as described in the *WHO model formulary* were evaluated: if, according to the *WHO model formulary*, there is always a need for specialist medical care or facilities for use of a medicine for a given indication, the medicine was classified as "complementary" for that indication; where there was uncertainty, evidence of consistently higher cost or less attractive cost-effectiveness in most settings was used as the secondary criterion for putting the medicine on the complementary list. In cases where there was still doubt, the medicine was classified as a core list medicine.

At its present meeting, the Committee agreed to define the criteria for core and complementary listing as follows:

- The core list presents a list of minimum medicine needs for a basic health care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

- The complementary list presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In cases of doubt, medicines may also be listed as complementary on the basis of consistently higher costs or less attractive cost-effectiveness in a variety of settings.

The Committee recommended that core and complementary medicines, previously presented in two separate lists, be combined into one list, with the complementary medicines printed in italics or otherwise identified (see Annex 1).

In reviewing the proposals for changes to the classification of medicines as "core" or "complementary", the Committee decided not to make recommendations for changes to items in those sections of the Model List which were also recommended for systematic review; changes of this nature would be recommended as part of such reviews (e.g. see section 5.4 Review of the antihypertensive medicines (section 12.3 of the Model List)).

The Committee recommended that the following medicines be moved from the core list to the complementary list:

— aminophylline (section 25.1 Antiasthmatic medicines);
— amphotericin B (section 6.3 Antifungal medicines);
— azathioprine (in section 2.4 Disease-modifying agents used in rheumatoid disorders);
— clomifene (section 18.6 Ovulation inducers);
— diethylcarbamazine (section 6.1.2 Antifilarials);
— dopamine (section 12.4 Medicines used in heart failure);
— ethosuximide (section 5 Anticonvulsants/antiepileptics);
— hydrocortisone (rectal preparations in section 17.4 Gastrointestinal anti-inflammatory medicines);
— intraperitoneal dialysis solution (section 23 Peritoneal dialysis solution);
— methotrexate (in section 2.4 Disease-modifying agents used in rheumatoid disorders);
— penicillamine (in section 2.4 Disease-modifying agents used in rheumatoid disorders),
— pentamidine (in section 6.5.2 Anti-leishmaniasis medicines, in section 6.5.4 Antipneumocystosis and antitoxoplasmosis medicines and in section 6.5.5a Antitrypanosomal medicines — African trypanosomiasis),
— pyridostigmine (section 20 Muscle relaxants (peripherally-acting) and cholinesterase inhibitors);
— sulfadiazine (section 6.2.2 Other antibacterials);
— sulfasalazine (in section 2.4 Disease-modifying agents used in rheumatoid disorders).

The Committee recommended that the following medicines be moved from the complementary list to the core list:

— amoxicillin + clavulanic acid (section 6.2.1 β-lactam medicines);
— chloramphenicol (oily suspension for injection in section 6.2.2 Other antibacterials);
— epinephrine (adrenaline) (in section 12.2 Antiarrhythmic medicines);
— levonorgestrel (30μg tablets in section 18.3.1 Hormonal contraceptives);
— mannitol (section 16 Diuretics);
— norethisterone enantate (section 18.3.1 Hormonal contraceptives).

The Committee also recommended that the following items be deleted from the Model List for the reason(s) stated:

- *Cyclophosphamide (section 2.4 Disease-modifying agent in rheumatoid arthritis)*. The Committee noted the findings of a recent Cochrane Review (*34*) on the efficacy and safety of cyclophosphamide as a disease-modifying agent in rheumatoid arthritis, and recommended that this item be deleted for this particular indication.
- *Desmopressin (section 10.2 Medicines affecting coagulation)*. The Committee recommended the deletion of this item on the grounds of the rarity of the indication.
- *Iron dextran (section 10.1 Antanaemia medicines)*. The Committee recommended the deletion of this item on the basis of its unfavourable benefit–risk ratio.
- *Pethidine (section 2.2 Opioid analgesics)*. The Committee noted that pethidine was listed on 19 out of 25 national essential medicine lists; that pethidine was considered inferior to morphine due to its toxicity on the central nervous system; and that it is generally more expensive than morphine. The Committee concluded that there was insufficient justification to keep pethidine on the Model List and recommended that it be deleted. The Committee stressed that all national programmes should ensure that sufficient quantities of morphine are always available for those who need it.
- *Trimethoprim* (*injection in section 6.2.2 Other antibacterials*). The Committee recommended that the injectable form of trimethoprim be deleted because of the lack of need of this particular administration route for this medicine.

5.3 Review of the use of the square box symbol (including a review of the corticosteroids)

The 12th Model List contains 113 items that are marked with a "square box" symbol; this symbol is used to indicate that "a listed medicine should be seen as a representative example from a group of clinically equivalent medicines with wide experience of use, within a pharmacological class. The medicines listed on the Model List would generally be the least costly therapeutic equivalent within the group. National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price." (*2*).

At its previous meeting, the Expert Committee acknowledged that there had been some inconsistency in the way the symbol had been used in the past. For example, in the 12th Model List neostigmine is listed with a square box, yet has no pharmacological or therapeutic

equivalent; in the case of the corticosteroids, of which there are several in various sections of the Model List, some are marked with boxes for some indications while others are not. The Committee therefore recommended that a review of the use of the square box symbol be undertaken with a view to restricting its use (*2*).

As a precursor to the review of the use of the square box symbol, it was necessary to reassess the meaning of the square box symbol, and in particular to consider the definitions of the terms "equivalence" and "interchangeability" as they apply to medicines. In this context, there are three possible ways of defining equivalence and interchangeability, as outlined below.

The first definition of equivalence is based on the notion of *generic* equivalence, where products contain the same chemical compound. In this respect, the Committee recommended the use of the existing WHO description which states:

> The term "generic product" has somewhat different meanings in different jurisdictions and in this document use of the term is avoided as much as possible, and the term "multisource pharmaceutical product" has been applied. Generic products may be marketed either under the nonproprietary approved name or under a new brand (proprietary) name. They may sometimes be marketed in dosage forms and/or strengths different from those of the innovator products. However, where the term 'generic product' has to be used it means a pharmaceutical product, usually intended to be interchangeable with the innovator product, which is usually manufactured without a licence from the innovator company and marketed after expiry of patent or other exclusivity rights (*35*)."

Generic substitution was assumed to be acceptable for medicines on the Model List as it is constructed by chemical compound, not by brand name. However, it was proposed that square boxes should not be used to indicate substances for which there are known to be multiple suppliers of acceptable products.

The second definition of interchangeability is at the level of pharmacological class (e.g. angiotensin-converting enzyme (ACE) inhibitors). There has been some considerable debate in the scientific literature about "class effects" of medicines and whether efficacy and safety can be assumed to be interchangeable throughout a class of medicines; this debate has yet to be concluded. There is some evidence to suggest that efficacy can be assumed across a class of medicines if equipotent doses of the medicines can be established, but that safety cannot necessarily be generalized in the same way. From a policy point of view, it can be useful to specify those pharmacological items that are deemed to be clinically similar within a class on the basis of the best comparative evidence, and then to set medicine reimbursement levels accordingly.

It was agreed that for the purposes of the Model List, the square box symbol should be used primarily to indicate similar clinical performance within a pharmacological class. Thus, the medicine listed should be that member of a given pharmacological class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in others, subsequently licensed compounds may be safer or more effective. Where there is no difference between medicines in terms of efficacy and safety, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources.

The third definition of interchangeability is based on therapeutic indication. However, determining therapeutic equivalence is a complex matter: for example, to claim therapeutic equivalence would be tantamount to saying that all classes of medicines used to treat hypertension are therapeutically interchangeable (i.e. a beta-blocker has the same therapeutic effect as a calcium-channel blocker), a suggestion that has been hotly contested. Defining therapeutic groups of medicines for specific indications demands detailed and comprehensive review of clinical data on comparative effectiveness and safety, and is often the subject of considerable controversy.

In light of the above considerations, the description of the square box symbol was modified as follows:

> The square box symbol is primarily intended to indicate similar clinical performance within a pharmacological class. The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. Therapeutic equivalence is only indicated on the basis of reviews of efficacy and safety and when consistent with WHO clinical guidelines. National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price.

The review of the use of the square box symbol in the Model List was conducted using the following principles:

1. As far as possible, items on the Model List should be listed without a square box symbol; the symbol should only be used if there is at least one other member of its pharmacological class that can be considered to be clinically similar; such item(s) should be identified and listed in the WHO Essential Medicines Library and/or the *WHO model formulary*.

2. If for any item there is uncertainty about the clinical similarity of any potential alternatives, a square box symbol should not be used.

Based on the outcome of the square box review, the Committee recommended that the square box symbol be removed from the following items on the Model List:

— amiloride (section 16 Diuretics);
— amoxicillin (section 6.2.1 β-Lactam medicines);
— amoxicillin + clavulinic acid (section 6.2.1 β-Lactam medicines);
— antitetanus immunoglobulin (section 19.2 Sera and immunoglobulins);
— azathioprine (in section 8.1 Immunosuppressive medicines),
— chloramphenicol (capsule, oral suspension and powder for injection in section 6.2.2 Other antibacterials);
— chloroquine (in section 6.5.3a Antimalarial medicines for curative treatment);
— ciclosporin (section 8.1 Immunosuppressive medicines);
— clomifene (section 18.6 Ovulation inducers);
— charcoal, activated (section 4.1 Non-specific antidotes and other substances used in poisonings);
— codeine (in section 2.2 Opioid analgesics and section 17.7.2 Antidiarrhoeal (symptomatic) medicines);
— cycloserine (section 6.2.4 Antituberculosis medicines)
— dexamethasone (in section 3 Antiallergics and medicines used in anaphylaxis);
— diloxanide (section 6.5.1 Antiamoebic and antigiardiasis medicines);
— doxorubicin (section 8.2 Cytotoxic medicines);
— doxycycline (6.5.3a Antimalarial medicines for curative treatment)
— epinephrine (adrenaline) (in section 25.1 Antiasthmatic medicines);
— ethionamide (section 6.2.4 Antituberculosis medicines);
— glibenclamide (section 18.5 Insulins and other antidiabetic agents);
— ibuprofen (section 2.1 Non-opioid analgesics and antipyretics and non-steroidal anti-inflammatory medicines);
— mannitol (section 16 Diuretics);
— DL-methionine (section 4.2 Specific antidotes and other substances used in poisonings);
— morphine (in section 1.3 Preoperative medication and sedation for short-term procedures and 2.2 Opioid analgesics);
— neostigmine (section 20 Muscle relaxants (peripherally-acting) and cholinesterase inhibitors);

— promethazine (in section 1.3 Preoperative medication and sedation for short-term procedures and section 17.2 Antiemetic medicines);
— quinine (section 6.5.3a Antimalarial medicines for curative treatment);
— sodium nitroprusside (section 12.3 Antihypertensive medicines);
— retinol (section 27 Vitamins and minerals);
— sulfadiazine (6.2.2 Other antibacterials);
— sulfadoxine + pyrimethamine (section 6.5.3a Antimalarial medicines for curative treatment),
— sulfamethoxazole + trimethoprim (in section 6.2.2 Other antibacterials);
— verapamil (section 12.1 Antianginal medicines).

In making its recommendations the Committee noted the following:

- The square box on ibuprofen was removed because there are significant differences in efficacy and safety within this pharmacological class.
- The square box on morphine was removed because of the lower benefit–risk ratio and higher price of the alternatives. The Committee urged all national programmes to ensure that sufficient quantities of morphine are always available to those who need it.

In the following cases, the Committee recommended that the square box symbol be retained but the listed medicine be changed (for the reasons stated in parentheses):

- Captopril (section 12.3 Antihypertensive medicines) to be replaced by enalapril (enalapril has a simpler dosing regimen and is available as a generic).
- Cimetidine (section 17.1 Antacids and other antiulcer medicines) to be replaced by ranitidine (ranitidine has a simpler dosing regimen and less potential for pharmacokinetic interactions, and is available as a generic).

The Committee also recommended that examples of possible alternatives for the medicines listed with a square box symbol should not be included in the Model List itself, but that they should be mentioned in the WHO Essential Medicines Library and the *WHO model formulary*.

The corticosteroids

During the course of the review of the use of the square box symbol, it was noted that the present Model List is not very consistent in its

recommendations regarding the selection of, and the use of the square box symbol with, the corticosteroids. The Committee therefore recommended that the listing of these medicines for systemic use be reviewed. In reviewing the corticosteroids, the Committee commented on the scarcity of systematic data for comparing the safety and efficacy of various corticosteroids in human use and also on the fact that only a limited amount of information on the relationship between dose and effect in the treatment of various conditions is currently available. Nevertheless, the Committee recommended that the listing of the corticosteroids for systemic use be simplified as follows:

- *Section 3 (Antiallergics and medicines used in anaphylaxis)*. Dexamethasone tablets (500 µg, 4 mg) should be removed and a 25 mg prednisolone tablet added. The injectable dosage forms, dexamethasone (injection, 4 mg dexamethasone phosphate (as disodium salt) in 1-ml ampoule) and hydrocortisone (powder for injection, 100 mg (as sodium succinate) in vial) should be retained, but neither with a square box symbol. Thus prednisolone tablets (5 mg and 25 mg) become the only oral corticosteroidal preparations in this section of the Model List to have a square box, on account of their slightly lower price per defined daily dose (DDD) and considerably higher turnover by not-for-profit generic suppliers relative to dexamethasone (500 µg). In this regard, dexamethasone should be mentioned as the possible alternative, and the entry for prednisolone annotated with the following footnote:

  > There is no evidence for complete clinical similarity between prednisolone and dexamethasone at high doses.

- *Section 8.3 (Hormones and antihormones)*. The injectable forms of dexamethasone (injection, 4 mg dexamethasone phosphate (as disodium salt) in 1-ml ampoule) and hydrocortisone (powder for injection, 100 mg (as sodium succinate) in vial) should be added to this section (as complementary list medicines). The tablet form only of prednisolone should be retained (5 mg) and a higher dosage form added (25 mg), and the entry annotated with the same footnote as in section 3 (see above).

- *Section 18.1 (Adrenal hormones and synthetic substitutes*). All four corticosteroids (dexamethasone in the core list; fludrocortisone in the complementary list, hydrocortisone in the core list and prednisolone in the core list) should be deleted for this indication (i.e. the treatment of Addison's disease) in view of the rarity of the condition; however, the section heading in the Model List should be maintained but with the addition of the following note:

Addison's disease is a rare condition; adrenal hormones for the treatment of this condition are already included in section 3.

The Committee also made the following recommendations:

- *Section 13.3 (Anti-inflammatory and antipruritic medicines).* Betamethasone (ointment or cream, 0.1% (as valerate)) and hydrocortisone (cream or ointment, 1% (acetate)) should be retained, with square box symbols, pending a full review of section 13 (Dermatological medicines) of the Model List.
- *Section 17.4 (Anti-inflammatory medicines).* Hydrocortisone (suppository, 25 mg (acetate) and retention enema) should be retained, with a square box symbol, but moved to the complementary list.
- *Section 21.2 (Anti-inflammatory agents).* Prednisolone (eye drops, 0.5% (sodium phosphate)) should be retained, with a square box symbol, pending a full review of section 21 (Ophthalmological preparations) of the Model List.

Changes to the listing of the individual corticosteroids are summarized in Table 2.

5.4 Review of the antihypertensive medicines

At its previous meeting, the Committee recommended that the section 12.3 of the Model List (Antihypertensive medicines) be reviewed in the light of new clinical guidelines for the treatment of hypertension that were being prepared jointly by WHO and the International Society for Hypertension (ISH) (*2*). The new guidelines update the WHO/ISH clinical guidelines for the treatment of hypertension published in 1999 (*36*).

At the present meeting, the Committee was informed by the Department of Cardiovascular Diseases that WHO plans to incorporate the updated WHO/ISH guidelines into a set of guidelines for cardiovascular risk assessment and management, so as to bring about a paradigm shift from single risk factor management to comprehensive cardiovascular risk management. It was envisaged that this work would not be completed until the end of 2003. As an interim measure, it had been agreed that a draft statement on the management of hypertension would be prepared by the group of experts assigned to update the 1999 WHO/ISH guidelines that reflected their evidence-based work.

