WHO Technical Report Series
946

THE SELECTION AND USE OF ESSENTIAL MEDICINES

Report of the WHO Expert Committee, 2007
(including the 15th Model List of Essential Medicines)

World Health Organization

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Geneva, 19–23 March 2007

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1. Introduction

The WHO Expert Committee on the Selection and Use of Essential Medicines met in Geneva from 19 to 23 March 2007. The meeting was opened on behalf of the Director-General by Dr Howard Zucker, Assistant Director-General for Health Technology and Pharmaceuticals. He stated that WHO's medicines programme is very important to Member States and that the recommendations made by its Expert Committees were critical. He briefly explained some aspects of the Committee procedures. He stated that the Committee is not a representative one, that all members participated in their personal capacity and are not allowed to take instructions from any government or any other authority. (See Annex 1 for Committee members' declarations of interest.)

Prior to the open session, Dr Hans V. Hogerzeil, Director of the Department of Medicines Policy and Standards, addressed the Committee. He noted that this would be the fourth meeting of the Expert Committee operating under the new procedures approved in 2002 and that the early posting of most documents on the web site, together with the rounds of review and comments prior to the meeting ensured the transparency of the process. Dr Hogerzeil also noted that this year is the 30th anniversary of the Essential Medicines List, and that it was timely to examine the future role of the list particularly in the context of supporting primary health care, identified by the Director-General as a priority for WHO.

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 was to allow all stakeholders to participate in the discussions and to comment on issues relating to the WHO Model List of Essential Medicines. Furthermore, for members of the Expert Committee it provides an opportunity to receive, at first-hand, additional information and opinion on matters under consideration. Discussions and opinions put forward during the open session are reflected in the report of the meeting.

The Committee decided to maintain the reporting format adopted at previous meetings. A summary of the Committee's deliberations on each of the items under discussion is presented in the main body of the report. The updated version of the Model List (the 15th Model List), including a general introduction and explanatory notes, is presented in Annex 2. This Annex is also posted on the WHO web site and available in printed form in all six official languages of the Organization. A list of items on the Model List ordered by their corresponding Anatomical Therapeutical Chemical (ATC) classification code number(s) is attached as Annex 3.

The full texts of the applications for changes, additions or deletions with all the evidence and references, as well as the external reviews and comments

received, are not included in this report but remain available on the WHO web site, and are accessible through the Essential Medicines Library (http://mednet3.who.int/EMLib/). Information on medicines deleted from the Model List in the past is retained in a separate section of the library.

2. Open session

The open session of the meeting was opened by Dr Howard Zucker, on behalf of the Director-General. He stated that all information submitted to the Committee in support of the evidence-based decisions would be placed in the public domain through the WHO web site. He reminded participants that all comments made during the open session would be noted and taken into consideration by the Committee when formulating final recommendations in subsequent private sessions.

Dr Zucker noted that 2007 was the 30th year of the Essential Medicines List. It was appropriate that in the 30th year, the 120th session of the WHO Executive Board had adopted two important draft resolutions in relation to medicines that would be discussed by the Committee. One resolution recommended an approach to rational use of medicines and the second recommended a programme of activities to improve medicines for children. Dr Zucker requested the Committee to give careful consideration to the proposal for a formal subcommittee to establish a list of essential medicines for children.

As part of the open session, participants were briefed about various activities relating to the Model List (see Section 3).

A number of issues were raised and debated during the open session.

HIV

The participants were informed about the current public health approach being used by the WHO HIV/AIDS Department. Professor Gilks described this as "managed public sector care", with the aim of scaling up the programme on the basis of the principles of universal access and limited choices rather than based on the needs of individual patients. He outlined guidelines developed by the Department in 2006, the strategic and programmatic importance of fixed-dose combinations to increase adherence to medication regimens, to decrease pill burden and, over time, to contribute to reduced drug resistance. The methods being used by the HIV/AIDS Department to identify the preferred treatment options were outlined.

Safety

A representative from the Quality Assurance and Safety: Medicines (QSM) team presented a summary of the fourth meeting of the WHO Advisory

Committee on the Safety of Medicinal Products (ACSoMP) held in February 2007. Key discussion points for the meeting were a strategy document for safety of medicines, a document on promoting the safety of medicines used to treat children and preparation of an advocacy document for pharmacovigilance. The QSM team had prepared documents addressing safety issues relevant to a number of applications under consideration by the Expert Committee.

International Union of Basic and Clinical Pharmacology

A presentation was made to the Committee on behalf of the Paediatric Subcommittee of the Clinical Pharmacology Division of the International Union of Basic and Clinical Pharmacology (IUPHAR), describing children as a neglected population. Children are "neglected" in the sense that they do not have access to treatment with medicinal products that meet the same standards of quality, safety and efficacy as the treatments available to adults, although international agreements on human rights give children the right to the same level of health and health care enjoyed by others. The presentation highlighted the challenges of developing medicines for children, and the need to recognize five phases of development, each of which differed with regard to metabolism and drug handling. Progress had been made within the regulatory authorities in the USA and the European Union (EU), reflecting a commitment to the development of medicines for children. IUPHAR has formed a number of Paediatric Expert Groups at the European Agency for the Evaluation of Medical Products (EMEA) in the last three years to assess the needs of children in major clinical areas.

Médecins Sans Frontières

The Committee was informed about the Médecins Sans Frontières Campaign for Access to Essential Medicines. Médecins Sans Frontières supported the initiative to create an Essential Medicines List for children, encouraged WHO to accelerate the publication of this list, and urged WHO to ensure that the research and development of products for children takes place. Médecins Sans Frontières acknowledged the importance of fixed-dose combinations in the treatment of AIDS and commented on specific applications to be considered by the Expert Committee (fixed-dose combinations for HIV/AIDS and antitrypanosomal medicines). Médecins Sans Frontières recognized the role of listing medicines on the Model List in creating an incentive for producers and providers to improve the quality of a product. Médecins Sans Frontières urged the Committee not to consider the cost of a product in its deliberations.

International Society of Paediatric Oncology

A written statement was provided to the Committee by the President of the International Society of Paediatric Oncology (SIOP). The President

expressed the Society's commitment to an Essential Medicines List for Children and requested that the Society be able to participate in the deliberations with WHO. The Society recognized that about 80% of children worldwide who develop cancer currently do not receive optimal care and often do not even receive any supportive or palliative care. The Society has identified a number of important steps required to make progress in the area of improved oncology and palliative care medicines for children. It wishes to encourage countries to adopt the principle of dedicated specialist units to concentrate expertise, reduce wastage and improve survival and quality of life of children with life-threatening conditions.

Polyvalent human immunoglobulins

Representatives from Chandigarh Hospital, India, and the Primary Immunodeficiency Association, England, addressed the Committee on the application for the reinstatement of polyvalent human immunoglobulins (IGs). They outlined the role of IGs as replacement therapy for primary immunodeficiency disorders, a number of which occurred in children, and as immunomodulatory agents. The representative from Chandigarh Hospital addressed what he described as misunderstandings about the treatment of these diseases, pointing out that without IGs morbidity and mortality from these conditions were substantial. The representative of the Primary Immunodeficiency Association spoke as a patient and reiterated the statements of his co-speaker and suggested that his own experience illustrated the efficacy and safety of IGs and the value of treatment with them.

Additional comments

Discussion was invited on the matters raised in the open session. The IUPHAR representative provided further comments on paediatric medicines. Comments on the application for immunoglobulins were made on behalf of the International Patient Organisation for Primary Immunodeficiencies (IPOPI). A representative of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) stressed the importance of the Committee considering the availability of quality products in its deliberations. Support from Health Action International (HAI) for the establishment of a steering group to engage stakeholders as part of the Rational Use of Medicines proposal was expressed.

3. Update on current activities

3.1 Procedure to update and disseminate the Model List

The current "Procedure to update and disseminate the WHO Model List of Essential Medicines" was approved by the Executive Board in 2001 and

has been used by the Expert Committee on Selection and Use of Essential Medicines since that time. The Committee has now had considerable experience in the use of these procedures, and some changes have been made as experience in evidence-based selection of medicines has developed. The Secretariat therefore proposed an update to the "Procedure" to reflect that experience. The amendments are generally minor and reflect the methods of reviewing applications and seeking public comment through the web site, as well as the need to ensure that adequate information is provided about each medicine in an application.