The Committee assessed all seven antihypertensive medicines currently included in section 12.3 of the Model List in the light of the draft statement on the management of hypertension. According to

Table 2
Summary of the Committee's recommendations regarding the listing of the corticosteroids (April 2003)

Medicine	Model List section number	Dosage form and strength	Recommendation
betamethasone	13.3	ointment or cream, 0.1% (as valerate)	Retained with no change pending review of section 13 of the Model List
dexamethasone	3	tablet, 500 ug, 4 mg	Oral preparation removed for this indication
		injection, 4 mg dexamethasone phosphate (as disodium salt) in 1-ml ampoule	Retained but without the square box symbol
	8.3	injection, 4 mg dexamethasone phosphate (as disodium salt) in 1-ml ampoule	Added to this section of the Model List as a complementary list medicine
	18.1	tablet, 500 ug, 4 mg	Deleted for this indication; new footnote added to section 18.1 of the Model List: *Addison's disease is a rare condition; adrenal hormones for the treatment of this condition are already included in section 3 of the Model List.*
		injection, 4 mg dexamethasone phosphate (as disodium salt) in 1-ml ampoule	Deleted for this indication
fludrocortisone	18.1	tablet, 100 ug (acetate)	Deleted for this indication; new footnote added to section 18.1 of the Model List: *Addison's disease is a rare condition; adrenal hormones* for *the treatment of this condition are already included in section 3 of the Model List*
hydrocortisone	3	powder for injection, 100 mg (as sodium succinate) in vial	Retained with no change
	8.3	powder for injection, 100 mg (as sodium succinate) in vial	Added to this section of the Model List as a complementary list medicine
	13.3	ointment or cream, 1% (acetate)	Retained with no change pending review of section 13 of the Model List

Table 2

Continued

Medicine	Model List section number	Dosage form and strength	Recommendation
	17.4	suppository, 25 mg (acetate)	Retained but moved to the complementary list
		retention enema	Retained but moved to the complementary list
	18.1	powder for injection, 100 mg (as sodium succinate) in vial	Deleted for this indication; new footnote added to section 18.1 of the Model List: *Addison's* disease *is a rare condition; adrenal hormones for the treatment of this condition are already included in section 3 of the Model List.*
prednisolone	3	tablet, 5 mg	Retained with the addition of a 25 mg tablet and the footnote: *There is no evidence for complete similarity between prednisolone and dexamethasone at high doses.*
	8.3	tablet, 5 mg	Retained with the addition of a 25 mg tablet and the footnote: *There is no evidence for complete similarity between prednisolone and dexamethasone at high doses.*
		powder for injection, 20 mg, 25 mg (as sodium phosphate or sodium succinate) in vial	Injectable dosage form deleted for this indication
	18.1	tablet, 1 mg, 5 mg	Deleted for this indication; new footnote added to section 18.1 of the Model List: *Addison's* disease *is a rare condition; adrenal hormones for the treatment of this condition are already included in section 3 of the Model List.*
	21.2	solution (eye drops), 0.5% (sodium phosphate)	Retained with no change pending review of section 21 of the Model List

the draft statement, current evidence indicates that thiazide diuretics, beta-blockers or ACE inhibitors should be used as first-line drug treatment for hypertension. The role of calcium-channel blockers is less certain; they should be used as first-line treatment only in selected populations, for example, in the elderly (where trials have indicated potential benefits in terms of stroke (*37*)) or in African Americans (*38*).

The Committee noted that the role of the older medicines for the treatment of essential hypertension (i.e. reserpine, hydralazine and methyldopa) is now considered to be questionable. Systematic reviews of trials of each of these three medicines have been carried out and have been submitted for publication, in the Cochrane database (*39*, *40*). On the basis of these reviews, it would appear that:

— there are few large randomized trials that report clinical outcomes (e.g. mortality, stroke, acute myocardial infarction) for these medicines (*36*, *37*);
— there are no large comparative clinical trials that report comparative efficacy and safety;
— all of these medicines are associated with significant side effects.

The Committee's attention was also drawn to the findings of a recently published study, the Anti-Hypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (the ALLHAT trial), which have also brought into question the role of alpha-blockers in the treatment of hypertension (*41*). In that study, patients treated with the alpha-blocker, doxazosin, had higher mortality rates than those in other treatment groups (i.e. patients treated with chlorthalidone, amlodipine and lisinopril) and the doxazosin arm of the study was suspended early. There was no significant difference between the chlorthalidone, amlodipine and lisinopril treatment groups in terms of the primary outcome of the study, namely, the development of coronary heart disease.

The Committee also noted that hydralazine, reserpine and methyldopa are all off-patent and therefore usually relatively inexpensive. However, this alone is no justification to keep these medicines on the Model List as some of the ACE inhibitors and calcium-channel blockers are now also off-patent, and are probably safer and more effective.

On the basis of the evidence before it, the Committee recommended that reserpine and hydralazine be deleted from the Model List for the treatment of essential hypertension on the grounds of the lack of evidence of long-term effects on mortality and morbidity and the

availability of better and safer alternatives. Subsequent to the meeting Committee Members agreed that hydralazine should remain on the list for the acute treatment of severe pregnancy-induced hypertension pending a further evidence review. The Committee also recommended that prazosin be deleted as a complementary list medicine, because of the lack of evidence as to its additional benefit and given that the adverse effects of doxazosin on mortality and morbidity may be a class effect. In addition, the Committee recommended that captopril (an ACE inhibitor) be replaced by enalapril as the listed example of the therapeutic group, on the basis of its simpler dosage schedule.

With respect to the use of calcium-channel blockers, preliminary evidence was presented to the Committee suggesting that dihydropyridine calcium-channel blockers as a class should not be used as first-line drug treatment for hypertension, because of the potential increased risk of adverse outcomes. The Committee thus recommended that there should be a thorough and critical review of the evidence supporting the use of dihydropyridine calcium-channel blockers as first-line drug treatment for hypertension before its next meeting, at which time a decision about their retention or deletion from the Model List would be made.

The Committee considered the question of the appropriate treatment of pregnancy-induced hypertension (PIH), something that is not specifically addressed in the draft statement. Two Cochrane reviews have been published on the topic, one on mild-to-moderate PIH, last updated in 2000 (*42*) and one on severe PIH, updated in 2002 (*43*). The former concluded that data were insufficient to determine whether or not drug treatment was worthwhile at all; the second review concluded that treatment should be with a medicine with which the physician was familiar. Subsequent studies have suggested that, in terms of effects on the child, methyldopa is the medicine of choice, as it appears to have least impact on long-term development (*44*). The Committee therefore recommended that methyldopa be retained on the Model List (as a core list medicine) but with the addition of the following note:

> Methyldopa is listed for use in the management of pregnancy-induced hypertension only. Its use in the treatment of essential hypertension is not recommended in view of the availability of further evidence of the efficacy and safety of other medicines.

The Committee acknowledged that there is only limited evidence for its recommendation regarding the use of methyldopa in pregnancy, but that methyldopa seems to be the safest alternative for the fetus.

The Committee recommended that more research be conducted on the treatment of hypertension in pregnancy, especially with regard to long-term outcomes and effects on child development.

The Committee reviewed a proposal from the Secretariat to include magnesium sulphate in the Model List as an antihypertensive, specifically for treatment of pre-eclampsia. It was noted that pre-eclampsia is estimated to complicate 2–8% of pregnancies and is a major cause of morbidity and mortality for both the woman and her child. This disorder is usually associated with raised blood pressure. Anticonvulsant medicines have been used to treat women with pre-eclampsia in the belief that they reduce the risk of seizure. Following a systematic review of existing treatment trials, magnesium sulphate was identified as the most promising agent for further investigation in large-scale trials. According to the recently published results of the MAGnesium sulphate for Prevention of Eclampsia (MAGPIE) trial, covering 10141 women in 33 countries, treatment with magnesium sulphate halves the risk of eclampsia and probably reduces the risk of maternal death (*45, 46*).

The Committee noted that magnesium sulfate is already on the Model List (as a core list medicine in Section 5 Anticonvulsants/antiepileptics) and recommended that the following footnote be added to this entry:

> For use in eclampsia and severe pre-eclampsia and not for other convulsant disorders.

The Committee also urged that magnesium sulfate be made more generally available in view of the strong evidence demonstrating its benefit in the treatment of eclampsia and severe pre-eclapmsia.

With regard to the two remaining medicines in this section of the Model List, nifedipine and sodium nitroprusside, the Committee made the following recommendations:

- *Nifedipine*. Nifedipine should be included in the list of candidate items for fast-track deletion at the next meeting of the Expert Committee (see section 6 below).
- *Sodium nitroprusside*. The square box symbol should be removed.

The Committee's recommendations regarding the listing of the antihypertensive medicines in section 12.3 of the Model List are summarized in Table 3.

Table 3
Changes made to the listing of medicines for the treatment of hypertension during the present revision of the Model List (April 2003)

Medicine	Administration route and dosage forms	Recommendation
Core list medicines		
atenolol	tablet, 50 mg, 100 mg	Retained with no change
captopril	scored tablet, 25 mg	Replaced by enalapril, tablet 25 mg
hydralazine	tablet, 25 mg, 50 mg (hydrochloride) powder for injection, 20 mg (hydrochloride) in ampoule	Footnote added: *For the acute treatment of severe hypertension pregnancy-induced*
hydrochlorothiazide	scored tablet, 25 mg	Retained with no change
methyldopa	tablet, 250 mg	Footnote added: *Methyldopa is listed for use in the management of pregnancy-induced hypertension only. Its use in the treatment of essential hypertension is not recommended in view of the availability of further evidence of the efficacy and safety of other medicines.*
nifedipine	tablet, 10 mg sustained-release formulations	Footnote added: *The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee.*
reserpine	tablet, 100 µg, 250 µg injection, 1 mg in 1-ml ampoule	Deleted
Complementary list medicines		
prazosin	tablet, 500 µg, 1 mg	Deleted
sodium nitroprusside	powder for infusion, 50 mg in ampoule	Square box symbol removed

6. Priorities for future reviews

The Committee identified a number of sections of the Model List that it considered to be in need of systematic review. These are listed in Table 4, together with an indication of the level of priority of the review.

Table 4
Sections of the Model List recommended for review, with level of priority

Section number	Title	Priority (notes)
1	Anaesthetics (including muscle relaxants and preoperative medication)	High
2.4	Disease-modifying agents used in rheumatoid disorders	Low
3	Antiallergics and medicines used in anaphylaxis	Low
6.2.1	Cefalosporins	High
6.3	Antifungal medicines	High
7.2	Antimigraine medicines (prophylaxis)	Low
8	Antineoplastics, immuno-suppressives and medicines used in palliative care	High
11.1	Plasma substitutes	High
11.2	Plasma fractions for specific uses	High
12.2	Antiarrhythmic medicines	High
13	Dermatological medicines	Medium
14	Diagnostic agents	Medium
15	Disinfectants and antiseptics	Low
17.6	Laxatives	Low
20	Muscle relaxants (peripherally-acting) and cholinesterase inhibitors)	With anaesthetics (see section 1)
21	Ophthalmological preparations	High
25.1	Antiasthmatic medicines	High
26	Solutions correcting water, electrolyte and acid–base disturbances (intravenous solutions)	Medium

The Committee also recommended that a special review be carried out on the use of medicines in paediatrics.

The following medicines were identified as possible candidates for deletion according to the fast-track procedure at the next meeting of the Committee in 2004:

— ether (review actual consumption) (section 1.1 General anaesthetics and oxygen);
— colchicine (section 2.3 Medicines used to treat gout);
— clonazepam (section 5 Anticonvulsants/antiepileptics);
— niclosamide (section 6.1.1 Intestinal anthelminthics);
— pyrantel (section 6.1.1 Intestinal anthelminthics);
— triclabendazole (section 6.1.3 Antischistosomals and other antitrematode medicines);
— oxamniquine (section 6.1.3 Antischistosomals and other antitrematode medicines);

— imipenem + cilastatin (section 6.2.1 β-Lactam medicines);
— nalidixic acid (section 6.2.2 Other antibacterials);
— spectinomycin (section 6.2.2 Other antibacterials);
— levofloxacin (section 6.2.4 Antituberculosis medicines);
— thioacetazone + isoniazid (section 6.2.4 Antituberculosis medicines);
— diethyltoluamide (section 6.6 Insect repellents);
— ergotamine (section 7.1 Antimigraine medicines for treatment of acute attack);
— polygeline (section 11.1 Plasma substitutes);
— factor VIII and factor IX concentrates (section 11.2 Plasma fractions for specific uses);
— isoprenaline (section 12.2 Antiarrhythmic medicines);
— procainamide (section 12.2 Antiarrhythmic medicines);
— quinidine (section 12.2 Antiarrhythmic medicines);
— nifedepine (section 12.3 Antihypertensive medicines);
— topical sun protection agent (section 13.7 Ultraviolet-blocking agent);
— local anaesthetic, astringent and anti-inflammatory preparations (section 17.3 Antihaemorrhoidal medicines);
— atropine (in section 17.5 Antispasmodic medicines);
— codeine (in section 17.7.2 Antidiarrhoeal medicines (symptomatic) medicines);
— medroxyprogesterone acetate (in section 18.3.1 Hormonal contraceptives and section 18.7 Progestogens);
— silver nitrate (section 21.1 Anti-infective agents — Ophthalmological preparations);
— ergometrine (section 22.1 Oxytocics);
— salbutamol (in section 22.2 Antioxytocics);
— aminophylline (section 25.1 Antiasthmatic medicines);
— cromoglicic acid (section 25.1 Antiasthmatic medicines);
— theophylline (section 25.1 Antiasthmatic medicines);
— calcium gluconate (in section 27 Vitamins and minerals);
— sodium fluoride (section 27 Vitamins and minerals).

The Committee recommended that these items be identified in the present revision of the Model List with the following footnote:

> The public health relevance and/or efficacy and/or safety of this item or group has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee.

7. Recommendations

7.1 Additions, deletions and other changes to the Model List

1. The Committee recommended that amodiaquine (tablet, 153 mg, 200 mg (base)) be added to the Model List (as a core list medicine) with the following footnote:

> Amodiaquine should preferably be used as part of combination therapy.

The Committee also recommended that the place of amodiaquine in curative treatment be further defined by WHO guidelines and that the following text be added at the beginning of the relevant section of the Model List (section 6.5.3a Antimalarial medicines for curative treatment):

> Medicines for the treatment of *P. falciparum* malaria cases should be used in combination.

2. The Committee recommended that azithromycin (capsule, 250 mg, 500 mg and oral suspension, 200 mg/5 ml) be added to the Model List (as a core list medicine) for the single dose treatment of genital *C. trachomatis* infection and of trachoma only with the following footnote:

> Only listed for single-dose treatment of genital *C. trachomatis* and of trachoma.

3. The Committee recommended that the applications for the addition of paediatric ibuprofen, porcine insulin suspension (insulin semilente), miconazole nitrate buccal tablets, misoprostol and valaciclovir to the Model List be rejected.

4. The Committee recommended that the following footnote be added to paracetamol in section 2.1 (Non-opioid analgesics and antipyretics and non-steroidal anti-inflammatory medicines):

> Not recommended for anti-inflammatory use due to lack of proven benefit to that effect.

5. The Committee recommended that levonorgestrel (tablet, 1.5 mg) be added as a new dosage form of levonorgestrel and that ethinylestradiol + levonorgestrel (tablet, 50 µg + 250 µg (pack of four)) be deleted from the Model List.

6. The Committee recommended that the references to nonoxynol and spermicides in the entry for condoms and diaphragms be deleted.

7. The Committee recommended that the following text be inserted at the beginning of section 6.2.3 (Antileprosy medicines):

> Medicines used in the treatment of leprosy should never be used except in combination (i.e. as multidrug therapy (MDT)). Combination therapy is

essential to prevent the emergence of drug resistance. Colour-coded blister packs (MDT blister packs) containing standard two-medicine (paucibacillary leprosy) or three-medicine (multibacillary leprosy) combinations for adult and childhood leprosy should be used. MDT blister packs can be supplied free of charge through WHO.

The Committee also recommended that the same information be included in the WHO Essential Medicines Library and the *WHO model formulary*.

8. The Committee recommended that the composition of oral rehydration salts be changed to 75 mEq/l sodium (sodium chloride 2.6 g/l) and 75 mmol/l (13.5 g/l) glucose and that the following footnote be added:

In cases of cholera a higher concentration of sodium may be required.

9. The Committee recommended that the dosage form for streptokinase be changed to powder for injection, 1.5 million IU in vial and that the existing footnote, "For use in rare disorders or in exceptional circumstances." be removed.

10. The Committee recommended that chloral hydrate, dextromethorphan, fludrocortisone, folic acid, immunoglobulin, human normal and ipecacuanha be deleted from the Model List on the basis of the fast-track deletion procedure.

11. The Committee recommended that cyclophosphamide in section 2.4 (due to unfavourable benefit–risk ratio), desmopressin (due to rarity of the indication), iron dextran (due to unfavourable benefit–risk ratio), pethidine (due to a higher risk of central nervous toxicity relative to morphine) and the injectable form of trimethoprim (due to lack of need for this administration route) be deleted.

7.2 Core versus complementary listing of medicines

1. The Committee decided to refine the criteria for classifying medicines as either core or complementary list medicines as follows:

- The core list presents a list of minimum medicine needs for a basic health care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.
- The complementary list presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities and/or specialist medical care and/or specialist training are needed. In case of doubt, medicines may also be listed as complementary

on the basis of consistently higher costs or less attractive cost-effectiveness in a variety of settings.

The Committee recommended that the previously separate core and complementary lists be combined to form a single list, with the complementary list medicines printed in italics or otherwise identified.

2. The Committee recommended that the following medicines be moved from the core list to the complementary list: aminophylline, (in section 25.1 Antiasthmatic medicines), amphotericin B (section 6.3 Antifungal medicines), azathioprine (in section 2.4 Disease-modifying agents used in rheumatic disorders), clomifene, diethylcarbamazine, dopamine, ethosuximide, hydrocortisone (in section 17.4 Gastrointestinal anti-inflammatory medicines), intraperitoneal dialysis solution, methotrexate (in section 2.4 Disease-modifying agents used in rheumatic disorders), penicillamine (in section 2.4 Disease-modifying agents used in rheumatic disorders), pentamidine (in section 6.5.2 Antileishmaniasis medicines section 6.5.4 Antipneumocystosis and antitoxoplasmosis medicines and section 6.5.5a Antitrypanosomal medicines-African trypanosomiasis), pyridostigmine, sulfadiazine and sulfasalazine (in section 2.4 Disease-modifying agents used in rheumatic disorders).

3. The Committee recommended that the following medicines be moved from the complementary list to the core list: amoxicillin + clavulanic acid, chloramphenicol (oily suspension for injection in section 6.2.2 Other antibacterials), epinephrine (adrenaline) (in section 12.2 Antiarrhythmic medicines), levonorgestrel (30 µg tablet in section 18.3.1 Hormonal contraceptives), mannitol and norethisterone enantate.

7.3 Use of the square box symbol (including review of the corticosteroids

1. The Committee agreed to use the square box symbol on the basis of the following description:

> The square box symbol is primarily intended to indicate similar clinical performance within a pharmacological class. The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. Therapeutic equivalence is only indicated on the basis of reviews of efficacy and safety and when consistent with WHO clinical guidelines. National lists should not use a similar symbol and should be

specific in their final selection, which would depend on local availability and price.

2. The Committee recommended that the square box symbol be removed from the following items: amiloride, amoxicillin, amoxicillin + clavulinic acid, antitetanus immunoglobulin, azathioprine (in section 8.1 Immunosuppressive medicines), chloramphenicol, chloroquine (in section 6.5.3a Antimalarial medicines for curative treatment), ciclosporin, clomifene, charcoal activated, codeine (in section 2.2 Opioid analgesics and section 17.7.2 Antidiarrhoeal (symptomatic) medicines), cycloserine, dexamethasone (in section 3 Antiallergics and medicines used in anaphylaxis), diloxanide, doxorubicin, doxycycline (section 6. 5.3a Antimalarial medicines for curative treatment), epinephrine/adrenaline (in section 25.1 Antiasthmatic medicines), ethionamide, glibenclamide, ibuprofen, mannitol, DL-methionine, morphine (in section 1.3 Preoperative medication and sedation for short-term procedures and section 2.2 Opioid analgesics), neostigmine, promethazine (in section 1.3 Preoperative medication and sedation for short-term procedures and section 17.2 Antiemetic medicines), quinine, sodium nitroprusside, retinol, sulfadiazine, sulfadoxine + pyrimethamine, sulfamethoxazole + trimethoprim (in section 6.2.2 Other antibacterials) and verapamil.

3. The Committee recommended that the square box symbol be retained but that the example within the pharmacological class listed be changed in the following cases: captopril by enalapril and cimetidine by ranitidine.

4. The Committee recommended that for those medicines that are listed with a square box symbol examples of possible alternatives should be included in the Essential Medicines Library and in the *WHO model formulary*.

5. The Committee recommended the following changes be made to the listing of the corticosteroids currently included in the Model List:

- In section 3 (Antiallergics and medicines used in anaphylaxis), the tablet form of dexamethasone (500 µg, 4 mg) should be removed and a new dosage form added for prednisolone (tablet, 25 mg) making prednisolone tablets (5 mg and 25 mg) the only oral preparation for this indication. The entry for prednisolone should retain its square box symbol but should be annotated with a new footnote:

  There is no evidence for complete clinical similarity between prednisolone and dexamethasone at high doses.

The Committee also recommended that the two injectable dosage forms, dexamethasone (injection, 4 mg dexamethasone phosphate (as

disodium salt) in 1-ml ampoule) and hydrocortisone (powder for injection, 100 mg (as sodium succinate) in vial) should be retained in this section, but neither with a square box symbol.

- Section 8.3 (Hormones and antihormones) should include the same three corticosteroids as section 3 (i.e. dexamethasone, hydrocortisone and prednisolone) in the same dosage forms and strengths, and with the same footnote.
- In section 18.1 (Adrenal hormones and synthetic substances) all three corticosteroids (i.e. dexamethasone, hydrocortisone and prednisolone) should be deleted. The section heading should be maintained and the following text inserted:

  > Addison's disease is a rare condition; adrenal hormones for the treatment of this condition are already included in section 3.

7.4 Review of the antihypertensive medicines

1. The Committee recommended that the following modifications be made to the medicines listed in section 12.3 of the Model List (Antihypertensive medicines):

- Reserpine and prazosin should be deleted.
- Captopril should be replaced by enalapril as the listed example of the therapeutic group.
- Methyldopa should be retained as a core list medicine but with the addition of the following footnote:

  > Methyldopa is listed for use in the management of pregnancy-induced hypertension only. Its use in the treatment of essential hypertension is not recommended in view of the availability of more evidence of efficacy and safety of other medicines.

- The square box symbol should be removed from sodium nitroprusside.

2. In sum, the Committee recommended that section 12.3 (Antihypertensive medicines) comprise: atenolol (tablet, 50 mg, 100 mg) with a square box; enalapril (tablet, 25 mg); hydrochlorothiazide (scored tablet, 25 mg) with a square box; methyldopa (tablet, 250 mg) and nifedipine (tablet, 10 mg and as slow-release formulations) with a square box as core list medicines and sodium nitroprusside (powder for infusion, 50 mg in ampoule) as a complementary list medicine.

3. The Committee recommended that more research be done on the treatment of hypertension in pregnancy, in particular on long-term outcomes and effects on child development, and that a thorough and

critical review be carried out of the justification of the use of dihydropyridine calcium-channel blockers as first-line treatment drug for hypertension.

7.5 Future priorities

1. The Committee recommended that the following items be presented for fast-track deletion at its next meeting: ether, colchicine, clonazepam, niclosamide, pyrantel, triclabendazole, oxamniquine, imipenem + cilastatin, nalidixic acid, spectinomycin, levofloxacin, thioacetazone + isoniazid, diethyltoluamide, ergotamine, polygeline, factor VIII and factor IX concentrates, isoprenaline, procainamide, quinidine, nifedepine, topical sun protection agent, antihaemorrhoidal local anaesthetic, astringent and anti-inflammatory preparations, atropine (in section 17.5 Antispasmodic medicines), codeine (in section 17.7.2 Antidiarrhoeal (symptomatic) medicines), medroxyprogesterone acetate (in section 18.3.1 Hormonal contraceptives and section 18.7 Progestogens), silver nitrate, ergometrine, salbutamol (in section 22.2 Antioxytocics), aminophylline, cromoglicic acid, theophylline, calcium gluconate (in section 27 Vitamins and minerals) and sodium fluoride.

2. The Committee recommended that these items be marked in the Model List with the following footnote:

> The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee.

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Annex 1
The 13th WHO Model List of Essential Medicines

Introduction

The concept of essential medicines

Essential medicines are those that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford. The implementation of the concept of essential medicines is intended to be flexible and adaptable to many different situations; exactly which medicines are regarded as essential remains a national responsibility. Experience has shown that careful selection of a limited range of essential medicines results in a higher quality of care, better management of medicines (including improved quality of prescribed medicines), and a more cost-effective use of available health resources (*1*, *2*).

The WHO Model List of Essential Medicines

Most countries require that a pharmaceutical product be approved on the basis of efficacy, safety and quality before it can be prescribed. The majority of health care and insurance schemes will only cover the cost of medicines on a given list of approved medicines. Medicines on such lists are selected after careful study of the medicines used to treat particular conditions and a comparison of the value they provide in relation to their cost. The WHO Model List of Essential Medicines (the Model List) is an example of such a list.

The first WHO Model List was drawn up in 1977 (*3*) in response to a request from the World Health Assembly (resolution WHA28.66) to the Director-General of WHO to provide Member States with advice on the selection and procurement, at reasonable costs, of essential medicines of established quality corresponding to their national health needs (*4*). The Model List has since been revised and updated 11 times (excluding the present revision) at intervals of approximately 2 years (*5–15*). Over the past two decades, the regular updating of the

Model List has not only been at the heart of WHO's revised drug strategy (*16*) but has also formed a key component of the information required by Member States in relation to their medicine procurement and supply programmes.

The Model List was originally intended as a guide for the development of national and institutional essential medicine lists. It was not designed as a global standard. Nevertheless, since its introduction 25 years ago, the Model List has led to a global acceptance of the concept of essential medicines as a powerful tool for promoting health equity. By the end of 1999, 156 Member States had official essential medicines lists, of which 127 had been updated in the previous 5 years. Most countries have national lists; some have provincial or state lists as well.

The concept of essential medicines has also been adopted by many international organizations, including the United Nations Children's Fund (UNICEF) and the Office of the United Nations High Commissioner for Refugees (UNHCR), as well as by nongovernmental organizations and international non-profit supply agencies. Many of these organizations base their medicine supply system on the Model List. Lists of essential medicines also guide the procurement and supply of medicines in the public sector, schemes that reimburse medicine costs, medicine donations and local medicine production, and, furthermore, are widely used as informational and educational tools by health professionals. Health insurance schemes too are increasingly using national lists of essential medicines for reference purposes.

The way in which national lists of essential medicines are developed and used has evolved over time. Initially, lists were drawn up primarily as a means to guide the procurement of medicines. More recently, however, greater emphasis has been placed on the development of treatment guidelines as the basis for medicine selection and supply, and on the evidence underlying the development of those treatment guidelines. Consequently, there has been an increasing demand for information on why a particular medicine is included in the Model List and also for references to the underlying evidence. Activities are now underway to strengthen the links between the Model List and the treatment guidelines developed by WHO.

In its present form, the Model List aims to identify cost-effective medicines for priority conditions, together with the reasons for their inclusion, linked to evidence-based clinical guidelines and with special emphasis on public health aspects and considerations of value for money. Information that supports the selection of essential medicines, such as summaries of relevant WHO clinical guidelines, system-

atic reviews, key references and indicative cost information is being made available via the WHO web site as the WHO Essential Medicines Library[1]. The latter provides links to other relevant sources of information, including the *WHO model formulary* and information on nomenclature and quality assurance standards. The Essential Medicines Library is under construction and will be expanded over time. Its primary function is to facilitate the work of national and institutional committees in developing national and institutional lists of essential medicines.

Medicines on the Model List are classified as either "core" list or "complementary" list medicines. The core list presents a list of minimum medicine needs for a basic health care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment. The complementary list presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities and/or specialist medical care and/or specialist training are needed. In case of doubt, medicines may also be listed as complementary on the basis of consistently higher costs or less attractive cost-effectiveness in a variety of settings.

A number of medicines are labelled with a square box symbol. This symbol is primarily intended to indicate similar clinical performance within a pharmacological class. The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in others, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of the efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. Therapeutic equivalence is only indicated on the basis of reviews of efficacy and safety and when consistent with WHO clinical guidelines. National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price. Examples of alternatives for the medicines with a square box symbol are not included in the Model List, but such information is provided in the *WHO model formulary* and in the Essential Medicines Library.

[1] http://www.who.int/medicines.

Procedures for updating the Model List

The procedures for updating the Model List are in line with the WHO recommended process for developing clinical practice guidelines (*17*). The key components are a systematic approach to collecting and reviewing evidence and a transparent development process with several rounds of external review. The procedures are intended to serve as a model for developing or updating national and institutional clinical guidelines and lists of essential medicines. Further information on the procedures for updating the Model List, including descriptions of the applications and details of the review process, is available from the WHO web site[1].

Selection criteria

The choice of essential medicines depends on several factors, including public health relevance and the availability of data on the efficacy, safety and comparative cost-effectiveness of available treatments. Factors such as stability in various conditions, the need for special diagnostic or treatment facilities and pharmacokinetic properties are also considered if appropriate. In adapting the Model List to their own needs, countries often consider factors such as local demography and the pattern of prevalent diseases; treatment facilities; training and experience of available personnel; local availability of individual pharmaceutical products; financial resources; and environmental factors.

The selection of essential medicines must be based on valid scientific evidence; only medicines for which sound and adequate data on efficacy and safety are available should be selected. In the absence of adequate scientific evidence on current treatment of a priority disease, the WHO Expert Committee on the Selection and Use of Essential Medicines may either defer its decision regarding selection until more evidence becomes available, or choose to make recommendations based on expert opinion and experience.

Most essential medicines should be formulated as single compounds. Fixed-dose combination products are selected only when the combination has a proven advantage over single compounds administered separately in therapeutic effect, safety, adherence or in delaying the development of drug resistance in malaria, tuberculosis and HIV/AIDS.

When making cost comparisons between medicines, the cost of the total treatment, not just the unit cost of the medicine, is considered. Cost and cost-effectiveness comparisons may be made among

[1] http://www.who.int/medicines.

alternative treatments within the same therapeutic group, but are generally not made across therapeutic categories (e.g. between the treatment of tuberculosis and the treatment of malaria). The absolute cost of the treatment does not constitute a reason to exclude a medicine from the Model List that otherwise meets the stated selected criteria. The patent status of a medicine is not considered when selecting medicines for the Model List.

Quality assurance

Priority should be given to ensuring that available medicines have been made according to good manufacturing practices (*18*) and are of assured quality. Factors that need to be considered include:

— knowledge of, and confidence in, the origin of the product;
— the pharmaceutical stability of the product, particularly in the environment that it will be used;
— where relevant, bioavailability and bioequivalence information.

It is recommended that all medicines be purchased from known manufacturers, their duly accredited agents, or recognized international agencies known to apply high standards in selecting their suppliers.

Promoting rational use of essential medicines

The selection of essential medicines is only one step towards the improvement of the quality of health care; selection needs to be followed by appropriate use. Each individual should receive the right medicine, in an adequate dose for an adequate duration, with appropriate information and follow-up treatment, and at an affordable cost. Within different countries and settings, this is influenced by a number of factors, such as regulatory decisions, procurement, information, training, and the context in which medicines are prescribed or recommended.