The Committee supported the proposed updates and recommended that the Secretariat take appropriate steps to finalize them.

3.1.2 Procedure for between-meeting decisions

The WHO Expert Committee on Selection and Use of Essential Medicines has met nearly every two years since it was first established in 1977. In accordance with the WHO Regulations for Expert Advisory Panels and Expert Committees, the report of each committee has been finalized at the end of its meeting. No between-meeting decisions have been taken so far, although occasionally changes have been made to the report of the meeting and its recommendations after the conclusion of the meeting, based on written approval by all Expert Committee members.

A number of other WHO programmes are reliant to a greater or lesser extent on the Model List of Essential Medicines. In particular, the programmes on HIV/AIDS, malaria and tuberculosis (TB) link their procured medicines closely to those included on the Model List, and the Prequalification Programme also considers whether a medicine is on the Model List when specifying the "Expressions of Interest" for its programme. In these areas, and in the area of emerging diseases, there is an increasing need to update the Model List more often than every two years.

The Regulations do not specify the methods for making decisions between formal meetings of the Committee. To accommodate the possibility of between-meeting decisions being required, it is therefore proposed to have the Committee adjourn at the end of its formal meeting and formally remain in existence until the next Committee is appointed.

The Committee supported the need for making decisions about amending the Model List more often than every two years. The "between meetings" proposal of the Secretariat was one option but the Committee recommended that other options, such as more frequent meetings or virtual meetings, should also be considered.

The Committee discussed whether regulatory approval of a medicine would be a prerequisite for its inclusion in the Model List. Although the decision

to include a medicine in the Model List is generally post-regulatory, this may not always be possible.

3.2 Proposal for subcommittee on essential medicines for children

In August 2006, a joint WHO–UNICEF expert consultation on essential medicines for children was held to review some of the problems associated with access to essential medicines for children. The report of the meeting is available at: http://www.who.int/medicines/publications/UNICEFconsultation.pdf

The meeting produced a list of recommended actions to be undertaken by WHO and UNICEF to improve access to essential medicines for children. One of the key recommendations was to update the WHO Model List of Essential Medicines to include essential medicines for children, based on their clinical needs and the burden of disease.

In January 2007, the 120th Session of the Executive Board of the World Health Assembly (WHA) adopted a draft resolution (EB120.13) requesting the Director-General and Member States to take action to make available better medicines for children. This resolution outlines a comprehensive programme for the work needed.

The WHO Secretariat has commissioned a number of preliminary papers as part of the evidence needed to support the recommendation for updating the Model List to meet the needs of children. In so doing, it has become clear that developing an up-to-date list of essential medicines for children is likely to require additional meetings of appropriate experts, as there is more work than can be completed as part of the usual agenda of the regular meetings of the Expert Committee. The are several reasons for this. The technical scope of the work needed requires additional consultation and time, for example, for developing the criteria for defining essential medicines for children, including defining age groups within "childhood", as different age groups have different patterns of disease and different needs. A position statement on the types of dosage form to be defined as "essential" needs to be developed. All existing dosage forms currently on the list for children would need to be reviewed and ratified as essential, and additional products would need to be reviewed, according to priorities to be established.

Furthermore, the technical expertise necessary to review applications for essential medicines for children requires skills additional to those needed for a review of adult medicines. It needs to take account not only of paediatric clinical medicines, but also of factors such as the different pharmacokinetics of medicines in children of different ages.

In terms of advocacy and promoting access to essential medicines for children there are distinct advantages to initially having a separate process for

determining essential medicines for children, although in the medium-term (3–5 years) it is unlikely to be necessary to maintain a separate system.

According to WHO regulations governing Expert Committees, the mechanism that can be used for this purpose is the establishment of a subcommittee of the Expert Committee with specific terms of reference. Formal subcommittees of Expert Committees need to be recommended by the relevant Expert Committee and approved by the Executive Board or World Health Assembly (Regulations for Expert Advisory Panels and Committees, 4.10 and 4.11). The rules governing the operation of subcommittees are the same as those governing the operation of the parent Expert Committee. Through UNITAID, the International Drug Purchase Facility being established with funding from Brazil, France, Chile, Norway and the United Kingdom, resources are now available to allow the first meeting of such a subcommittee to take place in July 2007. UNITAID is being established as an innovative funding mechanism to accelerate access to high-quality drugs and diagnostics for HIV/AIDS, malaria and TB in countries with a high burden of disease.

The Secretariat proposed that the first meeting in July 2007 would be followed by a second meeting in mid-2008, to complete development of an Essential Medicines List for Children. It is unlikely that the subcommittee would need to continue to exist after the second meeting. It could therefore report to the 2009 regular meeting of the Expert Committee, and make proposals on how the specialized functions necessary to maintain the Essential Medicines List for Children could be carried forward. The subcommittee could be dissolved if the work were complete.

The Expert Committee considered the proposal to establish a subcommittee on the Selection and Use of Essential Medicines for Children, with the following terms of reference:

— develop a WHO Model List of Essential Medicines for Children, based on their clinical needs and the burden of disease;
— develop suitability criteria for dosage forms of medicines for children with particular reference to the developing world;
— review the feasibility of manufacturing appropriate formulations for those priority medicines for which none currently exist, specifically considering requirements for use in resource-limited settings and availability of data on efficacy and safety in the appropriate age groups;
— identify the gaps in clinical research regarding safety and efficacy of essential medicines for children to improve suboptimal prescribing and dosing, and also to facilitate regulatory approval of paediatric formulations; and
— report to the Expert Committee on the Selection and Use of Essential Medicines in 2009.

The Committee noted the comments from the representatives of SIOP and IUPHAR supporting the proposal. It also noted the resolution from the 120th session of the Executive Board, EB120.13, requesting the Director-General and Member States to take action to make available better medicines for children. It therefore decided to recommend to the Director-General and the Executive Board that a subcommittee be established as proposed in the Secretariat documents.

3.3 Proposal on listing fixed-dose combination products for infectious diseases

The "Procedure to update and disseminate the WHO Model List of Essential Medicines, Criteria for Selection" was modified in 2005 to include the following statement regarding fixed-dose combination products (FDCs):

> "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."

Given that the agenda for this meeting required consideration of several applications for new FDCs for the three main infectious diseases, the Secretariat sought clarification of the principles on which drug selection should be based, before any individual application is considered.

From a regulatory viewpoint, for FDCs it would also be necessary to demonstrate bioequivalence of the single combined dose unit with the components administered at the same doses separately but concomitantly. These requirements for efficacy of the combination beyond that of the individual drugs and for bioequivalence are relevant to all clinical areas, including infectious diseases.

The Committee noted the report of the 2005 Expert Committee (*1)* which described a number of different scenarios for possible registration of FDC products. It seemed likely that most products to be considered by the Committee would be described according to "Scenario 2" in the specifications i.e.

> "the new FDC contains the same actives in the same doses as an established regime of single entity products, and the dosage regimen is the same or the established regimen may involve combinations of single entities and FDCs, for example a single entity finished pharmaceutical product (FPP) combined with an FDC–FPP that contains two actives. In all cases, the established regime has a well characterized safety and efficacy profile, and all the FPPs used in obtaining clinical evidence have been shown to be of good quality."

Accepting this, the Committee noted that for products fitting this description, this would imply that clinical trials of the FDC would not usually be required; bioequivalence between the FDC and the components could be used to infer clinical efficacy and safety of the combination.

The Committee considered the evidence available to support the proposal that FDCs improve adherence, noting the results from two recent systematic reviews (*2*, *3*) that address the question of whether FDCs have a positive effect on adherence to medication regimens and also the WHO report from a meeting in 2003.[1]

These reviews reveal that there have been very few clinical trials that have assessed the relationship between FDCs and adherence to treatment, and those studies that exist have significant methodological flaws. There is therefore limited direct evidence that strongly supports the benefits of use of FDCs. However, the WHO report of 2003 noted that "FDCs/CBCs are very important tools for scaling up treatment for HIV and AIDS, TB and malaria and remain the first choice when they are available. Fixed-dose combinations and co-blistered combinations (CBCs) must be considered as one element in an effort to ensure adherence that also includes supportive counselling, appropriate information and other measures."