Training, education and the provision of medicines information

To ensure the safe, effective and prudent use of essential medicines, access to relevant, reliable and independent information on medicines is vital. Health care professionals should receive education about the use of medicines not only during their training but also throughout their careers. The more highly trained individuals should be encouraged to assume responsibility for educating those with less training. Health care providers and pharmacists who are responsible for dispensing medicines should take every opportunity to inform consumers about the rational use of products, including those for self-medication, at the time they are dispensed.

Governments, universities and professional associations have a critical role to play with regard to the improvement of undergraduate, postgraduate and continuing education in clinical pharmacology, therapeutics and medicines information issues. Problem-based pharmacotherapy teaching has been shown to be a particularly effective strategy in this area (*19*).

Well presented and appropriate information about medicines not only ensures that they are used properly but also decreases the inappropriate use of medicines. Health ministries have a responsibility to arrange for the provision of such information. Independent medicines information activities should also be properly funded and, if necessary, financed through health care budgets. Electronic, readily accessible sources of medicines information are becoming more widely available and can form the basis of reliable medicines information systems in many settings.

Standard clinical guidelines

Standard clinical guidelines are an effective tool for assisting health professionals to choose the most appropriate medicine for a given patient with a given condition. They should be developed at national and local levels and updated on a regular basis. In order to be effective, however, standard clinical guidelines require the support of appropriate education and training programmes aimed at encouraging their use.

Drugs and therapeutic committees

Drugs and therapeutic committees can play an important role in the development and implementation of effective essential medicines programmes. Such committees should be encouraged to select products for local use from a national essential medicines list, to measure and monitor the use of these products in their own environments and to undertake interventions to improve their rational use. There is good evidence to suggest that involving both drugs and therapeutic committees and prescribers in guideline development can contribute to improved prescribing behaviour (*20*).

Measuring and monitoring medicine use

The purpose of drug utilization studies is to examine the development, regulation, marketing, distribution, prescription, dispensing and use of medicines within a society, with special emphasis on the medical, social and economic consequences. Studies of this type consider all levels of the therapeutic chain, from the development of medicines to their use by consumers. Drug utilization studies can be

medicine-oriented (i.e. focused on the use of a particular medicine or group of medicines) or problem-oriented (i.e. focused on the treatment of a particular condition or disease) and can provide consumption indicators for a given country, area or institution.

Consumption can be measured in terms of economic expenditure (either in absolute terms or as a percentage of the total health budget), the number of units, or as Defined Daily Doses (DDDs) (*21*). However, it is generally recommended that drug utilization studies be conducted using the Anatomical Therapeutic Chemical (ATC) classification and the DDD as the measuring unit, especially when making international comparisons on the use of medicines.

The efficacy of a medicine is best assessed on the basis of randomized clinical trials, which, if well conducted, provide reliable estimates of the treatment effect of a new medicine. However, clinical trials cannot be conducted in all possible populations or settings and therefore their results must be translated into routine clinical practice with care. Given that drug utilization studies generally provide evidence on the use and the effects of medicines in routine conditions, they can provide additional evidence for the evaluation of the effectiveness of a medicine.

Drug utilization studies and clinical trials are important tools for identifying those factors or elements of the therapeutic chain in need of improvement or change. The results of such studies should be taken into consideration when taking regulatory action, selecting medicines, or designing information, training and teaching programmes.

Monitoring of medicine safety and pharmacovigilance

Safety monitoring is an important part of the overall surveillance of medicine use. The aims of the various forms of pharmacovigilance are to identify new, previously unrecognized adverse effects of medicines, to quantify their risks, and to communicate these to drug regulatory authorities, health professionals, and, when relevant, the public. Voluntary reporting of adverse effects of medicines, on which the International WHO Programme for Drug Monitoring is based, has been effective in identifying a number of previously undescribed effects. Voluntary reporting schemes, together with other methods for assembling case series, can identify certain local safety problems, and thus form the basis for specific regulatory or educational interventions. The magnitude of the risk of adverse effects is generally evaluated using observational epidemiological methods, such as case–control, cohort and case–population studies. Each country and institution

should set up simple schemes aimed at identifying problems related to the safety of medicines.

Explanatory notes

The core list presents a list of minimum medicine needs for a basic health care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

The complementary list presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities and/or specialist medical care and/or specialist training are needed. In case of doubt, medicines may also be listed as complementary on the basis of consistently higher costs or less attractive cost-effectiveness in a variety of settings. In the present Model List (the 13th), complementary list medicines are distinguished by italicized typeface.

When the strength of a medicine 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".

The square box symbol (□) is primarily intended to indicate similar clinical performance within a pharmacological class. The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in others, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of the efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. Therapeutic equivalence is only indicated on the basis of reviews of efficacy and safety and when consistent with WHO clinical guidelines. National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price.

Medicines are grouped according to therapeutic categories. The numbers preceding the sections and subsections have, in general, been allocated in accordance with English alphabetical order; they have no formal significance. Within sections, medicines are listed in alphabetical order.

Certain pharmacological effects have many therapeutic uses. Medicines with multiple uses could be listed under several therapeutic categories in the Model List. However, the inclusion of such

medicines in more than one therapeutic category has been limited to those circumstances that the Expert Committee wishes to emphasize. Medicines on the Model List are therefore not listed in all of the therapeutic categories in which they are of value. Detailed information on the therapeutic use of essential medicines is available in the *WHO model formulary* (*22*).

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

[a] The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee.

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

□ Recommended of example within a pharmaceutical class. See Explanatary notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
1. Anaesthetics (*continued*)	
morphine	injection, 10 mg (hydrochloride or sulfate) in 1-ml ampoule
promethazine	elixir or syrup, 5 mg (hydrochloride)/5 ml
2. Analgesics, antipyretics, non-steroidal anti-inflammatory medicines, medicines used to treat gout and disease-modifying agents used in rheumatoid disorders	
2.1 ***Non-opioid analgesics and antipyretics, and non-steroidal anti-inflammatory medicines***	
acetylsalicylic acid	tablet, 100–500 mg
	suppository, 50–150 mg
ibuprofen	tablet, 200 mg, 400 mg
paracetamol[a]	tablet, 100–500 mg
	suppository, 100 mg
	syrup, 125 mg/5 ml
2.2 ***Opioid analgesics***	
codeine	tablet, 30 mg (phosphate)
morphine	injection, 10 mg (hydrochloride or sulfate) in 1-ml ampoule
	oral solution, 10 mg (hydrochloride or sulfate)/5 ml
	tablet, 10 mg (sulfate)
2.3 ***Medicines used to treat gout***	
allopurinol	tablet, 100 mg
colchicine[b]	tablet, 500 µg
2.4 ***Disease-modifying agents used in rheumatoid disorders***	
chloroquine	tablet, 100 mg, 150 mg (as phosphate or sulfate)

[a] Not recommended for anti-inflammatory use due to lack of proven benefit to that effect.

[b] The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee.

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
2. Analgesics, antipyretics, non-steroidal anti-inflammatory medicines, medicines used to treat gout and disease-modifying agents used in rheumatoid disorders (*continued*)	
Complementary list medicines	
azathioprine	tablet, 50 mg
methotrexate	tablet, 2.5 mg (as sodium salt)
penicillamine	capsule or tablet, 250 mg
sulfasalazine	tablet, 500 mg
3. Antiallergics and medicines used in anaphylaxis	
□ chlorphenamine	tablet, 4 mg (hydrogen maleate)
	injection, 10 mg (hydrogen maleate) in 1-ml ampoule
dexamethasone	injection, 4 mg dexamethasone phosphate (as disodium salt) in 1-ml ampoule
epinephrine (adrenaline)	injection, 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule
hydrocortisone	powder for injection, 100 mg (as sodium succinate) in vial
□ prednisolone[a]	tablet, 5 mg, 25 mg
4. Antidotes and other substances used in poisonings	
4.1 *Non-specific*	
charcoal, activated	powder
4.2 *Specific*	
acetylcysteine	injection, 200 mg/ml in 10-ml ampoule
atropine	injection, 1 mg (sulfate) in 1-ml ampoule
calcium gluconate	injection, 100 mg/ml in 10-ml ampoule
deferoxamine	powder for injection, 500 mg (mesilate) in vial
dimercaprol	injection in oil, 50 mg/ml in 2-ml ampoule
DL-methionine	tablet, 250 mg

[a] There is no evidence for complete clinical similarity between prednisolone and dexamethasone at high doses.

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
4. Antidotes and other substances used in poisonings (*continued*)	
methylthioninium chloride (methylene blue)	injection, 10 mg/ml in 10-ml ampoule
naloxone	injection, 400 µg (hydrochloride) in 1-ml ampoule
penicillamine	capsule or tablet, 250 mg
potassium ferric hexacyanoferrate(II)·$2H_2O$ (Prussian blue)	powder for oral administration
sodium calcium edetate	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	scored tablet, 100 mg, 200 mg
□ diazepam	injection, 5 mg/ml in 2-ml ampoule (intravenous or rectal)
magnesium sulfate[a]	injection, 500 mg/ml in 2-ml ampoule, 500 mg/ml in 10-ml ampoule
phenobarbital	tablet, 15–100 mg
	elixir, 15 mg/5 ml
phenytoin	capsule or tablet, 25 mg, 50 mg, 100 mg (sodium salt)
	injection, 50 mg (sodium salt)/ml in 5-ml vial
valproic acid	enteric coated tablet, 200 mg, 500 mg (sodium salt)
Complementary list medicines	
□ *clonazepam*[b]	scored tablet, 500 µg
ethosuximide	capsule, 250 mg
	syrup, 250 mg/5 ml

[a] For use in eclampsia and severe pre-eclampsia and not for other convulsant disorders.

[b] The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee.

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
6. Anti-infective medicines	
6.1 *Anthelminthics*	
6.1.1 *Intestinal anthelminthics*	
albendazole	chewable tablet, 400 mg
levamisole	tablet, 50 mg, 150 mg (as hydrochloride)
□ mebendazole	chewable tablet, 100 mg, 500 mg
niclosamide[a]	chewable tablet, 500 mg
praziquantel	tablet, 150 mg, 600 mg
pyrantel[a]	chewable tablet, 250 mg (as embonate)
	oral suspension, 50 mg (as embonate)/ml
6.1.2 *Antifilarials*	
ivermectin	scored tablet, 3 mg, 6 mg
Complementary list medicines	
diethylcarbamazine	tablet, 50 mg, 100 mg (dihydrogen citrate)
suramin sodium	powder for injection, 1 g in vial
6.1.3 *Antischistosomals and other antitrematode medicines*	
praziquantel	tablet, 600 mg
triclabendazole[a]	tablet, 250 mg
Complementary list medicine	
oxamniquine[a]	capsule, 250 mg
	syrup, 250 mg/5 ml
6.2 *Antibacterials*	
6.2.1 *β-Lactam medicines*	
amoxicillin	capsule or tablet, 250 mg, 500 mg (anhydrous)
	powder for oral suspension, 125 mg (anhydrous)/5 ml

[a] The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee.

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
6. Anti-infective medicines (*continued*)	
amoxicillin + clavulanic acid[a]	tablet, 500 mg + 125 mg
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
Complementary list medicines	
ceftazidime[a]	powder for injection, 250 mg (as pentahydrate) in vial
□ *ceftriaxone*[a]	powder for injection, 250 mg (as sodium salt) in vial
imipenem + cilastatin[a,b]	powder for injection, 250 mg (as monohydrate) + 250 mg (as sodium salt), 500 mg (as monohydrate) + 500 mg (as sodium salt) in vial

[a] Reserve antimicrobial for use only when there is significant resistance to other medicines on the Model List.

[b] The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee.

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
6. Anti-infective medicines (*continued*)	
6.2.2 *Other antibacterials*	
azithromycin[a]	capsule, 250 mg, 500 mg
	oral suspension, 200 mg/5 ml
chloramphenicol	capsule, 250 mg
	oral suspension, 150 mg (as palmitate)/5 ml
	powder for injection, 1 g (sodium succinate) in vial
	oily suspension for injection, 0.5 g (as sodium succinate)/ml in 2-ml ampoule
□ ciprofloxacin[b]	tablet, 250 mg (as hydrochloride)
□ doxycycline[b]	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[b]	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[c]	tablet 250 mg, 500 mg
nitrofurantoin	tablet, 100 mg

[a] Only listed for single-dose treatment of genital *Chlamydia trachomatis* and of trachoma.

[b] Final selection depends on indication for use.

[c] The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee.

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
6. Anti-infective medicines (*continued*)	
spectinomycin[a]	powder for injection, 2 g (as hydrochloride) in vial
sulfamethoxazole + trimethoprim	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	tablet, 100 mg, 200 mg
Complementary list medicines	
clindamycin	capsule, 150 mg
	injection, 150 mg (as phosphate)/ml
sulfadiazine	tablet, 500 mg
	injection, 250 mg (sodium salt) in 4-ml ampoule
vancomycin[b]	powder for injection, 250 mg (as hydrochloride) in vial
6.2.3 *Antileprosy medicines*	
Medicines used in the treatment of leprosy should never be used except in combination (i.e. as multidrug therapy (MDT)). Combination therapy is essential to prevent the emergence of drug resistance. Colour-coded blister packs (MDT blister packs) containing standard two-medicine (paucibacillary leprosy) or three-medicine (multibacillary leprosy) combinations for adult and childhood leprosy should be used. MDT blister packs can be supplied free of charge through WHO.	
clofazimine	capsule, 50 mg, 100 mg
dapsone	tablet, 25 mg, 50 mg, 100 mg
rifampicin	capsule or tablet, 150 mg, 300 mg
6.2.4 *Antituberculosis medicines*	
ethambutol	tablet, 100–400 mg (hydrochloride)

[a] The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee.

[b] Reserve antimicrobial for use only when there is significant resistance to other medicines on the Model List.

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
6. Anti-infective medicines (*continued*)	
isoniazid	tablet, 100–300 mg
isoniazid + ethambutol	tablet, 150 mg + 400 mg
pyrazinamide	tablet, 400 mg
rifampicin	capsule or tablet, 150 mg, 300 mg
rifampicin + isoniazid	tablet, 60 mg + 30 mg, 150 mg + 75 mg, 300 mg + 150 mg, 60 mg + 60 mg[a], 150 mg + 150 mg[a]
rifampicin + isoniazid + pyrazinamide	tablet, 60 mg + 30 mg + 150 mg, 150 mg + 75 mg + 400 mg, 150 mg + 150 mg + 500 mg[a]
rifampicin + isoniazid + pyrazinamide + ethambutol	tablet, 150 mg + 75 mg + 400 mg + 275 mg
streptomycin	powder for injection, 1 g (as sulfate) in vial
Complementary list medicines	
amikacin[b]	powder for injection, 1 g in vial
p-aminosalicylic acid[b]	tablet, 500 mg
	granules, 4 g in sachet
capreomycin[b]	powder for injection, 1 g in vial
ciprofloxacin[b]	tablet, 250 mg, 500 mg
cycloserine[b]	capsule or tablet, 250 mg
ethionamide[b]	tablet, 125 mg, 250 mg
kanamycin[b]	powder for injection, 1 g in vial
levofloxacin[b,c]	tablet, 250 mg, 500 mg
ofloxacin[b]	tablet, 200 mg, 400 mg

[a] For intermittent use three times weekly.

[b] Reserve second-line medicine for the treatment of multidrug-resistant tuberculosis which should be used in specialized centres adhering to WHO standards for tuberculosis control.

[c] The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee.

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
6. Anti-infective medicines (*continued*)	
thioacetazone + *isoniazid*[a]	tablet, 50 mg + 100 mg, 150 mg + 300 mg
6.3 Antifungal medicines	
□ fluconazole	capsule, 50 mg
	injection, 2 mg/ml in vial
	oral suspension, 50 mg/5 ml
griseofulvin	capsule or tablet, 125 mg, 250 mg
nystatin	tablet, 100 000 IU, 500 000 IU
	lozenge, 100 000 IU
	pessary, 100 000 IU
Complementary list medicines	
amphotericin B	powder for injection, 50 mg in vial
flucytosine	capsule, 250 mg
	infusion, 2.5 g in 250 ml
potassium iodide	saturated solution
6.4 *Antiviral medicines*	
6.4.1 *Antiherpes medicines*	
□ aciclovir	tablet, 200 mg
	powder for injection, 250 mg (as sodium salt) in vial

6.4.2 *Antiretroviral medicines*

The antiretroviral medicines do not cure the HIV infection, they only temporarily suppress viral replication and improve symptoms. They have various adverse effects and patients receiving these medicines require careful monitoring by adequately trained health professionals. For these reasons, continued rigorous promotion of measures to prevent new infections is essential and the need for this has not been diminished in any way by the addition of antiretroviral medicines to the Model List. Adequate resources and trained health professionals are a prerequisite for the introduction of this class of medicines. Effective therapy requires commencement of three or four medicines simultaneously, and alternative regimens are necessary to meet specific

[a] The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee.

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
6. Anti-infective medicines (*continued*)	
requirements at start-up, to substitute for first-line regimens in the case of toxicity, or to replace failing regimens. The Committee strongly recommends the use of three- or four-medicine combinations as specifically recommended in the WHO treatment guidelines (*23*). The use of fixed-dose preparations for these combinations is also recommended, with assured pharmaceutical quality and interchangeability with the single products as approved by the relevant drug regulatory authority.	
(a) Nucleoside reverse transcriptase inhibitors	
abacavir (ABC)	tablet, 300 mg (as sulfate)
	oral solution, 100 mg (as sulfate)/5 ml
didanosine (ddI)	buffered chewable dispersible tablet, 25 mg, 50 mg, 100 mg, 150 mg, 200 mg
	buffered powder for oral solution, 100 mg, 167 mg, 250 mg packets
	unbuffered enteric coated capsule, 125 mg, 200 mg, 250 mg, 400 mg
lamivudine (3TC)	tablet, 150 mg
	oral solution, 50 mg/5 ml
stavudine (d4T)	capsule, 15 mg, 20 mg, 30 mg, 40 mg
	powder for oral solution, 5 mg/5 ml
zidovudine (ZDV or AZT)	tablet, 300 mg
	capsule, 100 mg, 250 mg
	oral solution or syrup, 50 mg/5 ml
	solution for IV infusion injection, 10 mg/ml in 20-ml vial
(b) Non-nucleoside reverse transcriptase inhibitors	
efavirenz (EFV or EFZ)	capsule, 50 mg, 100 mg, 200 mg
	oral solution, 150 mg/5 ml
nevirapine (NVP)	tablet, 200 mg
	oral suspension, 50 mg/5 ml
(c) Protease inhibitors	
Selection of two or three protease inhibitors from the Model List will need to be determined by each country after consideration of local clinical guidelines and experience, as well as the comparative costs of available products. Ritonavir is recommended for use in combination with indinavir, lopinavir and saquinavir as a booster, and not as a medicine in its own right.	

Medicine	*Route of administration, dosage forms and strengths*
6. Anti-infective medicines (*continued*)	
indinavir (IDV)	capsule, 200 mg, 333 mg, 400 mg (as sulfate)
lopinavir + ritonavir (LPV/r)	capsule, 133.3 mg + 33.3 mg
	oral solution, 400 mg + 100 mg/5 ml
nelfinavir (NFV)	tablet, 250 mg (as mesilate)
	oral powder, 50 mg/g
ritonavir (r)	capsule, 100 mg
	oral solution, 400 mg/5 ml
saquinavir (SQV)	capsule, 200 mg
6.5 *Antiprotozoal medicines*	
6.5.1 *Antiamoebic and antigiardiasis medicines*	
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 medicines*	
□ meglumine antimoniate	injection, 30%, equivalent to approximately 8.1% antimony, in 5-ml ampoule
Complementary list medicines	
amphotericin B	powder for injection, 50 mg in vial
pentamidine	powder for injection, 200 mg, 300 mg (isetionate) in vial
6.5.3 *Antimalarial medicines*	
(a) For curative treatment	
Medicines for the treatment of *P. falciparum* malaria cases should be used in combination.	
amodiaquine[a]	tablet, 153 mg, 200 mg (base)

[a] Amodiaquine should preferably be used as part of combination therapy.

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
6. Anti-infective medicines (*continued*)	
artemether + lumefantrine[a]	tablet, 20 mg + 120 mg
chloroquine	tablet, 100 mg, 150 mg (as phosphate or sulfate)
	syrup, 50 mg (as phosphate or sulfate)/5 ml
	injection, 40 mg (as hydrochloride, phosphate or sulfate)/ml in 5-ml ampoule
primaquine	tablet, 7.5 mg, 15 mg (as diphosphate)
quinine	tablet, 300 mg (as bisulfate or sulfate)
	injection, 300 mg (as dihydrochloride)/ml in 2-ml ampoule
Complementary list medicines	
artemether[b]	injection, 80 mg/ml in 1-ml ampoule
artesunate[b]	tablet, 50 mg
doxycycline[c]	capsule or tablet, 100 mg (hydrochloride)
mefloquine	tablet, 250 mg (as hydrochloride)
sulfadoxine + pyrimethamine	tablet, 500 mg + 25 mg
(b) For prophylaxis	
chloroquine	tablet, 150 mg (as phosphate or sulfate)
	syrup, 50 mg (as phosphate or sulfate)/5 ml
doxycycline	capsule or tablet, 100 mg (hydrochloride)
mefloquine	tablet, 250 mg (as hydrochloride)
proguanil[d]	tablet, 100 mg (hydrochloride)

[a] Recommended for use in areas with significant drug resistance and not in pregnancy or in children below 10 kg.

[b] Reserve antimicrobial for use only when there is significant resistance to other medicines on the Model List.

[c] For use only in combination with quinine.

[d] For use only in combination with chloroquine.

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
6. Anti-infective medicines (*continued*)	
6.5.4 *Antipneumocystosis and antitoxoplasmosis medicines*	
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
Complementary list medicine	
pentamidine	tablet, 200 mg, 300 mg
6.5.5 *Antitrypanosomal medicines*	
(a) African trypanosomiasis	
melarsoprol	injection, 3.6% solution
suramin sodium	powder for injection, 1 g in vial
Complementary list medicines	
eflornithine	injection, 200 mg (hydrochloride)/ml in 100-ml bottle
pentamidine	powder for injection, 200 mg, 300 mg (isetionate) in vial
(b) American trypanosomiasis	
benznidazole	tablet, 100 mg
nifurtimox	tablet, 30 mg, 120 mg, 250 mg
6.6 *Insect repellents*	
diethyltoluamide[a]	topical solution, 50%, 75%
7. Antimigraine medicines	
7.1 *For treatment of acute attack*	
acetylsalicylic acid	tablet, 300–500 mg
ergotamine[a]	tablet, 1 mg (tartrate)
paracetamol	tablet, 300–500 mg

[a] The public health relevance and/or efficacy and or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee.

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
7. Antimigraine medicines (*continued*)	
7.2 *For prophylaxis*	
□ propranolol	tablet, 20 mg, 40 mg (hydrochloride)
8. Antineoplastics, immunosuppressives and medicines used in palliative care	
8.1 *Immunosuppressive medicines*	
Complementary list medicines	
azathioprine	tablet, 50 mg
	powder for injection, 100 mg (as sodium salt) in vial
ciclosporin[a]	capsule, 25 mg
	concentrate for injection, 50 mg/ml in 1-ml ampoule
8.2 *Cytotoxic medicines*	
Complementary list medicines	
asparaginase	powder for injection, 10 000 IU in vial
bleomycin	powder for injection, 15 mg (as sulfate) in vial
calcium folinate	tablet, 15 mg
	injection, 3 mg/ml in 10-ml ampoule
chlorambucil	tablet, 2 mg
chlormethine	powder for injection, 10 mg (hydrochloride) in vial
cisplatin	powder for injection, 10 mg, 50 mg in vial
cyclophosphamide	tablet, 25 mg
	powder for injection, 500 mg in vial
cytarabine	powder for injection, 100 mg in vial
dacarbazine	powder for injection, 100 mg in vial
dactinomycin	powder for injection, 500 µg in vial
daunorubicin	powder for injection, 50 mg (as hydrochloride)

[a] For organ transplantation.

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
8. Antineoplastics, immunosuppressives and medicines used in palliative care (*continued*)	
doxorubicin	powder for injection, 10 mg, 50 mg (hydrochloride) in vial
etoposide	capsule, 100 mg
	injection, 20 mg/ml in 5-ml ampoule
fluorouracil	injection, 50 mg/ml in 5-ml ampoule
levamisole	tablet, 50 mg (as hydrochloride)
mercaptopurine	tablet, 50 mg
methotrexate	tablet, 2.5 mg (as sodium salt)
	powder for injection, 50 mg (as sodium salt) in vial
procarbazine	capsule, 50 mg (as hydrochloride)
vinblastine	powder for injection, 10 mg (sulfate) in vial
vincristine	powder for injection, 1 mg, 5 mg (sulfate) in vial
8.3 ***Hormones and antihormones***	
Complementary list medicines	
dexamethasone	injection, 4 mg dexamethasone phosphate (as disodium salt) in 1-ml ampoule
hydrocortisone	powder for injection, 100 mg (as sodium succinate) in vial
□ *prednisolone*[a]	tablet, 5 mg, 25 mg
tamoxifen	tablet, 10 mg, 20 mg (as citrate)

8.4 ***Medicines used in palliative care***

The Committee recommended that all the medicines mentioned in the WHO publication, *Cancer pain relief: with a guide to opioid availability*, 2nd ed., be considered essential (*24*). The medicines are included in the relevant sections of the Model List, according to their therapeutic use, e.g. as analgesics.

[a] There is no evidence for complete clinical similarity between prednisolone and dexamethasone at high doses.

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
9. Antiparkinsonism medicines	
□ biperiden	tablet, 2 mg (hydrochloride)
	injection, 5 mg (lactate) in 1-ml ampoule
levodopa + □carbidopa	tablet, 100 mg + 10 mg, 250 mg + 25 mg
10. Medicines affecting the blood	
10.1 *Antianaemia medicines*	
ferrous salt	tablet, equivalent to 60 mg iron
	oral solution, equivalent to 25 mg iron (as sulfate)/ml
ferrous salt + folic acid[a]	tablet, equivalent to 60 mg iron + 400 µg folic acid
folic acid	tablet, 1 mg, 5 mg
hydroxocobalamin	injection, 1 mg in 1-ml ampoule
10.2 *Medicines affecting coagulation*	
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	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[b]	injectable solution, 3.5%
11.2 *Plasma fractions for specific use*	

All plasma fractions should comply with the Requirements for the Collection, Processing and Quality Control of Blood, Blood Components, and Plasma Derivatives (Revised 1992) as published in the forty-third report of the WHO Expert Committee on Biological Standardization (*25*).

[a] Nutritional supplement for use during pregnancy.

[b] The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee.

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
11. Blood products and plasma substitutes (*continued*)	
Complementary list medicines	
□ *factor VIII concentrate*[a]	dried
□ *factor IX complex (coagulation factors II, VII, IX, X) concentrate*[a]	dried
12. Cardiovascular medicines	
12.1 *Antianginal medicines*	
□ atenolol	tablet, 50 mg, 100 mg
glyceryl trinitrate	tablet (sublingual), 500 µg
□ isosorbide dinitrate	tablet (sublingual), 5 mg
verapamil	tablet, 40 mg, 80 mg (hydrochloride)
12.2 *Antiarrhythmic medicines*	
□ atenolol	tablet, 50 mg, 100 mg
digoxin	tablet, 62.5 µg, 250 µg
	oral solution, 50 µg/ml
	injection, 250 µg/ml in 2-ml ampoule
epinephrine (adrenaline)	injection, 1 mg (as hydrochloride)/ml in ampoule
lidocaine	injection, 20 mg (hydrochloride)/ml in 5-ml ampoule
verapamil	tablet, 40 mg, 80 mg (hydrochloride)
	injection, 2.5 mg (hydrochloride)/ml in 2-ml ampoule
Complementary list medicines	
isoprenaline[a]	injection, 20 µg (hydrochloride)/ml in ampoule
□ *procainamide*[a]	injection, 100 mg (hydrochloride)/ml in 10-ml ampoule
□ *quinidine*[a]	tablet, 200 mg (sulfate)

[a] The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee.

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
12. Cardiovascular medicines (*continued*)	
12.3 *Antihypertensive medicines*	
□ atenolol	tablet, 50 mg, 100 mg
□ enalapril	tablet, 2.5 mg
hydralazine	tablet 25 mg, 50 mg (hydrochloride)
	powder for injection, 20 mg (hydrochloride)
	in ampoule
□ hydrochlorothiazide	scored tablet, 25 mg
methyldopa[a]	tablet, 250 mg
□ nifedipine[b]	sustained-release formulations
	tablet, 10 mg
Complementary list medicine	
sodium nitroprusside	powder for infusion, 50 mg in ampoule
12.4 *Medicines used in heart failure*	
digoxin	tablet, 62.5 µg, 250 µg
	oral solution, 50 µg/ml
	injection, 250 µg/ml in 2-ml ampoule
□ enalapril	tablet, 2.5 mg
□ hydrochlorothiazide	scored tablet, 25 mg
Complementary list medicine	
dopamine	injection, 40 mg (hydrochloride)/ml in 5-ml vial
12.5 *Antithrombotic medicines*	
acetylsalicylic acid	tablet, 100 mg
Complementary list medicine	
streptokinase	powder for injection, 1.5 million IU in vial

[a] Methyldopa is listed for use in the management of pregnancy-induced hypertension only. Its use in the treatment of essential hypertension is not recommended in view of the availability of further evidence of the efficacy and safety of other medicines.

[b] The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee.

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
12. Cardiovascular medicines (*continued*)	
12.6 *Lipid-lowering agents*	
The Committee recognizes the value of lipid-lowering medicines in treating patients with hyperlipidaemia. β-Hydroxy-β-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, often referred to as "statins", are a family of potent and effective lipid-lowering medicines with a good tolerability profile. Several of these medicines have been shown to reduce the incidence of fatal and non-fatal myocardial 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 medicine 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 medicine for use in patients at highest risk should be decided at the national level.	
13. Dermatological medicines (topical)	
13.1 *Antifungal medicines*	
benzoic acid + salicylic acid	ointment or cream, 6% + 3%
□ miconazole	ointment or cream, 2% (nitrate)
sodium thiosulfate	solution, 15%
Complementary list medicine	
selenium sulfide	detergent-based suspension, 2%
13.2 *Anti-infective medicines*	
□ methylrosanilinium chloride (gentian violet)	aqueous solution, 0.5% tincture, 0.5%
neomycin + □bacitracin	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 medicines*	
□ betamethasone	ointment or cream, 0.1% (as valerate)
□ calamine lotion	lotion
□ hydrocortisone	ointment or cream, 1% (acetate)

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
13. Dermatological medicines (topical) (*continued*)	
13.4 *Astringent medicines*	
aluminium diacetate	solution, 13% for dilution
13.5 *Medicines 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	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 list medicine	
topical sun protection agent with activity against ultraviolet A and ultraviolet B[a]	cream, lotion or gel
14. Diagnostic agents	
14.1 *Ophthalmic medicines*	
fluorescein	eye drops, 1% (sodium salt)
□ tropicamide	eye drops, 0.5%
14.2 *Radiocontrast media*	
□ amidotrizoate	injection, 140–420 mg iodine (as sodium or meglumine salt)/ml in 20-ml ampoule

[a] The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee.