One advantage of FDCs compared to loose combinations is that if one component of a loose combination is missing, resistance is more likely to develop. A disadvantage is that the optimal combinations of components may change rapidly. The Committee recognized the rapid development of the science of therapeutics in the area of infectious disease and that new FDCs may be conceptually appropriate. The Committee recognized that some FDCs could encourage rational prescribing (e.g. because they would avoid use of antagonist compounds together).

The Committee also considered whether or not a decision to list an FDC requires the existence of a prequalified product or whether the Committee wishes to identify FDCs that are clinically desirable, to list them and use this mechanism to encourage reputable manufacturers to produce quality products to recognized specifications.

On balance the Committee decided that it will consider listing some existing FDCs that would be useful to countries that use the list for procurement. However, the Committee also wants to encourage the development of new FDCs and trials comparing these.

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[1] *Fixed-dose combinations for HIV/AIDS, tuberculosis, and malaria. Report of a Meeting held 16–18 December 2003, Geneva,* at: http://www.who.int/medicinedocs

The Committee decided that co-packaged products for use in combination but not formulated as an FDC, can be assumed to be covered by listing individual components.

Overall, the Committee, having reviewed its current criteria for listing FDCs as essential medicines, decided to retain them unchanged.

3.4 Report from the Advisory Committee on Safety of Medicinal Products

The fourth meeting of the Advisory Committee on Safety of Medicinal Products (ACSoMP) took place on 26–27 February 2007. Reports on the safety of medicines proposed for addition to the Model List were provided by members of the Advisory Committee for review by the Expert Committee.

The Committee recognized the usefulness of the reports provided. The Committee noted that it would also be helpful to have:

— summaries of safety data (in contrast to the raw data) that also distinguish between data from areas with rigorous adverse event reporting systems and those from areas with no such reporting systems;
— interpretation of and opinion on the safety data; and
— safety data in advance of the meeting, for experts to review with the application.

The Expert Committee also noted that it would be useful if the ACSoMP could develop a mechanism for collecting and interpreting safety data on currently listed medicines and reporting these data to the Committee on a regular basis. Such a reporting system could be used to promote safe use of medicines by providing early warnings of problems and could contribute to developing a process for the rapid deletion of products for safety reasons. The Safety Committee could also point out gaps in the available safety data.

3.5 Update of dosage forms and strengths for products on the Model List

In 2006, the University of Liverpool, England, carried out a complete review of the web site of the WHO Medicines Library. The Committee noted the detailed report of the review.

During the review, a number of products on the 14th WHO Model List of Essential Medicines were identified for which the dosage form and strength given in the List were not available in a sample of markets. For some products alternative dosage forms and strengths exist in at least one of the markets. Subsequent review of the missing products in additional markets finally led to identification of six medicines that do not appear to be registered products and in addition an important error in the strength of

a medicine. The Secretariat carried out a limited review of the evidence for each and proposed actions for the Committee to consider:

— *aluminium acetate*: proposed for fast-track deletion on the grounds that there was no evidence of benefit;
— *iopanoic acid*: proposed for fast-track deletion on the grounds of only being used as diagnostic agent in an obsolete investigation;
— *neomycin/bacitracin*: proposed for possible deletion on the grounds of limited evidence of benefit and alternatives being available;
— *nifurtimox*: proposal that this medicine should be retained on the grounds of evidence of benefit in the treatment of Chagas disease and that further information be sought about dosage form and strength;
— *propyliodone*: proposed for fast-track deletion, on the grounds of being used for an investigation that is now obsolete;
— *triclabendazole*: proposal that this medicine should be retained on the grounds of evidence of benefit in fascioliasis and paragonimiasis and that further information be sought about dosage form and strength;
— *epinephrine*: proposed change in dosing strength from 1 mg to 100 microgram/ml.

The Committee agreed to delete iopanoic acid and propyliodone and to change the dose for epinephrine. The Committee noted that these proposed actions had been posted on the meeting web site for 2 months and were also circulated through e-drug, the electronic discussion group, and no comments or objections to the proposed deletions had been received. The Committee proposed to retain aluminium acetate and neomycin/bacitracin as different strengths of products had been identified. However, it was noted that Section 13 of the Model List – Dermatological Medicines – was in need of general review.

The Committee agreed upon the following principles for specifying dosage form and strength, and recommended that the list be revised accordingly.

In general:

- When a product has been in use for some years and there is a traditional means of expressing dose, change would lead to confusion. In such cases no change should be made.
- WHO should follow the guidelines in the *International Pharmacopoeia* as to expression of dose.
- Even if changes to expression of dose are desirable, it is not appropriate for the Essential Medicines Committee to make such changes unilaterally.

Subject to the above, in general:

- The dose of acids and bases should be expressed in terms of the free acid or free base, even if the product is presented as a salt. The salt

form should be indicated in brackets in the form "(present as the [hydrochloride])".

- When a drug is formulated as a solvate, dose should be expressed in terms of the anhydrous substance.
- The dose of esters should be expressed in terms of the ester. Different esters may have different potencies.
- If:

— a new product has been formulated to contain a "rounded" dose; and
— pivotal clinical trials have been conducted with the specified product and
— one or more major regulatory authorities have approved the product in these terms, or the product is widely available;

then the dose should continue to be expressed in this manner even if it does not meet the above criteria.

It was also noted that clarification of dose expression will highlight anomalies on the Model List but the clinical importance of differences may not be so clear.

3.6 Rare diseases proposal

In 2005, the Committee considered the issue of rare diseases as a result of concerns expressed about the possible deletion from the Model List of factor VIII and factor IX and medicines for other rare diseases also known as "orphan diseases". At that time the Committee suggested that there was a need for WHO to establish a policy advisory group on rare diseases to study this issue. The discussion paper has now been published by Stolk et al. (*4*) in the *Bulletin of the World Health Organization* with an accompanying editorial (*5*).

The Committee further considered the option of establishing an advisory group to consider medicines for rare diseases and to agree on selection criteria for medicines for orphan diseases. The alternative proposal is to develop mechanisms to formally incorporate cost-effectiveness analysis as a basis for decision-making for all products.

The technical requirements for cost-effectiveness evaluation of pharmaceuticals at the global level are substantial, and require methodological development. The Committee might need to define "acceptable" cost-effectiveness thresholds, as has emerged from decision-making systems using cost-effectiveness evaluations in Australia and the UK (*6*). The Committee acknowledged the methodological difficulties related to assessing applications for medicines for rare diseases.

The Committee decided to maintain the current approach for selecting essential medicines including medicines for rare diseases. This is, effectively, maintaining the approach of considering comparative effectiveness, safety,

cost and need, taking overall public health into consideration. WHO is encouraged to develop relevant cost-effectiveness methodologies for the selection of essential medicines for rare diseases.

3.7 Procedure for updating the content of the Interagency Emergency Health Kit

The agencies of the United Nations system and international and nongovernmental organizations are increasingly called upon to respond to large-scale emergencies, many of which pose a serious threat to health. Much of the assistance provided in such situations is in the form of medicines and medical devices (renewable and equipment).

During the 1980s, WHO took up the question of how emergency responses could be facilitated through effective emergency preparedness measures. The aim was to encourage the standardization of medicines and medical supplies needed in emergencies to permit a swift and effective response to the need for medicines and medical devices by providing standard, pre-packed kits that could be kept in readiness to meet priority health needs in emergencies.

The "WHO Emergency Health Kit" was the first such kit when it was launched in 1990. The second kit, "The New Emergency Health Kit 98" was the outcome of the revision and further harmonization by WHO in collaboration with a large number of international and nongovernmental agencies. The third kit, the "Interagency Emergency Health Kit 2006" (IEHK 2006), accommodates emergency care of people with AIDS, the increasing antimicrobial resistance to commonly available antimalarials and antibiotics, injection safety policy, and the experience of agencies using the emergency health kit in the field.

The content of the emergency health kit is based on the health needs of 10 000 people for a period of three months, the acute phase of an emergency. The kit is composed of 10 basic units and one supplementary unit.

Over the years, the number of partners included has risen from two in the early 1980s to more than 10 partners and suppliers in 2006. The kit was last updated by consensus and there were some difficulties and delays in doing so. As a result, the Secretariat has proposed a process to formalize future revisions, including oversight by the Expert Committee after appropriate consultation.

The Committee reviewed the proposal to update the procedures for revising the Emergency Health Kit and, with the following modifications, endorsed the proposal from the Secretariat. The Model List will serve as a basis for including medicines in the IEHK. Therefore, if a medicine already appears on the Model List, a full application will not be required. Supplementary

information on quantities and sources of the medicines may be required. The Committee noted that the IEHK does not currently address the needs of children. The procedures are described in Annex 6.

3.8 Late agenda item on medicines for acute care

The Committee commented on a late agenda item, which proposed identifying medicines used for acute or emergency care. The Secretariat was requested to systematically gather data to create a list of the types of medicines currently used in emergency care and to compare this list with the Model List.

3.9 Report on WHO Model Formulary

The WHO Model Formulary (WMF) was first published in 2002, after the WHO Expert Committee on Selection and Use of Essential Medicines recommended its development in 1995. The original purpose of the Formulary was:

> "to provide general information and information on prototype drugs in the Model List of Essential Drugs according to the specifications as shown in the sample drug information sheet overleaf. This information could then be adapted by countries according to their own needs and would be a key element in rational drug use."

The WMF was updated in 2004, and published as a book, a CD and in an online version. In addition, a manual designed to assist countries to adapt the WMF to national needs was published. Both the 2002 and 2004 editions of the WMF were prepared by the Royal Pharmaceutical Society (RPS) of Great Britain on contract to WHO, and the manual benefited from considerable input from the Society as well. The preparation for the 2006 edition did not start until October 2005. There were numerous subsequent delays in the process and the 2006 edition was not published on the web site until January 2007.

The Committee noted the review of the need for the formulary carried out by the Medicines Policy and Standards department of WHO. From the relatively limited feedback, it would seem that the WMF is used in a variety of ways for many different purposes, including as a reference in clinical practice or as a policy tool. Importantly, the print version was reported to be used by more respondents than the electronic version. The WMF is also used by UNICEF as the source of drug information related to the products it supplies, is included (in printed form) as a reference book in emergency health kits, and has been adapted by several countries and organizations. The WMF can serve as a source document for a national formulary. This could be achieved by providing an electronic document that can be edited and adapted.

The Committee considered the report from the Secretariat, the response from the RPS and comments by expert reviewers. Overall, it is apparent that there is a need for the Model Formulary, as it is an important source of drug information in settings with limited resources. The printed version is essential. However, the Committee agreed that the current production process was not satisfactory and therefore supported the proposal by the Secretariat to consider other ways of generating and maintaining the text. Possible options discussed were:

— full technical review of monographs only for newly added medicines;
— less frequent production of the formulary;
— development of mechanisms for dealing with different electronic formats;
— local producton of print copies, or invitation of competitive bids for production.

The Committee recommended a pilot project to produce national formularies derived from an electronic version of the WMF and sufficient funding to accomplish this goal.

The Committee also noted the report on the technical update of the Essential Medicines Library.

3.10 Report on Drug Bulletin manual

In 2005, WHO and the International Society of Drug Bulletins (ISDB) published a manual entitled "*Starting or strengthening a drug information bulletin*". The authors came from both developed and developing countries. The manual provides detailed information on drug bulletins, planning, the editorial process, reviewing a new drug, design and production of the bulletin, dissemination, evaluating quality and usefulness of the product, and partnership and collaboration. The first 100 copies of the manual were produced with the financial support of the European Union. ISDB objected to this arrangement and the manual is now only available electronically on the WHO and ISDB web sites.

The Committee noted the report on the manual, regretted the lack of adequate publication and dissemination and endorsed the proposal that the manual be included on the CD-ROM with the WHO Model Formulary.

3.11 Review of proposal regarding critically important antibiotics

In 2005, the Committee considered a report from a working group consultation that took place in February 2005 in Canberra, Australia, with the remit of developing the concept of critically important antibiotics. This involved defining criteria for classifying antibiotics according to their level of importance for use in humans and then classifying all antibiotics according

to these criteria. It is envisaged that recommendations will be made that antibiotics deemed critically important should not be used in non-humans. The results of the consultation are reported in the document *Critically important antibacterial agents for human medicine for risk management strategies of non-human use.* The Committee noted the value of this report and recognized its importance for human health. The Committee endorsed the concept of identifying antibiotics that should be reserved for use only in humans and supports WHO taking the initiative to identify these antibiotics. It was noted that the labels of "critically" and "highly" important could be confusing and the full definitions of these categories could be used instead.

In response to the specific questions put to the Committee, the following comments were made:

- How does the concept of critically important antibiotics fit in with that of essential antibiotics? If the two concepts are different, how can we ensure there is a clear understanding of the two concepts by Member States and other interested parties? This will necessarily require consideration of the criteria for defining essential antibiotics and critically important antibiotics.

The Committee noted that the report states that this list of antibiotics is different to the antibiotics on the Model List.

- What process should be used for taking forward the issue of critically important antibiotics that are also essential antibiotics? Should a committee of experts sit regularly to advise WHO on how to preserve the effectiveness of these drugs taking into consideration human use as well as animal use? What should be its structure, procedures and membership?

The Committee recommends that WHO establish an advisory group that will meet regularly to produce and update the list of antibiotics that are permissible or not for non-human use. This should be an interagency structure involving the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE).

- How should antibiotics that are deemed essential (i.e. included in the Model List of Essential Medicines), but not critically important be dealt with? Should specific recommendations be made with regard to their use in animals?

The Committee urges the newly constituted Advisory Group to consider these questions.

3.12 Advice on draft resolution on rational use of medicines

In 2005, the 58th World Health Assembly discussed *Rational use of medicines by prescribers and patients* (*7*) in the context of the threat posed to global

health security by antimicrobial resistance and adopted resolution WHA58.27 on *Improving the containment of antimicrobial resistance*. At that time many Member States underlined the need for more to be done to rectify the serious global problem of irrational use of medicines. Thus, the Executive Board discussed *Rational use of medicines: progress in implementing the WHO Medicines Strategy* (*8*) at its 118th session in May 2006 and again at its 120th session in January 2007. EB resolution 120.R12 was adopted for further consideration at the World Health Assembly in May 2007.

The Committee considered the resolution and the Secretariat's report, together with the other referenced documents and the proposed plan of implementation, and considered the following questions:

- Does the present EB resolution to be submitted to the WHA in May 2007 sufficiently address the needs outlined in the Secretariat's report? If not, what is missing and what needs to be added?

The Committee felt that the resolution provided a good starting point for implementing the proposed global programme to promote rational drug use.

- Should a steering committee be established to oversee implementation of a global programme to promote rational use of medicines as envisioned in the present Secretariat's report and draft resolution? If so:
  — Should it be a subcommittee of the Expert Committee on Selection and Use of Essential Medicines?
  — What should be its membership?
  — How often should it meet?

The Committee endorsed the formation of an Advisory Group which could draw members from WHO panels or Expert Committees, including, for example, the Essential Medicines Committee. The Committee recommended that the Advisory Group include technical advisers and that the Secretariat choose the specific structure for the group. Members of the Essential Medicines Committee expressed interest in being part of the Advisory Group.

- What major steps in addition to those suggested above should be undertaken to implement the resolution and establish a global programme to promote rational use of medicines that includes the setting up of national programmes as recommended by the second International Conference on Improving Use of Medicines (ICIUM) 2004?

A first step would be to form a multidisciplinary Advisory Group with appropriate membership, including representation from the WHO regions.

The Committee acknowledged the importance of WHO taking a leadership role in promoting rational drug use worldwide. The Model List of Essential Medicines is a mechanism for promoting rational drug use and the Committee supports additional efforts to promote rational use.

The Committee recognized the lack of coordination within rational use programmes at the country level and the difficulty in gaining access to local data on medicine use. The proposed resolution could assist Member States in taking advantage of programmes that WHO has already set up. WHO could expand its network of relevant people in each country who are active in promoting rational use of medicines. The Committee raised concerns about the diffuse nature of the specific programme proposed, and thus supported the idea of an Advisory Group to guide implementation of the programme.