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
14. Diagnostic agents (*continued*)	
barium sulfate	aqueous suspension
□ iohexol	injection, 140–350 mg iodine/ml in 5-ml, 10-ml or 20-ml ampoule
□ iopanoic acid	tablet, 500 mg
□ propyliodone	oily suspension, 500–600 mg/ml in 20-ml ampoule[a]
Complementary list medicine	
□ *meglumine iotroxate*	solution, 5–8 g iodine in 100–250 ml
15. Disinfectants and antiseptics	
15.1 *Antiseptics*	
□ chlorhexidine	solution, 5% (digluconate) for dilution
□ ethanol	solution, 70% (denatured)
□ 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	tablet, 5 mg (hydrochloride)
□ furosemide	tablet, 40 mg
	injection, 10 mg/ml in 2-ml ampoule
□ hydrochlorothiazide	scored tablet, 25 mg
mannitol	injectable solution, 10%, 20%
spironolactone	tablet, 25 mg

[a] For administration only into the bronchial tree.

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
17. Gastrointestinal medicines	
17.1 *Antacids and other antiulcer medicines*	
aluminium hydroxide	tablet, 500 mg
	oral suspension, 320 mg/5 ml
magnesium hydroxide	oral suspension, equivalent to 550 mg magnesium oxide/10 ml
□ ranitidine	tablet, 150 mg (as hydrochloride)
	oral solution, 75 mg/5 ml
	injection, 25 mg/ml in 2-ml ampoule
17.2 *Antiemetic medicines*	
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 medicines*	
□ local anaesthetic, astringent and anti-inflammatory medicine[a]	ointment or suppository
17.4 *Anti-inflammatory medicines*	
□ sulfasalazine	tablet, 500 mg
	suppository, 500 mg
	retention enema
Complementary list medicine	
□ *hydrocortisone*[b]	suppository, 25 mg (acetate)
	retention enema

[a] The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee.

[b] The square box symbol (□) applies only to hydrocortisone, retention enema.

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
17. Gastrointestinal medicines (*continued*)	
17.5 *Antispasmodic medicines*	
□ atropine[a]	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 *Medicines used in diarrhoea*	
17.7.1 *Oral hydration*	
oral rehydration salts (for glucose–electrolyte solution)	powder, 20.5 g/l
	Components (for 1 litre of glucose–electrolyte solution)[b]: glucose 13.5 g/l sodium chloride 2.6 g/l potassium chloride 1.5 g/l trisodium citrate dihydrate[c] 2.9 g/l
	These components provide a glucose–elecrolyte solution with the following molar concentrations: glucose 75 mEq sodium 75 mEq or mmol/l chloride 65 mEq or mmol/l potassium 20 mEq or mmol/l citrate 10 mmol/l osmolarity 245 mOsm/l
17.7.2 *Antidiarrhoeal (symptomatic) medicines*	
codeine[a]	tablet, 30 mg (phosphate)

[a] The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee.

[b] In cases of cholera a higher concentration of sodium may be required.

[c] 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.

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
18. Hormones, other endocrine medicines and contraceptives	
18.1 *Adrenal hormones and synthetic substitutes*	
Addison's disease is a rare condition; adrenal hormones for the treatment of this condition are already included in section 3.	
18.2 *Androgens*	
Complementary list medicine	
testosterone	injection, 200 mg (enantate) in 1-ml ampoule
18.3 Contraceptives	
18.3.1 *Hormonal contraceptives*	
□ ethinylestradiol +	tablet, 30 µg + 150 µg
□ levonorgestrel	
□ ethinylestradiol +	tablet, 35 µg + 1.0 mg
□ norethisterone	
levonorgestrel	tablet, 30 µg, 750 µg (pack of two), 1.5 mg
norethisterone enantate	oily solution, 200 mg/ml in 1-ml ampoule
Complementary list medicine	
medroxyprogesterone acetate[a]	depot injection, 150 mg/ml in 1-ml vial
18.3.2 *Intrauterine devices*	
copper-containing device	
18.3.3 *Barrier methods*	
condoms	
diaphragms	
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] The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee.

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
18. Hormones, other endocrine medicines and contraceptives (*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*	
Complementary list medicine	
clomifene	tablet, 50 mg (citrate)
18.7 *Progestogens*	
norethisterone	tablet, 5 mg
Complementary list medicine	
medroxyprogesterone acetate[a]	tablet, 5 mg
18.8 *Thyroid hormones and antithyroid medicines*	
levothyroxine	tablet, 50 µg, 100 µg (sodium salt)
potassium iodide	tablet, 60 mg
□ propylthiouracil	tablet, 50 mg
19. Immunologicals	
19.1 *Diagnostic agents*	
All tuberculins should comply with the Requirements for Tuberculins (Revised 1985), as published in the thirty-sixth report of the WHO Expert Committee on Biological Standardization (*26*).	
tuberculin, purified protein derivative (PPD)	injection
19.2 *Sera and immunoglobulins*	
All plasma fractions should comply with the Requirements for the Collection, Processing and Quality Control of Blood, Blood Components and Plasma Derivatives (Revised 1992) as published in the forty-third report of the WHO Expert Committee on Biological Standardization (*25*).	
anti-D immunoglobulin (human)	injection, 250 µg in single-dose vial

[a] The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee.

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
19. Immunologicals (*continued*)	
antitetanus immunoglobulin (human)	injection, 500 IU in vial
antivenom sera[a]	injection
diphtheria antitoxin	injection, 10 000 IU, 20 000 IU in vial
□ rabies immunoglobulin	injection, 150 IU/ml in vial

19.3 Vaccines

All vaccines should comply with the following requirements for biological substances, as published in the reports of the WHO Expert Committee on Biological Standardization. BCG vaccines should comply with the Requirements for Dried BCG Vaccine (Revised 1985), as published in the thirty-sixth report of the WHO Expert Committee on Biological Standardization (*27*) and subsequent Amendment 1987 as published in the thirty-eighth report of the WHO Expert Committee on Biological Standardization (*28*). Diphtheria, pertussis and tetanus vaccines should comply with the Requirements for Diphtheria, Tetanus, Pertussis and Combined Vaccines (Revised 1989), as published in the fortieth report of the WHO Expert Committee on Biological Standardization (*29*). Hepatitis B vaccines should comply with the Requirements for Hepatitis B Vaccine Prepared from Plasma (Revised 1994), as published in the forty-fifth report of the WHO Expert Committee on Biological Standardization (*30*). Measles, mumps and rubella vaccines should comply with the Requirements for Measles, Mumps and Rubella Vaccines and Combined Vaccine (Live) (Revised 1992), as published in the forty-third report of the WHO Expert Committee on Biological Standardization (*31*) and subsequent Note, as published in the forty-fourth report of the WHO Expert Committee on Biological Standardization (*32*). Poliomyelitis vaccines should comply with the Requirements for Poliomyelitis Vaccine (Oral) (Revised 1989), as published in the fortieth report of the WHO Expert Committee on Biological Standardization (*33*) or the Requirements for Poliomyelitis Vaccine (Inactivated) (Revised 1981), as published in the report of the WHO Expert Committee on Biological Standardization (*34*) and subsequent Addendum 1985, as published in the thirty-sixth report of the WHO Expert Committee on Biological Standardization (*35*). Influenza vaccines should comply with the Requirements for Influenza Vaccine (Inactivated) (Revised 1990), as published in the forty-first report of the WHO Expert Committee on Biological Standardization (*36*). Meningococcal meningitis vaccines should comply with the Requirements for Meningococcal Polysaccharide Vaccine, as published in the report of the WHO Expert Committee on Biological Standardization (*37*) and subsequent Addendum 1980, incorporating Addendum 1976 and Addendum 1977, as published in the thirty-first report of the WHO Expert Committee on

[a] Exact type to be defined locally.

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*

19. Immunologicals (*continued*)

Biological Standardization (*38*). Rabies vaccines should comply with the Requirements for Rabies Vaccine for Human Use (Revised 1980), as published in the thirty-first report of the WHO Expert Committee on Biological Standardization (*39*) and subsequent Amendment 1992, as published in the forty-third report of the WHO Expert Committee on Biological Standardization (*40*), or the Requirements for Rabies Vaccine (Inactivated) for Human Use Produced in Continuous Cell Lines (Revised 1986), as published in the thirty-seventh report of the WHO Expert Committee on Biological Standardization (*41*) and subsequent Amendment 1992, as published in the forty-third report of the WHO Expert Committee on Biological Standardization (*42*). Typhoid vaccines should comply with the Requirements for Typhoid Vaccine (Live, Attenuated, Ty 21a, Oral), as published in the report of the WHO Expert Committee on Biological Standardization (*43*) or the Requirements for Vi Polysaccharide Typhoid Vaccine, as published in the forty-third report of the WHO Expert Committee on Biological Standardization (*44*). Yellow fever vaccines should comply with Requirements for Yellow Fever Vaccine (Revised 1995), as published in the forty-sixth report of the WHO Expert Committee on Biological Standardization (*45*).

19.3.1 *For universal immunization*

BCG vaccine

diphtheria vaccine

hepatitis B vaccine

measles vaccine

pertussis vaccine

poliomyelitis vaccine

tetanus vaccine

19.3.2 *For specific groups of individuals*

influenza vaccine

meningococcal meningitis vaccine

mumps vaccine

rabies vaccine (inactivated) (prepared in cell culture)

rubella vaccine

typhoid vaccine

yellow fever vaccine

Medicine	*Route of administration, dosage forms and strengths*
20. Muscle relaxants (peripherally-acting) and cholinesterase inhibitors	
□ alcuronium	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
suxamethonium	injection, 50 mg (chloride)/ml in 2-ml ampoule
	powder for injection (chloride), in vial
Complementary list medicines	
pyridostigmine	tablet, 60 mg (bromide)
	injection, 1 mg in 1-ml ampoule
vecuronium	powder for injection, 10 mg (bromide) in vial
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[a]	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)

[a] The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee.

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
21. Ophthalmological preparations (*continued*)	
21.4 *Miotics and antiglaucoma medicines*	
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 list medicine	
epinephrine (adrenaline)	solution (eye drops), 2% (as hydrochloride)
22. Oxytocics and antioxytocics	
22.1 *Oxytocics*	
□ ergometrine[a]	tablet, 200 μg (hydrogen maleate)
	injection, 200 μg (hydrogen maleate) in 1-ml ampoule
oxytocin	injection, 10 IU in 1-ml ampoule
22.2 *Antioxytocics*	
□ salbutamol[a]	tablet, 4 mg (as sulfate)
	injection, 50 μg (as sulfate)/ml in 5-ml ampoule
23. Peritoneal dialysis solution	
Complementary list medicine	
intraperitoneal dialysis solution (of appropriate composition)	parenteral solution

[a] The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee.

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
24. Psychotherapeutic medicines	
24.1 *Medicines 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	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 *Medicines used in mood disorders*	
24.2.1 *Medicines used in depressive disorders*	
□amitriptyline	tablet, 25 mg (hydrochloride)
24.2.2 *Medicines used in bipolar disorders*	
carbamazepine	scored tablet, 100 mg, 200 mg
lithium carbonate	capsule or tablet, 300 mg
valproic acid	enteric coated tablet, 200 mg, 500 mg (sodium salt)
24.3 *Medicines used in generalized anxiety and sleep disorders*	
□ diazepam	scored tablet, 2 mg, 5 mg
24.4 *Medicines used in obsessive–compulsive disorders and panic attacks*	
clomipramine	capsule, 10 mg, 25 mg (hydrochloride)
25. Medicines acting on the respiratory tract	
25.1 *Antiasthmatics and medicines for chronic obstructive pulmonary disease*	
□ beclometasone	inhalation (aerosol), 50 µg, 250 µg (dipropionate) per dose
epinephrine (adrenaline)	injection, 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule
ipratropium bromide	inhalation (aerosol), 20 µg/metered dose

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
25. Medicines acting on the respiratory tract (*continued*)	
□ 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[a]	tablet, 100 mg, 200 mg, 300 mg
Complementary list medicines	
□ *aminophylline*[a]	injection, 25 mg/ml in 10-ml ampoule
□ *cromoglicic acid*[a]	inhalation (aerosol), 20 mg (sodium salt) per dose
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
potassium chloride	powder for solution
26.2 *Parenteral*	
glucose	injectable solution, 5%, 10% isotonic, 50% hypertonic
glucose with sodium chloride	injectable solution, 4% glucose, 0.18% sodium chloride (equivalent to Na^+ 30 mmol/l, Cl^- 30 mmol/l)
potassium chloride	solution, 11.2% 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)

[a] The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee.

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
26. Solutions correcting water, electrolyte and acid–base disturbances (*continued*)	
sodium hydrogen carbonate	injectable solution, 1.4% isotonic (equivalent to Na^+ 167 mmol/l, HCO_3^- 167 mmol/l), 8.4% (equivalent to Na^+ 1000 mmol/l, HCO_3^- 1000 mmol/l) in 10-ml ampoule
□ sodium lactate, compound	injectable solution
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)
retinol	sugar-coated tablet, 10 000 IU (as palmitate) (5.5 mg)
	capsule, 200 000 IU (as palmitate) (110 mg)
	oral oily solution, 100 000 IU (as palmitate)/ml in multidose dispenser
	water-miscible injection, 100 000 IU (as palmitate) (55 mg) in 2-ml ampoule
riboflavin	tablet, 5 mg

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

Medicine	*Route of administration, dosage forms and strengths*
27. Vitamins and minerals (*continued*)	
□ sodium fluoride[a]	in any appropriate formulation
thiamine	tablet, 50 mg (hydrochloride)
Complementary list medicine	
calcium gluconate[a]	injection, 100 mg/ml in 10-ml ampoule

[a] The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee.

□ Recommended example within a pharmaceutical class. See Explanatory notes on page 61.

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Annex 2
The Anatomical Therapeutic Chemical (ATC) classification system[1]

The following list provides the corresponding Anatomical Therapeutic Chemical (ATC) classification codes for all items on the 13th WHO Model List of Essential Medicines, sorted by ATC code number.

ATC code	ATC group/medicine or item
A	**ALIMENTARY TRACT AND METABOLISM**
A02	**Drugs for acid related disorders**
A02A	**Antacids**
A02AA	*Magnesium compounds*
A02AA04	magnesium hydroxide
A02AB	*Aluminium compounds*
A02AB01	aluminium hydroxide
A02B	**Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)**
A02BA	*H_2-receptor antagonists*
A02BA02	ranitidine
A03	**Drugs for functional gastrointestinal disorders**
A03B	**Belladonna and derivatives, plain**
A03BA	*Belladonna alkaloids, tertiary amines*
A03BA01	atropine
A03F	**Propulsives**
A03FA	*Propulsives*
A03FA01	metoclopramide
A06	**Laxatives**
A06A	**Laxatives**
A06AB	*Contact laxatives*
A06AB06	senna*
A07	**Antidiarrheals, intestinal antiinflammatory/antiinfective agents**
A07A	**Intestinal antiinfectives**
A07AA	*Antibiotics*
A07AA02	nystatin

[1] Based on the ATC list as of January 2003 and prepared with the assisance of the WHO Collaborating Centre for Drug Statistics Methodology, Oslo, Norway.