The Committee noted that the issue of irrational use of medicines is global and that a global approach coordinated by WHO is essential. The Committee, therefore, strongly endorses Resolution EB120.R12 "Rational Use of Medicines" and is eager to see WHO implement more vigorous leadership and evidence-based advocacy of rational use of medicines.

4. Changes made in revising the Model List by section: medicines for all populations

4.1 Section 2: addition of prolonged-release morphine

An application for inclusion of morphine (as sulfate) 10, 30 and 60 mg modified-release tablets was submitted by the Cochrane Pain, Palliative and Supportive Care Group, with support from the International Association for Hospice and Palliative Care.

Expert reviews of the application were prepared by: Dr Liliana De Lima[1] and Dr Alar Irs.[2] Comments in support of the application were received from Dr Lembit Rägo, Coordinator, QSM/WHO. Additional supporting statements were received from Médecins Sans Frontières.

The Committee noted that the application provided a thorough review of the evidence regarding the effectiveness and safety of the prolonged-release morphine formulation for management of chronic pain, based on systematic review (*9*) of its use in patients with chronic cancer pain. The public health need for inclusion of a new formulation of morphine on the Model List was fully substantiated. The current problems of inadequate access to morphine for use in palliative care in many countries were also described. As noted by the expert reviewers, the clinical evidence showed that the modified-release formulation and immediate-release formulations are equivalent for pain management in chronically ill (cancer) patients. Quantitative estimates of the analgesic effect were not calculated by the authors of the review

[1] Dr Liliana de Lima, International Association for Hospice and Palliative Care, Houston, TX, USA, is a Member of the Expert Committee.

[2] Dr Alar Irs, State Agency of Medicines, University of Tartu, Tartu, Estonia, is a Member of the Expert Committee.

owing to the insufficiency of comparable data for a meta-analysis to be undertaken. The Committee noted that modified- and immediate-release morphine preparations share a common adverse effects profile (nausea, vomiting, constipation, drowsiness and confusion).

The Committee also noted that prolonged-release dosage forms may not be interchangeable because the nature of release modification (rate and mechanism) may differ, and owing to the effect of patient variables (e.g. altered gastrointestinal motility or food intake) may not be the same for all products.

Generic prolonged-release preparations of morphine are available worldwide and its inclusion on the Model List may stimulate production of generics.

Overall the evidence provided in the application supports the public health need, effectiveness and safety of prolonged-release morphine formulation. The Committee therefore recommended that morphine sulfate 10-, 30- and 60-mg prolonged-release tablets be added to the Model List. These dosages are not applicable for paediatric patients and will be reviewed at the meeting of the Subcommittee on Children's Medicines.

4.2 Section 6.1: deletion of levamisole as anthelminthic

Expert reviews of the application for the deletion of levamisole as an anthelminthic were prepared by: Dr Eva M.A. Ombaka[1] and Dr Usha Gupta.[2] Additional supporting statements were received from The Center for Drug Reevaluation, SFDA, People's Republic of China. After review, the Committee recommended that levamisole be retained on the Model List.

In 2005, the Advisory Committee on Safety of Medicinal Products reviewed adverse events associated with levamisole. This review was prompted by a report from China which suggested that levamisole was associated with an encephalitis-like syndrome, levamisole-induced demyelinating encephalopathy. The Chinese literature contains 543 published reports of cases of this event. The 2005 meeting of the Advisory Committee proposed that the product should be deleted from the Model List given that it had been withdrawn from the Chinese national formulary, and then reviewed this recommendation together with the adverse event data from China at its most recent meeting in 2007.

The main ground for the request for deletion was the toxicity of the medicine. The Committee noted the argument made that there are safer and more effective alternative anthelminthics, but no comparison of effectiveness was

[1] Dr Eva M.A. Ombaka is Coordinator of the Ecumenical Pharmaceutical Network.
[2] Dr Usha Gupta, Delhi Society for Promotion of Rational Use of Drugs, Delhi Government Dispensary, New Delhi, India, is a Member of the Expert Committee.

provided. In addition to the Chinese literature, a search of other scientific publications identified a further possible 4–6 cases of encephalopathy, but only in the context of cancer chemotherapy. Doses used to treat cancer patients are higher than doses for use as an anthelminthic and the duration of treatment is longer. No cases of encephalopathy were found in the Uppsala Monitoring Centre database.

Noteworthy in the Chinese data is the apparent concentration of cases in one region where levamisole was being sold by "folk doctors"; 75.5% of cases were apparently reported as having occurred in patients who had obtained the drug from this source. This may call into question the quality and content of the product used.

The Department of Control of Neglected Tropical Diseases opposed the deletion of levamisole for this indication. It noted that levamisole is effective, and may also be of value when used in combination with mebendazole in delaying the development of benzimidazole resistance, as noted in the recent treatment guidelines (*10*) which continue to recommend levamisole, for *treatment* of soil-transmitted helminthiasis but not in preventive programmes. In addition, there are few anthelminthics currently on the list or in development.

The Committee noted that the evidence in the application is from one country. Although the reaction is recognized in the context of cancer chemotherapy, it does not seem to have been reported in the context of use as an anthelminthic from other settings. The assessment was made more difficult by the absence of a review of comparative effectiveness.

The Committee therefore decided to retain levamisole on the Model List as an anthelminthic but will review it again in 2009. To inform this review, the Committee recommended that the ASCoMP gather additional information on the safety of levamisole at the doses and duration for which it is used as an anthelminthic. The Committee also anticipates a review of comparative effectiveness.

4.3 Section 6.2.1: Beta lactam: addition of cefazolin/cefalexin

Expert reviews of the application were prepared by: Dr A. Helali[1] and Dr Youping Li.[2]

In 2005, the Expert Committee considered the priority review on cefalosporins by the ISDB and requested that a formal application for the first-generation cefalosporins (cefazolin and cefalexin) be submitted for the 2007 meeting.

[1] Dr Abdelkader Helali, Centre National de Pharmacovigilance et Matériovigilance, Ministère de la Santé et de la Population, Alger, Algeria, is a Member of the Expert Committee.

[2] Dr Youping Li, Chinese Cochrane Centre, West China Hospital, Sichuan University, Chengdu, People's Republic of China, is a Member of the Expert Committee.

The application was therefore commissioned by the Department of Medicines Policy and Standards. The proposal is to list cefazolin (injectable, 1 g/vial) for surgery prophylaxis and cefalexin (capsules, 250 mg/capsule and 500 mg/capsule, and syrup (powder to be reconstituted with water – 125 mg/5 ml and 250 mg/5 ml) for treatment of skin infections which are a major public health problem especially in children and in developing countries. Both cefazolin and cefalexin are available as generic preparations.

Cefazolin

The application presented a summary of the evidence for the effectiveness of cefazolin for surgical prophylaxis. As noted by the expert reviewers, there is high-quality clinical evidence, based on a systematic review (*11*), that shows that cefazolin for surgical prophylaxis in women undergoing caesarean section is as effective as ampicillin (relative risk (RR) 1.24, 95% confidence interval (CI): 0.84 –1.83) or second- or third-generation cefalosporins (RR 1.17, 95% CI: 0.97– 1.40) in preventing endometritis. Cefazolin has also been shown to be effective in preventing wound infection in patients undergoing peripheral arterial reconstruction (*12*).

On balance, as the evidence provided in the application supported the public health need, effectiveness and safety of cefazolin, the Committee recommended that cefazolin (injectable, 1 gm/vial) be added to the core list, with a note "for use as surgical prophylaxis".

Cefalexin

Cefalexin has been shown to be effective in treating skin and soft tissue infections in multiple trials in which it was compared with erythromycin, azithromycin, other third-generation cefalosporins and dicloxacillin (*13*), although the evidence is comparatively limited. The evidence from these trials has not been the subject of a Cochrane systematic review. The application refers to one of the studies which demonstrated equal efficacy and safety of cefalexin compared to moxifloxacin in 401 adults with uncomplicated skin infections (*14*), although this may not be relevant as moxifloxacin is not on the Model List. A Cochrane review of interventions for impetigo (Koning, 2003) (*13*) was based on 57 trials involving 3533 participants, which compared 20 different oral medicines, including cefalexin, and 18 different topical treatments. The trials were in children and adults. Settings and countries were not specified. The results did not show significant differences in cure rates between oral antibiotics or topical and oral antibiotics. Cefalexin is generally well tolerated.

In making its decision, the Committee noted that:

- Cefalexin has been shown to be effective in treating skin and soft tissue infections in multiple trials and it is commonly used to treat staphylococcal infections.

- Addition of a narrow-spectrum antimicrobial to the list could promote rational prescribing.
- It can be an inexpensive alternative for patients who are allergic to penicillins.
- Cefalexin in liquid form may be more acceptable to children than penicillin preparations.

However, the Committee also recognized that cefalexin, in particular, is widely used for inappropriate treatment of viral infections of the upper respiratory tract in children in many countries.

On balance, the Committee decided in view of the lower quality of the evidence for the comparative effectiveness of cefalexin, and the overall concerns about inappropriate use of antibiotics, not to add cefalexin to the Model List at this time.

4.4 Section 6.2.4: Antituberculosis medicines

4.4.1 *Addition of rifampicin + isoniazid + ethambutol*

Fixed-dose combinations (FDCs) of anti-tuberculosis medicines (isoniazid + ethambutol tablet, rifampicin + isoniazid tablet, several strengths; rifampicin + isoniazid + pyrazinamide tablet, several strengths, including paediatric; and rifampicin + isoniazid + pyrazinamide + ethambutol tablet) are included on the Model List to improve adherence and are recommended by the WHO guidelines (*15*).

An application for inclusion of a 3-FDC rifampicin 150/isoniazid 75/ethambutol 275 mg (RHE) was received from the STOP-TB Partnership.

Expert reviews of the application were prepared by: Dr Alar Irs[1] and Dr Youping Li.[2]

The Committee noted that there were no published trials that had used either the proposed FDC or the components in loose combination. One small bioequivalence study was presented. The major justification for the product was as an additional fixed-dose formulation for treatment of TB diagnostic category II as recommended in the WHO treatment guidelines (*15*). The clinical role of the product is in the continuation phase of treatment for category II patients, after the first two months, when pyrazinamide is no longer effective. The doses of the components proposed in this combination are consistent with current dosing guidelines based on weight of patients (using four weight bands) and also with the quantities in the four-component

[1] Dr Alar Irs, State Agency of Medicines, University of Tartu, Tartu, Estonia, is a Member of the Expert Committee.

[2] Dr Youping Li, Chinese Cochrane Centre, West China Hospital, Sichuan University, Chengdu, People's Republic of China, is a Member of the Expert Committee.

FDC already on the Model List. Evidence for the safety of the three-component FDC is based on the use of the four products in combination.

The Committee noted that the product is available through one supplier, but that there are no stringent regulatory authority approvals. Adding the product to the Model List might therefore be a stimulus to making available additional quality products. The product is listed on the Prequalification Programme expression of interest (EOI) and as of the last public report, no triple FDCs were listed as prequalified.

The Committee considered its agreed criteria for FDCs (see Section 3). This combination is recommended in the relevant WHO treatment guidelines for category II TB patients, but there are only uncertain estimates of the size of this subpopulation. Although the Committee was concerned by the absence of clinical trial data, on the basis of pharmacological and microbiological evidence, it decided to include rifampicin 150 mg/isoniazid 75 mg/ethambutol 275 mg on the core list.

4.4.2 *Section 6.2.4: Review of quinolones for multidrug-resistant TB*

Expert reviews of the application were prepared by: Dr Rohini Fernandopulle[1] and Dr Marcus M. Reidenberg.[2] Comments in support of the application were received from Dr Mario Raviglione, Director, Stop TB (STB).

Ciprofloxacin 250 mg and 500 mg, levofloxacin 250 mg and 500 mg, ofloxacin 250 mg and 400 mg tablets are included in the 14th Model List as complementary medicines for second-line treatment for multidrug-resistant TB, to be used in specialized centres adhering to WHO standards for TB control. Levofloxacin is the S-isomer (the active isomer) of the racemic mixture ofloxacin. These medicines were marked for review at the meeting of the 15th Expert Committee.

A review was commissioned by Stop TB to revise the listing for fluoroquinolones. The review concluded that the single fluoroquinolone to be nominated on the list should be levofloxacin, but without a square box. The review argued that as levofloxacin is the S-isomer of ofloxacin, there is no need to list both medicines and therefore a square box is not needed. Ciprofloxacin was not considered an appropriate alternative for routine use. The Committee noted that there was a very limited evidence base upon which to assess the relative clinical effectiveness of ciprofloxacin, ofloxacin and levofloxacin. While there are some data to support lower minimum

[1] Dr Rohini Fernandopulle, Department of Pharmacology, Faculty of Medicine, University of Colombo, Sri Lanka, is a Member of the Expert Committee.

[2] Dr Marcus M. Reidenberg, Division of Clinical Pharmacology, Weill Medical College of Cornell University, New York, NY, USA, is a Member of the Expert Committee.

inhibitory concentrations (MICs) and higher peak concentration (C_{max})/MIC with levofloxacin, it is difficult to translate this evidence into clinical practice recommendations. There is some evidence from observational studies (retrospective analyses of a series of treated patients) to suggest that levofloxacin is superior to ofloxacin (*16*).

However, it is difficult to assess the influence of trends over time in prescribing, doses used and other clinical factors in the treatment decisions on these observations. The recommendation not to use ciprofloxacin as an equivalent first-line drug substitute is based on the observations from a small number of trials where ciprofloxacin substituted into first-line regimens in drug-sensitive TB resulted in an increased risk of relapse and prolonged time to cure (*17*).

No data were presented on the cost-effectiveness of the fluoroquinolones nor were comparative price data included in the review. However, International Drug Price Indicator estimates suggest that levofloxacin could be a substantially more expensive treatment option.

Given the absence of any randomized controlled trials comparing the relative effectiveness of the three fluoroquinolones and of any evidence of substantially different adverse event profiles for these drugs, the Committee agreed that there were no compelling grounds on which to select one agent over the others for the treatment of multidrug-resistant TB. Comparative studies are needed. Current studies are examining the roles of moxifloxacin and gatifloxacin in TB, so further trial data on these three fluoroquinolones are unlikely to become available.

Given some evidence of the higher price of levofloxacin than ofloxacin and ciprofloxacin and recognizing the concerns of STB about the costs of medicines if only levofloxacin is listed, the Committee decided to include ofloxacin on the complementary list. Rather than adding a square box, the Committee decided to add a footnote noting that the alternative is levofloxacin based on availability, cost and programme considerations.

4.5 Section 6.4.2: Antiretrovirals

4.5.1 *Section 6.4.2.1: Nucleoside reverse transcriptase inhibitors: addition of emtricitabine*

Expert reviews of the application were prepared by: Mr Andy Gray[1] and Dr Abdelkader Helali. Dr Albert Figueras[2] withdrew from the discussion of this and all other proposals on HIV medicines.

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[1] Mr Andy Gray, Department of Therapeutics and Medicines Management, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, South Africa, participated as Temporary Adviser in the Expert Committee.

[2] Dr Albert Figueras, Fundació Institut Català de Famacología, Servei de Farmacología Clínica, Hospital Vall d'Hebron, Barcelona, Spain, participated as Temporary Adviser to the Expert Committee.

In 2005, the Expert Committee considered an application from the manufacturer for inclusion of emtricitabine as an additional nucleoside reverse transcriptase inhibitor (NRTI). At that time, the application was based mainly on unpublished studies and the Committee deferred its decision on the product until the data were publicly available. The application has since been resubmitted.

Emtricitabine is listed in the current WHO guidelines for the treatment of adults and children (*18, 19*) as one option for first-line combination treatment as part of the NRTI backbone, and as an alternative to lamivudine (3TC). According to the guidelines, "FTC [emtricitabine] is an equivalent alternative to 3TC as it is structurally related to 3TC, shares the same efficacy against HIV and hepatitis B virus and has the same resistance profile."