ATC code	ATC group/medicine or item
A07B	**Intestinal adsorbents**
A07BA	*Charcoal preparations*
A07BA01	charcoal, activated*
A07C	**Electrolytes with carbohydrates**
A07CA	*oral rehydration salts**
A07E	**Intestinal antiinflammatory agents**
A07EA	*Corticosteroids for local use*
A07EA02	hydrocortisone
A07EC	*Aminosalicylic acid and similar agents*
A07EC01	sulfasalazine
A10	**Drugs used in diabetes**
A10A	**Insulins and analogues**
A10AB	*insulin injection (soluble)**
A10AC	*insulin, intermediate-acting**
A10B	**Oral blood glucose lowering drugs**
A10BA	*Biguanides*
A10BA02	metformin
A10BB	*Sulfonamides, urea derivatives*
A10BB01	glibenclamide
A11	**Vitamins**
A11C	**Vitamin A and D, incl. combinations of the two**
A11CA	*Vitamin A, plain*
A11CA01	retinol
A11CC	*Vitamin D and analogues*
A11CC01	ergocalciferol
A11D	**Vitamin B_1, plain and in combination with vitamin B_6 and B_{12}**
A11DA	*Vitamin B_1, plain*
A11DA01	thiamine
A11G	**Ascorbic acid (vitamin C), incl. combinations**
A11GA	*Ascorbic acid (vitamin C), plain*
A11GA01	ascorbic acid
A11H	**Other plain vitamin preparations**
A11HA	*Other plain vitamin preparations*
A11HA01	nicotinamide
A11HA02	pyridoxine
A11HA04	riboflavin
A12	**Mineral supplements**
A12A	**Calcium**
A12AA	*Calcium*
A12AA03	calcium gluconate

ATC code	ATC group/medicine or item
A12C	**Other mineral supplements**
A12CD	*Fluoride*
A12CD01	sodium fluoride
A12CX	*Other mineral products*
A12CX	iodine*
B	**BLOOD AND BLOOD FORMING ORGANS**
B01	**Antithrombotic agents**
B01A	**Antithrombotic agents**
B01AA	*Vitamin K antagonists*
B01AA03	warfarin
B01AB	*Heparin group*
B01AB01	heparin sodium*
B01AC	*Platelet aggregation inhibitors excl. heparin*
B01AC06	acetylsalicylic acid
B01AD	*Enzymes*
B01AD01	streptokinase
B02	**Antihemorrhagics**
B02B	**Vitamin K and other hemostatics**
B02BA	*Vitamin K*
B02BA01	phytomenadione
B02BD	*Blood coagulation factors*
B02BD01	factor IX complex (coagulation factors II, VII, IX, X) concentrate*
B02BD02	factor VIII concentrate*
B03	**Antianemic preparations**
B03A	**Iron preparations**
B03A	ferrous salt*
B03AD	*ferrous salt + folic acid**
B03B	**Vitamin B_{12} and folic acid**
B03BA	*Vitamin B_{12} (cyanocobalamin and analogues)*
B03BA03	hydroxocobalamin
B03BB	*Folic acid and derivatives*
B03BB01	folic acid
B05	**Blood substitutes and perfusion solutions**
B05A	**Blood and related products**
B05AA	*Blood substitutes and plasma protein fractions*
B05AA05	dextran 70*
B05AA06	polygeline*
B05B	**I.v. solutions**
B05BA	*Solutions for parenteral nutrition*
B05BA03	glucose*

ATC code	ATC group/medicine or item
B05BB	*Solutions affecting the electrolyte balance*
B05BB01	sodium lactate, compound solution*
B05BB02	glucose with sodium chloride*
B05BC	*Solutions producing osmotic diuresis*
B05BC01	mannitol
B05D	**Peritoneal dialytics**
B05DA	*intraperitoneal dialysis solution**
B05X	**I.v. solution additives**
B05XA	*Electrolyte solutions*
B05XA01	potassium chloride
B05XA02	sodium hydrogen carbonate*
B05XA03	sodium chloride
B05XA05	magnesium sulfate
C	**CARDIOVASCULAR SYSTEM**
C01	**Cardiac therapy**
C01A	**Cardiac glycosides**
C01AA	*Digitalis glycosides*
C01AA05	digoxin
C01B	**Antiarrhythmics, class I and III**
C01BA	*Antiarrhythmics, class Ia*
C01BA01	quinidine
C01BA02	procainamide
C01BB	*Antiarrhythmics, class Ib*
C01BB01	lidocaine
C01C	**Cardiac stimulants excl. cardiac glycosides**
C01CA	*Adrenergic and dopaminergic agents*
C01CA04	dopamine
C01CA24	epinephrine
C01D	**Vasodilators used in cardiac diseases**
C01DA	*Organic nitrates*
C01DA02	glyceryl trinitrate
C01DA08	isosorbide dinitrate
C02	**Antihypertensives**
C02A	**Antiadrenergic agents, centrally acting**
C02AB	*Methyldopa*
C02AB01	methyldopa*
C02D	**Arteriolar smooth muscle, agents acting on**
C02DB	*Hydrazinophthalazine derivatives*
CO2DB02	hydralazine
C02DD	*Nitroferricyanide derivatives*
C02DD01	sodium nitroprusside*
C03	**Diuretics**
C03A	**Low-ceiling diuretics, thiazides**
C03AA	*Thiazides, plain*
C03AA03	hydrochlorothiazide

ATC code	ATC group/medicine or item
C03C	**High-ceiling diuretics**
C03CA	*Sulfonamides, plain*
C03CA01	furosemide
C03D	**Potassium-sparing agents**
C03DA	*Aldosterone antagonists*
C03DA01	spironolactone
C03DB	*Other potassium-sparing agents*
C03DB01	amiloride
C05	**Vasoprotectives**
C05A	**Antihemorrhoidals for topical use**
C05A	antihaemorrhoidal preparation: local anaesthetic, astringent, and anti-inflammatory medicine*
C07	**Beta blocking agents**
C07A	**Beta blocking agents**
C07AA	*Beta blocking agents, non-selective*
C07AA05	propranolol
C07AB	*Beta blocking agents, selective*
C07AB03	atenolol
C08	**Calcium channel blockers**
C08C	**Selective calcium channel blockers with mainly vascular effects**
C08CA	*Dihydropyridine derivatives*
C08CA05	nifedipine
C08D	**Selective calcium channel blockers with direct cardiac effects**
C08DA	*Phenylalkylamine derivatives*
C08DA01	verapamil
C09	**Agents acting on the renin-angiotensin system**
C09A	**ACE inhibitors, plain**
C09AA	*ACE inhibitors, plain*
C09AA02	enalapril
D	**DERMATOLOGICALS**
D01	**Antifungals for dermatological use**
D01A	**Antifungals for topical use**
D01AA	*Antibiotics*
D01AA01	nystatin
D01AC	*Imidazole and triazole derivatives*
D01AC02	miconazole
D01AE	*Other antifungals for topical use*
D01AE02	methylrosanilinium chloride (gentian violet)*
D01AE12	salicylic acid
D01AE13	selenium sulfide
D01AE20	benzoic acid + salicylic acid*

ATC code	ATC group/medicine or item
D01B	**Antifungals for systemic use**
D01BA	*Antifungals for systemic use*
D01BA01	griseofulvin
D02	**Emollients and protectives**
D02A	**Emollients and protectives**
D02AB	*Zinc products*
D02AB	calamine lotion*
D02AE	*Carbamide products*
D02AE01	urea*
D02B	**Protectives against UV-radiation**
D02BA	*Protectives against UV-radiation for topical use*
D02BA	sun protection agent with activity against ultraviolet A and ultraviolet B*
D05	**Antipsoriatics**
D05A	**Antipsoriatics for topical use**
D05AA	*coal tar**
D05AC	*Antracen derivatives*
D05AC01	dithranol
D06	**Antibiotics and chemotherapeutics for dermatological use**
D06A	**Antibiotics for topical use**
D06AX	*Other antibiotics for topical use*
D06AX04	neomycin + bacitracin*
D06B	**Chemotherapeutics for topical use**
D06BA	*Sulfonamides*
D06BA01	silver sulfadiazine
D06BB	*Antivirals*
D06BB04	podophyllum resin*
D07	**Corticosteroids, dermatological preparations**
D07A	**Corticosteroids, plain**
D07AA	*Corticosteroids, weak (group I)*
D07AA02	hydrocortisone
D07AC	*Corticosteroids, potent (group III)*
D07AC01	betamethasone
D08	**Antiseptics and disinfectants**
D08A	**Antiseptics and disinfectants**
D08AC	*Biguanides and amidines*
D08AC02	chlorhexidine
D08AE	*Phenol and derivatives*
D08AE05	chloroxylenol
D08AG	*Iodine products*
D08AG02	polyvidone iodine*
D08AL	*Silver compounds*
D08AL01	silver nitrate

ATC code	ATC group/medicine or item
D08AX	*Other antiseptics and disinfectants*
D08AX	chlorine base compound*
D08AX06	potassium permanganate
D08AX08	ethanol
D10	**Anti-acne preparations**
D10A	**Anti-acne preparations for topical use**
D10AE	*Peroxides*
D10AE01	benzoyl peroxide
DIIAA	*Antihidrotics*
DIIAA	aluminium diacetate
G	**GENITO URINARY SYSTEM AND SEX HORMONES**
G01	**Gynecological antiinfectives and antiseptics**
G01A	**Antiinfectives and antiseptics, excl. combinations with corticosteroids**
G01AA	*Antibiotics*
G01AA01	nystatin
G02	**Other gynecologicals**
G02A	**Oxytocics**
G02AB	*Ergot alkaloids*
G02AB03	ergometrine
G02B	**Contraceptives for topical use**
G02BA	*Intrauterine contraceptives*
G02BA02	copper-containing intrauterine device*
G02BB	*Intravaginal contraceptives*
G02BB	diaphragms*
G03	**Sex hormones and modulators of the genital system**
G03A	**Hormonal contraceptives for systemic use**
G03AA	*Progestogens and estrogens, fixed combinations*
G03AA05	ethinylestradiol + norethisterone*
G03AB	*Progestogens and estrogens, sequential preparations*
G03AB03	ethinylestradiol + levonorgestrel*
G03AC	*Progestogens*
G03AC01	norethisterone enantate*
G03AC03	levonorgestrel
G03AC06	medroxyprogesterone acetate*
G03B	**Androgens**
G03BA	*3-Oxoandrosten (4) derivatives*
G03BA03	testosterone
G03C	**Estrogens**
G03CA	*Natural and semisynthetic estrogens, plain*
G03CA01	ethinylestradiol

ATC code	ATC group/medicine or item
G03D	**Progestogens**
G03DC	*Estren derivatives*
G03DC02	norethisterone
G03G	**Gonadotropins and other ovulation stimulants**
G03GB	*Ovulation stimulants, synthetic*
G03GB02	clomifene
H	**SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS**
H01	**Pituitary, hypothalamic hormones and analogues**
H01B	**Posterior pituitary lobe hormones**
H01BB	*Oxytocin and analogues*
H01BB02	oxytocin
H02	**Corticosteroids for systemic use**
H02A	**Corticosteroids for systemic use, plain**
H02AB	*Glucocorticoids*
H02AB02	dexamethasone
H02AB06	prednisolone
H02AB09	hydrocortisone
H03	**Thyroid therapy**
H03A	**Thyroid preparations**
H03AA	*Thyroid hormones*
H03AA01	levothyroxine*
H03B	**Antithyroid preparations**
H03BA	*Thiouracils*
H03BA02	propylthiouracil
H03C	**Iodine therapy**
H03CA	*potassium iodide**
J	**ANTIINFECTIVES FOR SYSTEMIC USE**
J01	**Antibacterials for systemic use**
J01A	**Tetracyclines**
J01AA	*Tetracyclines*
J01AA02	doxycycline
J01B	**Amphenicols**
J01BA	*Amphenicols*
J01BA01	chloramphenicol
J01C	**Beta-lactam antibacterials, penicillins**
J01CA	*Penicillins with extended spectrum*
J01CA01	ampicillin
J01CA04	amoxicillin
J01CE	*Beta-lactamase sensitive penicillins*
J01CE01	benzylpenicillin
J01CE02	phenoxymethylpenicillin
J01CE08	benzathine benzylpenicillin
J01CE09	procaine benzylpenicillin*

ATC code	ATC group/medicine or item
J01CF	*Beta-lactamase resistant penicillins*
J01CF02	cloxacillin
J01CR	*Combinations of penicillins, incl. beta-lactamase inhibitors*
J01CR02	amoxicillin + clavulanic acid*
J01D	**Other beta-lactam antibacterials**
J01DA	*Cephalosporins and related substances*
J01DA11	ceftazidime
J01DA13	ceftriaxone
J01DH	*Carbapenems*
J01DH51	imipenem + cilastatin*
J01E	**Sulfonamides and trimethoprim**
J01EA	*Trimethoprim and derivatives*
J01EA01	trimethoprim
J01EC	*Intermediate-acting sulfonamides*
J01EC02	sulfadiazine
J01EE	*Combinations of sulfonamides and trimethoprim, incl. derivatives*
J01EE01	sulfamethoxazole + trimethoprim
J01F	**Macrolides, lincosamides and streptogramins**
J01FA	*Macrolides*
J01FA01	erythromycin
J01FA10	azithromycin
J01FF	*Lincosamides*
J01FF01	clindamycin
J01G	**Aminoglycoside antibacterials**
J01GA	*Streptomycins*
J01GA01	streptomycin
J01GB	*Other aminoglycosides*
J01GB03	gentamicin
J01GB04	kanamycin
J01GB06	amikacin
J01M	**Quinolone antibacterials**
J01MA	*Fluoroquinolones*
J01MA01	ofloxacin
J01MA02	ciprofloxacin
J01MA12	levofloxacin
J01MB	*Other quinolones*
J01MB02	nalidixic acid
J01X	**Other antibacterials**
J01XA	*Glycopeptide antibacterials*
J01XA01	vancomycin
J01XD	*Imidazole derivatives*
J01XD01	metronidazole

ATC code	ATC group/medicine or item
J01XE	*Nitrofuran derivatives*
J01XE01	nitrofurantoin
J01XX	*Other antibacterials*
J01XX04	spectinomycin
J02	**Antimycotics for systemic use**
J02A	**Antimycotics for systemic use**
J02AA	*Antibiotics*
J02AA01	amphotericin B
J02AC	*Triazole derivatives*
J02AC01	fluconazole
J02AX	*Other antimycotics for systemic use*
J02AX01	flucytosine
J04	**Antimycobacterials**
J04A	**Drugs for treatment of tuberculosis**
J04AA	*Aminosalicylic acid and derivatives*
J04AA01	*p*-aminosalicylic acid*
J04AB	*Antibiotics*
J04AB01	cycloserine
J04AB02	rifampicin
J04AB30	capreomycin
J04AC	*Hydrazides*
J04AC01	isoniazid
J04AD	*Thiocarbamide derivatives*
J04AD03	ethionamide
J04AK	*Other drugs for treatment of tuberculosis*
J04AK01	pyrazinamide
J04AK02	ethambutol
J04AM	*Combinations of drugs for treatment of tuberculosis*
J04AM02	rifampicin + isoniazid*
J04AM02	rifampicin + isoniazid + pyrazinamide*
J04AM02	rifampicin + isoniazid + pyrazinamide + ethambutol*
J04AM03	isoniazid + ethambutol*
J04AM04	thioacetazone + isoniazid*
J04B	**Drugs for treatment of lepra**
J04BA	*Drug for treatment of leprosy*
J04BA01	clofazimine
J04BA02	dapsone
J05	**Antivirals for systemic use**
J05A	**Direct acting antivirals**
J05AB	*Nucleosides and nucleotides excl. reverse transcriptase inhibitors*
J05AB01	aciclovir

ATC code	ATC group/medicine or item
J05AE	*Protease inhibitors*
J05AE01	saquinavir (SQV)
J05AE02	indinavir (IDV)
J05AE03	ritonavir (r)
J05AE04	nelfinavir (NFV)
J05AE30	lopinavir + ritonavir (LPV/r)*
J05AF	*Nucleoside reverse transcriptase inhibitors*
J05AF01	zidovudine (ZDV or AZT)
J05AF02	didanosine (ddI)
J05AF04	stavudine (d4T)
J05AF05	lamivudine (3TC)
J05AF06	abacavir (ABC)
J05AG	*Non-nucleoside reverse transcriptase inhibitors*
J05AG01	nevirapine (NVP)
J05AG03	efavirenz (EFV or EFZ)
J06	**Immune sera and immunoglobulins**
J06A	**Immune sera**
J06AA	*Immune sera*
J06AA01	diphtheria antitoxin
J06AA03	antivenom sera*
J06B	**Immunoglobulins**
J06BB	*Specific immunoglobulins*
J06BB01	anti-D immunoglobulin (human)
J06BB02	antitetanus immunoglobulin (human)
J06BB05	rabies immunoglobulin
J07	**Vaccines**
J07A	**Bacterial vaccines**
J07AH	*meningococcal meningitis vaccine**
J07AJ	*Pertussis vaccines*
J07AJ51	diphteria-pertussis-tetanus vaccine*
J07AM	*Tetanus vaccines*
J07AM51	diphtheria-tetanus vaccine*
J07AN	*Tuberculosis vaccines*
J07AN01	BCG vaccine*
J07AP	*typhoid vaccine*
J07B	**Viral vaccines**
J07BB	*influenza vaccine*
J07BC	*Hepatitis vaccines*
J07BC01	hepatitis B vaccine
J07BD	*measles vaccine**
J07BD52	measles-mumps-rubella vaccine*
J07BF	*poliomyelitis vaccine*