The application provided an updated summary of the evidence, including seven trials in adults and two in children. The majority of the trials are those submitted for regulatory purposes, but most have now been published as peer reviewed papers. The trials were limited to developed countries and experience of the use of emtricitabine in developing countries remains limited. In summary, the trials show that:

- Emtricitabine can be used in both treatment-naive and experienced patients.
- The once daily treatment regimen is at least as effective as dosing with other medicines, as measured by effect on standard viral load and CD4 outcomes.
- Emtricitabine has been used in combination with different medicines, as outlined in the WHO treatment guidelines, and therefore can be used in a variety of different combination treatments.
- The effect on viral load is durable.
- The product can be used in children from 3 months of age.
- The safety profile of the product, particularly with regard to hyper-pigmentation, is acceptable.

There are no data on use of emtricitabine in pregnancy.

A summary of accumulated safety data to date was also provided. The majority of reported use is in developed countries. Adverse reactions to emtricitabine are similar to those reported for other medicines in the class.

The Committee considered the question of interchangeability with lamivudine, based on clinical trials directly comparing the two medicines. From the evidence provided, there did not appear to be any clinically significant difference in effectiveness.

No evidence of cost-effectiveness was provided. The Committee noted that there is a proposal from the current manufacturer for differential pricing for emtricitabine and tenofovir FDC, but not for emtricitabine alone.

The Committee concluded that there is sufficient evidence that emtricitabine is effective for treating HIV when used in combination regimens although little of this information comes from resource-poor settings. The safety profile is similar to that of other medicines in the class. Although in practical terms it seems to be used as an alternative to lamivudine, there is insufficient evidence that it is in fact completely interchangeable and therefore listing it by reference to lamivudine with a square box could not be justified. The major advantage of adding emtricitabine to the Model List would appear to be in promoting availability and access to an additional treatment option, as well as offering an alternative to other NRTIs. The Committee therefore added emtricitabine capsule and liquid formulation to the core Model List with a note that it is clinically interchangeable with lamivudine.

4.5.2 *Section 6.4.2.1: NRTI: addition of tenofovir disoproxil fumarate*

Expert reviews of the application were prepared by: Mr Andy Gray and Dr Abdelkader Helali. A comment from Médecins Sans Frontières on the application was noted.

In 2002, the following NRTIs were added to the core Model List: abacavir, didanosine, lamivudine, stavudine and zidovudine. In 2005, the Expert Committee considered an application from the manufacturer for tenofovir (TDF) as an additional NRTI. At that time the application was based mainly on unpublished studies and the Committee deferred a decision on the product until the data were publicly available. The application has since been resubmitted. Tenofovir is listed in current WHO treatment guidelines for adults and children (*18, 19*) as one option for first-line combination treatment as part of the NRTI backbone, and as an alternative to abacavir (ABC).

The application provides an updated summary of the evidence, but as noted by the Committee, did not adequately cover all published literature. Some of the supporting evidence is still in the form of conference proceedings and abstracts. The trials presented are restricted to phase III clinical trials comparing TDF to stavudine, or TDF plus TFC to zidovudine/lamivudine FDC or trials with TDF as an add-on treatment in patients with virological failure. The main evidence in the application consists of data from four key regulatory trials. There are ongoing trials in the African region and also in children, but there is as yet no approval for use of TDF in populations younger than 18 years of age.

The application provided an updated review of safety information, dated October 2005. The concerns noted by the Committee in 2005 were the potential for renal toxicity, interactions, lactic acidosis, bone problems and liver problems. Although the supplement to the application provides lists of references that are related to these problems, there was no synthesis or overview of the information provided. The expert review prepared for the

Committee summarized the information in the references, and notes that several other relevant publications have not been considered. Overall, renal problems with tenofovir appear to be real but rare and the uncertainty is therefore the level of monitoring that would be required. Changes in bone density do not appear to be clinically relevant and may be reversible. The data on interactions is based on the product information document and may or may not be sufficient for global use. Lactic acidosis and lipodystrophy may be less of a problem with tenofovir than other currently available antiretrovirals (ARVs), especially stavudine.

In summary, tenofovir has been found to be effective in terms of effect on standard end-points such as viral load measures, for the treatment of HIV-infected adults, when used in combination with other ARVs. The safety profile is now better characterized than when it was considered in 2005, and considerable data are in the public domain. It is not yet approved for use in children. There are ongoing trials of its use in resource-poor settings. The Committee recommended adding tenofovir to the core Model List and noted that the monitoring requirements for this medicine are no different to those for other ARVs.

4.5.3 *Section 6.4.2: Antiretrovirals*

Section 6.4.2.2: Non-nucleoside reverse transcriptase inhibitors: addition of new strength of efavirenz

Supporting statements for the addition of a new strength of efavirenz were received from Médecins Sans Frontières.

Efavirenz was added to the core Model List in 2002 as capsule, 50 mg, 100 mg and 200 mg and oral solution 150 mg/5 ml, when the Expert Committee added the section for non-nucleoside reverse transcriptase inhibitors to the Model List with a recommendation to use these medicines in addition to dual nucleoside core combinations as a third agent. An application for inclusion of a new dosage form of efavirenz, a 600-mg tablet, has now been submitted by Merck Sharp & Dohme Interpharma, La Celle Saint Cloud, France.

The major advantage of the proposed new dosage form is that it can be given once daily, with a resultant reduction of pill burden and a presumed increase in adherence. The application presented results from three studies (*20, 21, 22*) to support this claim: two controlled trials and one small prospective cohort study. These studies showed that when used as part of different combination treatment regimens, efavirenz once daily was at least no worse than comparators (indinavir, nelfinavir) in terms of its effects on viral load. The benefits of once daily dosing on adherence were poorly substantiated as it was only measured in the cohort study.

In addition, a Cochrane review (*23*), not included in the application, provides further evidence of the relative effectiveness and safety of efavirenz in combination treatment regimens, in comparison with nevirapine. Efavirenz is contraindicated in pregnancy and it is not approved for use in children under the age of 3 years. The Committee noted that when using the 600-mg form, safety considerations became important in patients whose body weight was less than 40 kg.

Generic preparations of efavirenz are not presently available; the current cost is regulated by the manufacturer according to the prevalence of HIV in adults. Overall, the evidence provided in the application supports the need for the new dosage form. The Committee therefore recommended that efavirenz 600-mg tablet be added to the Model List for the first-line therapy of patients with HIV as part of combination treatment regimens as recommended in the WHO treatment guidelines for HIV.

Section 6.4.2.3: Protease inhibitors

The Committee noted advice from the WHO Department of HIV/AIDS that the evidence for, and experience of use of protease inhibitors is rapidly evolving and new medicines in this class are becoming available. In addition, the dosage form and strength of lopinovir and ritonavir will need to reflect developments in formulation to make heat-stable products. It is anticipated that an application for a heat-stable tablet formulation containing 200/50 mg lopinavir + ritonavir will be submitted for the next meeting. Selection of protease inhibitor(s) from the Model List will need to be determined by each country after consideration of international and national treatment guidelines and experience. Ritonavir is recommended for use in combinations as a pharmacological booster, and not as an antiretroviral in its own right.

Therefore, the Committee recommended that the WHO Department of HIV/AIDS conduct an urgent review of protease inhibitors in section 6.4.2.3. Ideally, this review should be conducted according to any new procedures that are developed for updating the list between meetings as the situation regarding protease inhibitors has highlighted the need for capacity for urgent updates of the Model List.

4.5.4 *Fixed-dose combinations of antiretrovirals*

The HIV/AIDS Department of WHO provided an introduction to and overview of the programmatic aspects of use of FDC antiretrovirals. Based on the 2006 WHO treatment guidelines, a list of preferred combinations was presented, which the Committee then considered in its review of all of the proposals for FDCs for HIV.

4.5.4.1 Addition of lamivudine/zidovudine

In 2002, NRTIs were added to the core Model List: abacavir, didanosine, lamivudine, stavudine and zidovudine. At that time, an application for the combination product containing zidovudine 300 mg and lamivudine 150 mg was also presented, but the decision was to list only single components and to have a note in the Model List about FDC products.

Zidovudine and lamivudine are both listed in the WHO treatment guidelines for adults and children (*18, 24*) as one option for the NRTI backbone for first-line combination treatment, with either nevirapine or efavirenz as the NNRTI. Given as the combination, the dose is one FDC tablet twice daily with either nevirapine or efavirenz.