ATC code	ATC group/medicine or item
J07BG	*rabies vaccine*
J07BJ	*rubella vaccine*
J07BL	*yellow fever vaccine*
L	**ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS**
L01	**Antineoplastic agents**
L01A	**Alkylating agents**
L01AA	*Nitrogen mustard analogues*
L01AA01	cyclophosphamide
L01AA02	chlorambucil
L01AA05	chlormethine
L01AX	*Other alkylating agents*
L01AX04	dacarbazine
L01B	**Antimetabolites**
L01BA	*Folic acid analogues*
L01BA01	methotrexate
L01BB	*Purine analogues*
L01BB02	mercaptopurine
L01BC	*Pyrimidine analogues*
L01BC01	cytarabine
L01BC02	fluorouracil
L01C	**Plant alkaloids and other natural products**
L01CA	*Vinca alkaloids and analogues*
L01CA01	vinblastine
L01CA02	vincristine
L01CB	*Podophyllotoxin derivatives*
L01CB01	etoposide
L01D	**Cytotoxic antibiotics and related substances**
L01DA	*Actinomycines*
L01DA01	dactinomycin
L01DB	*Anthracyclines and related substances*
L01DB01	doxorubicin
L01DB02	daunorubicin
L01DC	*Other cytotoxic antibiotics*
L01DC01	bleomycin
L01X	**Other antineoplastic agents**
L01XA	*Platinum compounds*
L01XA01	cisplatin
L01XB	*Methylhydrazines*
L01XB01	procarbazine
L01XX	*Other antineoplastic agents*
L01XX02	asparaginase

ATC code	ATC group/medicine or item
L02	**Endocrine therapy**
L02B	**Hormone antagonists and related agents**
L02BA	*Anti-estrogens*
L02BA01	tamoxifen
L04	**Immunosuppressive agents**
L04A	**Immunosuppressive agents**
L04AA	*Selective immunosuppressive agents*
L04AA01	ciclosporin
L04AX	*Other immunosuppressive agents*
L04AX01	azathioprine
M	**MUSCULO-SKELETAL SYSTEM**
M01	**Antiinflammatory and antirheumatic products**
M01A	**Antiinflammatory and antirheumatic products, non-steroids**
M01AE	*Propionic acid derivatives*
M01AE01	ibuprofen
M01C	**Specific antirheumatic agents**
M01CC	*Penicillamine and similar agents*
M01CC01	penicillamine
M03	**Muscle relaxants**
M03A	**Muscle relaxants, peripherally acting agents**
M03AA	*Curare alkaloids*
M03AA01	alcuronium
M03AB	*Choline derivatives*
M03AB01	suxamethonium
M03AC	*Other quaternary ammonium compounds*
M03AC03	vecuronium
M04	**Antigout preparations**
M04A	**Antigout preparations**
M04AA	*Preparations inhibiting uric acid production*
M04AA01	allopurinol
M04AC	*Preparations with no effect on uric acid metabolism*
M04AC01	colchicine
N	**NERVOUS SYSTEM**
N01	**Anesthetics**
N01A	**Anesthetics, general**
N01AA	*Ethers*
N01AA01	ether, anaesthetic*
N01AB	*Halogenated hydrocarbons*
N01AB01	halothane
N01AF	*Barbiturates, plain*
N01AF03	thiopental

ATC code	ATC group/medicine or item
N01AX	*Other general anesthetics*
N01AX03	ketamine
N01AX13	nitrous oxide
N01B	**Anesthetics, local**
N01BB	*Amides*
N01BB01	bupivacaine
N01BB02	lidocaine
N01BB52	lidocaine + epinephrine (adrenaline)*
N02	**Analgesics**
N02A	**Opioids**
N02AA	*Natural opium alkaloids*
N02AA01	morphine
N02B	**Other analgesics and antipyretics**
N02BA	*Salicylic acid and derivatives*
N02BA01	acetylsalicylic acid
N02BE	*Anilides*
N02BE01	paracetamol
N02C	**Antimigraine preparations**
N02CA	*Ergot alkaloids*
N02CA02	ergotamine
N03	**Antiepileptics**
N03A	**Antiepileptics**
N03AA	*Barbiturates and derivatives*
N03AA02	phenobarbital
N03AB	*Hydantoin derivatives*
N03AB02	phenytoin
N03AD	*Succinimide derivatives*
N03AD01	ethosuximide
N03AE	*Benzodiazepine derivates*
N03AE01	clonazepam
N03AF	*Carboxamide derivatives*
N03AF01	carbamazepine
N03AG	*Fatty acid derivatives*
N03AG01	valproic acid
N04	**Anti-parkinson drugs**
N04A	**Anticholinergic agents**
N04AA	*Tertiary amines*
N04AA02	biperiden
N04B	**Dopaminergic agents**
N04BA	*Dopa and dopa derivatives*
N04BA02	levodopa + carbidopa*

ATC code	ATC group/medicine or item
N05	**Psycholeptics**
N05A	**Antipsychotics**
N05AA	*Phenothiazines with aliphatic side-chain*
N05AA01	chlorpromazine
N05AB	*Phenothiazines with piperazine structure*
N05AB02	fluphenazine
N05AD	*Butyrophenone derivatives*
N05AD01	haloperidol
N05AN	*Lithium*
N05AN01	lithium carbonate*
N05B	**Anxiolytics**
N05BA	*Benzodiazepine derivatives*
N05BA01	diazepam
N06	**Psychoanaleptics**
N06A	**Antidepressants**
N06AA	*Non-selective monoamine reuptake inhibitors*
N06AA04	clomipramine
N06AA09	amitriptyline
N07	**Other nervous system drugs**
N07A	**Parasympathomimetics**
N07AA	*Anticholinesterases*
N07AA01	neostigmine
N07AA02	pyridostigmine
P	**ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS**
P01	**Antiprotozoals**
P01A	**Agents against amoebiasis and other protozoal diseases**
P01AB	*Nitroimidazole derivatives*
P01AB01	metronidazole
P01AC	*Dichloroacetamide derivatives*
P01AC01	diloxanide
P01B	**Antimalarials**
P01BA	*Aminoquinolines*
P01BA01	chloroquine
P01BA03	primaquine
P01BA06	amodiaquine
P01BB	*Biguanides*
P01BB01	proguanil
P01BC	*Methanolquinolines*
P01BC01	quinine
P01BC02	mefloquine
P01BD	*Diaminopyrimidines*
P01BD01	pyrimethamine
P01BD51	sulfadoxine + pyrimethamine*

ATC code	ATC group/medicine or item
P01BE	*Artemisinin and derivatives*
P01BE02	artemether
P01BE03	artesunate
P01BE52	artemether + lumefantrine*
P01C	**Agents against leishmaniasis and trypanosomiasis**
P01CA	*Nitroimidazole derivatives*
P01CA02	benznidazole
P01CB	*Antimony compounds*
P01CB01	meglumine antimoniate
P01CC	*Nitrofuran derivatives*
P01CC01	nifurtimox
P01CD	*Arsenic compounds*
P01CD01	melarsoprol
P01CX	*Other agents against leishmaniasis and trypanosomiasis*
P01CX01	pentamidine*
P01CX02	suramin sodium
P01CX03	eflornithine
P02	**Anthelmintics**
P02B	**Antitrematodals**
P02BA	*Quinoline derivatives and related substances*
P02BA01	praziquantel
P02BA02	oxamniquine
P02BX	*Other antitrematodal agents*
P02BX04	triclabendazole
P02C	**Antinematodal agents**
P02CA	*Benzimidazole derivatives*
P02CA01	mebendazole
P02CA03	albendazole
P02CB	*Piperazine and derivatives*
P02CB02	diethylcarbamazine
P02CC	*Tetrahydropyrimidine derivatives*
P02CC01	pyrantel
P02CE	*Imidazothiazole derivatives*
P02CE01	levamisole
P02CF	*Avermectines*
P02CF01	ivermectin
P02D	**Anticestodals**
P02DA	*Salicylic acid derivatives*
P02DA01	niclosamide

ATC code	ATC group/medicine or item
P03	**Ectoparasiticides, incl. scabicides, insecticides and repellents**
P03A	**Ectoparasiticides, incl. scabicides**
P03AC	*Pyrethrines, incl. synthetic compounds*
P03AC04	permethrin
P03AX	*Other ectoparasiticides, incl. scabicides*
P03AX01	benzyl benzoate
P03B	**Insecticides and repellents**
P03BX	*Other insecticides and repellents*
P03BX01	diethyltoluamide
R	**RESPIRATORY SYSTEM**
R03	**Drugs for obstructive airway diseases**
R03A	**Adrenergics, inhalants**
R03AC	*Selective beta-2-adrenoreceptor agonists*
R03AC02	salbutamol
R03B	**Other drugs for obstructive airway diseases, inhalants**
R03BA	*Glucocorticoids*
R03BA01	beclometasone
R03BB	*Anticholinergics*
R03BB01	ipratropium bromide
R03BC	*Antiallergic agents, excl. corticosteroids*
R03BC01	cromoglicic acid
R03C	**Adrenergics for systemic use**
R03CA	*Alpha- and beta-adrenoreceptor agonists*
R03CA02	ephedrine
R03CB	*Non-selective beta-adrenoreceptor agonists*
R03CB01	isoprenaline
R03CC	*Selective beta-2-adrenoreceptor agonists*
R03CC02	salbutamol
R03D	**Other systemic drugs for obstructive airway diseases**
R03DA	*Xanthines*
R03DA04	theophylline
R03DA05	aminophylline
R05	**Cough and cold preparations**
R05D	**Cough suppressants, excl. combinations with expectorants**
R05DA	*Opium alkaloids and derivatives*
R05DA04	codeine
R06	**Antihistamines for systemic use**
R06A	**Antihistamines for systemic use**
R06AB	*Substituted alkylamines*
R06AB04	chlorphenamine
R06AD	*Phenothiazine derivatives*
R06AD02	promethazine

ATC code	ATC group/medicine or item
S	**SENSORY ORGANS**
S01	**Ophthalmologicals**
S01A	**Antiinfectives**
S01AA	*Antibiotics*
S01AA09	tetracycline
S01AA11	gentamicin
S01AD	*Antivirals*
S01AD01	idoxuridine
S01B	**Antiinflammatory agents**
S01BA	*Corticosteroids, plain*
S01BA04	prednisolone
S01E	**Antiglaucoma preparations and miotics**
S01EA	*Sympathomimetics in glaucoma therapy*
S01EA01	epinephrine
S01EB	*Parasympathomimetics*
S01EB01	pilocarpine
S01EC	*Carbonic anhydrase inhibitors*
S01EC01	acetazolamide
S01ED	*Beta blocking agents*
S01ED01	timolol
S01F	**Mydriatics and cycloplegics**
S01FA	*Anticholinergics*
S01FA01	atropine
S01FA06	tropicamide
S01H	**Local anesthetics**
S01HA	*Local anesthetics*
S01HA03	tetracaine
S01J	**Diagnostic agents**
S01JA	*Colouring agents*
S01JA01	fluorescein
V	**VARIOUS**
V03	**All other therapeutic products**
V03A	**All other therapeutic products**
V03AB	*Antidotes*
V03AB03	sodium calcium edetate*
V03AB06	sodium thiosulfate*
V03AB08	sodium nitrite
V03AB09	dimercaprol
V03AB14	protamine sulfate*
V03AB15	naloxone
V03AB17	methylthioninium chloride (methylene blue)
V03AB23	acetylcysteine
V03AB26	DL-methionine*
V03AB31	potassium ferric hexacyanoferrate (II).2H_2O (Prussian blue)

ATC code	ATC group/medicine or item
V03AC	*Iron chelating agents*
V03AC01	deferoxamine
V03AF	*Detoxifying agents for antineoplastic treatment*
V03AF03	calcium folinate
V03AN	*Medical gases*
V03AN	oxygen
V04	**Diagnostic agents**
V04C	**Other diagnostic agents**
V04CF	*Tuberculosis diagnostics*
V04CF01	tuberculin, purified protein derivative (PPD)*
V07	**All other non-therapeutic products**
V07A	**All other non-therapeutic products**
V07AB	*Solvents and diluting agents, incl. irrigating solutions*
V07AB	water for injection*
V07AV	*Technical disinfectants*
V07AV	glutaral
V08	**Contrast media**
V08A	**X-ray contrast media, iodinated**
V08AA	*Watersoluble, nephrotropic, high osmolar X-ray contrast media*
V08AA01	amidotrizoate*
V08AB	*Watersoluble, nephrotropic, low osmolar X-ray contrast media*
V08AB02	iohexol
V08AC	*Watersoluble, hepatotropic X-ray contrast media*
V08AC02	meglumine iotroxate*
V08AC06	iopanoic acid
V08AD	*Non-watersoluble X-ray contrast media*
V08AD03	propyliodone
V08B	**X-ray contrast media, non-iodinated**
V08BA	*Barium sulfate containing X-ray contrast media*
V08BA01	barium sulfate*

* Medicine or item name differs slightly from the name used in the ATC classification system.

Alphabetical list of essential medicines (with ATC classification code numbers)

Medicine or item	ATC code	Page
thioacetazone + isoniazid*	J04AM04	72
thiopental	N01AF03	63
timolol	S01ED01	92
triclabendazole	P02BX04	67
trimethoprim	J01EA01	70
tropicamide	S01FA06	83
tuberculin, purified protein derivative (PPD)*	V04CF01	88
typhoid vaccine	J07AP	90
urea*	D02AE01	83
valproic acid	N03AG01	66; 93
vancomycin	J01XA01	70
vecuronium	M03AC03	91
verapamil	C08DA01	80; 80
vinblastine	L01CA01	78
vincristine	L01CA02	78
warfarin	B01AA03	79
water for injection*	V07AB	95
yellow fever vaccine	J07BL	90
zidovudine (ZDV or AZT)	J05AF01	73

* Medicine or item name differs slightly from the name used in the ATC classification system

SELECTED WHO PUBLICATIONS OF RELATED INTEREST

The international pharmacopoeia, third edition.
Volume 1: general methods of analysis. 1979 (223 pages)
Volume 2: quality specifications. 1981 (342 pages)
Volume 3: quality specifications. 1988 (407 pages)
Volume 4: test, methods, and general requirements: quality specifications for pharmaceutical substances, excipients, and dosage forms. 1994 (358 pages)
Volume 5: tests and general requirements for dosage forms: quality specifications for pharmaceutical substances and dosage forms. 2003 (389 pages)

Basic tests for drugs: pharmaceutical substances, medicinal plant materials and dosage forms.
1998 (94 pages)

Basic tests for pharmaceutical dosage forms.
1991 (134 pages)

Quality assurance of pharmaceuticals: a compendium of guidelines and related materials.
Volume 1: 1997 (244 pages)
Volume 2, Updated edition: good manufacturing practices and inspection. 2004 (236 pages)

Quality control methods for medicinal plant materials.
1998 (123 pages)

WHO Expert Committee on Specifications for Pharmaceutical Preparations.
Thirty-eight report.
WHO Technical Report Series, No. 917, 2004 (125 pages)

International nonproprietary names (INN) for pharmaceutical substances. Cumulative list no. 10.
2002 (available as CD-ROM only)

The selection and use of essential medicines.
Report of the WHO Expert Committee (including the 12th Model List of Essential Medicines)
WHO Technical Report Series, No. 914, 2003 (126 pages)

WHO Expert Committee on Biological Standardization.
Fiftieth report.
WHO Technical Report Series, No. 904, 2002 (113 pages)

WHO model formulary.
2004 (528 pages)

Further information on these and other WHO publications can be obtained from Marketing and Dissemination, World Health Organization, 1211 Geneva 27, Switzerland.