Expert reviews of the application were prepared by: Dr Marcus M. Reidenberg. Additional statements were received from the Access to Essential Medicines Campaign, Médecins Sans Frontières.

The evidence for comparative effectiveness and safety in this application is an update of the review presented in 2002. It is stated in the application that "in compiling the application, it was recognized that there are large numbers of commercial products containing this particular combination, some of which have been subject to rigorous regulatory assessment while others have not." The application therefore proposes that adequately conducted trials of an FDC or trials involving the components concomitantly administered should be regarded as supportive evidence, i.e. studies that are indicative but not conclusive. The application also points out that if an individual product has been subject to stringent regulatory authority approval, bioequivalence between the FDC and the components can be accepted. Advantages of this two-drug FDC are:

— ease of storage, procurement and distribution; and
— harmonization of prevention of mother-to-child transmission.

This application cites two systematic reviews (*25, 26*) as the main source of evidence to support the use of the FDC containing zidovudine and lamivudine. It is not clear which of the trials actually used FDCs. Some of the trials are the early comparisons of double versus monotherapy that became the basis of the general recommendation to use combinations of three or more antiretrovirals, which is now accepted as standard. The application notes that AZT/3TC should not be used alone in treatment, but must be used in combination.

With respect to the impact of the FDC on adherence, the application describes two studies, one cohort study (Legoretta et al., 2005) (*27*) and one randomized controlled trial (RCT) (Enron et al.) (*28*) that compared adherence in patients who used FDCs containing AZT/3TC with adherence in those who used the individual components. The results of both studies

suggest better adherence in patients using the FDCs, including when used as part of triple combination treatment regimens.

The evidence for comparative safety combines the information on adverse events for the individual components with that on drop-out rates in the clinical trials. There do not appear to be any safety concerns that specifically relate to the use of the FDC. This combination has been used in a variety of settings as part of the roll-out of ARVs and a number of high-quality products are available.

The Committee noted that the unit price and average cost of treatment with AZT/3TC varies enormously. Overall, this combination, one of several proposed in the WHO treatment guidelines, is a preferred combination for first-line treatment, as one of the NRTI backbones. The combination can be used in most subpopulations of HIV patients, including pregnant women and children. Several products of adequate quality exist, containing appropriate doses of the components, and there have been clinical studies using the components of the FDC at the same doses, including two studies that show that its use leads to enhanced adherence, with no worse side-effects. There is also substantial experience of use of this product in resource-poor settings.

The Committee therefore recommended that the FDC should be added to the Model List.

4.5.4.2 Addition of lamivudine/zidovudine/nevirapine

In 2002, NRTIs were added to the core Model List: abacavir, didanosine, lamivudine, stavudine and zidovudine. As noted above, the role of FDCs in scale-up of treatment has become critical and the Department of HIV/AIDS, WHO, has proposed that an FDC product containing zidovudine, lamivudine and nevirapine be included on the Model List.

All three components are listed in the WHO treatment guidelines for adults and children (*18, 24*) as one option for first-line combination treatment. Given as the combination, the dose is one FDC tablet twice daily.

Expert reviews of the application were prepared by: Dr Marcus M. Reidenberg. Additional statements were received from the Access to Essential Medicines Campaign, Médecins Sans Frontières.

The evidence for comparative effectiveness and safety in this application is based on a trial of the components given individually. Products of assured quality, including three approved by the WHO Prequalification Programme exist. One observational study (*29*) evaluated FDC products in general, but it is not possible to separate results for AZT/3TC/NEV.

The five RCTs (*30–34*) using the components are comprehensively summarized in the application. The results of these trials show that:

— AZT/3TC/NEV is effective in treating HIV and equivalent to 3TC/stavudine/nevirapine.
— AZT/3TC/NEV my be superior to AZT/3TC/nelfinavir in terms of effect on viral load, and possibly health-related quality of life, but seems equivalent in terms of effect on immune recovery.
— AZT/3TC/NEV appears to be equivalent to AZT/3TC/abacavir in terms of effect on viral suppression.

Although AZT/3TC/NEV has been used in a number of countries, there is little information on total exposure. Safety data from the randomized trials are consistent with the known adverse effect profile of the three medicines. Lipodystrophy, rash and anaemia are well-characterized as adverse reactions. The Committee noted that this combination seems to be better tolerated that the stavudine-containing triple FDC and can be used in all relevant populations. No additional information on adherence with this FDC was found.

Overall, this combination is one of several proposed in the WHO treatment guidelines, and is a preferred combination for first-line treatment as it can be used in most subpopulations of HIV patients, including pregnant women and children. Several products of adequate quality exist, containing appropriate doses of the components and there are clinical studies using the components of the FDC at the same doses and one study using this FDC. There is substantial experience of use of this product in resource-poor settings. The Committee therefore recommended that the FDC containing zidovudine, lamivudine and nevirapine should be added to the Model List.

4.5.4.3 Addition of lamivudine/stavudine/nevirapine

In 2002, NRTIs were added to the core Model List: abacavir, didanosine, lamivudine, stavudine and zidovudine. As part of the general proposal on FDCs, the Department of HIV/AIDS, WHO, has proposed that two FDC products containing stavudine, lamivudine and nevirapine be included on the Model List. All three are listed in the WHO treatment guidelines for adults and children (*18, 24*) as one option for first-line combination treatment. Given as the combination, the dose is one FDC tablet twice daily. The strengths proposed are:

— stavudine 30 mg, lamivudine 150 mg, nevirapine 200 mg for patients under 60 kg;
— stavudine 40 mg, lamivudine 150 mg, nevirapine 200 mg (d4T/3TC/NEV) for patients over 60 kg.

Both products are available from multiple suppliers, including at least two prequalified products.

Expert reviews of the application were prepared by: Dr Marcus M. Reidenberg. Additional supporting statements were received from the Access to Essential Medicines Campaign, Médecins Sans Frontières.

The evidence for comparative effectiveness and safety in this application is based on trials of the components given individually. In addition, there have been several large observational studies (*29, 35*) using the FDC product that confirm its effectiveness and safety in a variety of settings, including in resource-poor countries. As noted in the application:

"Changes to viral load measures and CD4 counts are similar to what have been seen in randomized trials and cohort studies performed in developed countries, but clinical event rates and in particular mortality have been higher in the resource-poor settings. This suggests that patients are commencing treatment at a more advanced stage in their illness and co-morbidities, in particular opportunistic and intercurrent infections, are more frequent at baseline. Also, diagnostic and treatment facilities are lacking. The data reviewed here, and the comments of the researchers, indicate that these factors are the most important determinants of the poorer clinical outcomes, rather than poor adherence, viral resistance or inferior quality of the drugs themselves."

Comparative safety is comprehensively described. As noted, d4T is the NRTI most commonly associated with lactic acidosis, lipoatrophy and peripheral neuropathy and therefore countries should be planning to move away from treatment regimens that include it. However, treatment options that include d4T are currently the most readily available so appropriate monitoring for short- and long-term toxicities is required.

As noted by the Committee, this combination is one of several proposed in the WHO treatment guidelines, is a preferred combination for first-line treatment, and can be used in most subpopulations of HIV patients, including pregnant women and in children. Several products of adequate quality exist, containing appropriate doses of the components and there have been clinical studies using the components of the FDC at the same doses as well as several observational studies using this FDC. There is substantial experience of use of this product in resource-poor settings, but there is significant toxicity associated with this combination that may eventually lead to a decline in its use. It is widely available. The Committee also noted the advice from the HIV/AIDS Department that the FDC containing 40 mg stavudine would no longer be recommended, due to excess toxicity of the higher dose.

The Committee therefore recommended that the FDC containing stavudine 30 mg, lamivudine and nevirapine should be added to the Model List, but not the product containing stavudine 40 mg.

4.5.4.4 Addition of emtricitabine and tenofovir disoproxil fumarate fixed-dose combination

In 2005, the Expert Committee considered an application from the manufacturer for tenofovir (TDF) and emtricitabine as an FDC. At that meeting, the Committee noted "the fixed-dose combination had only recently been

approved by the US Food and Drug Administration, but that it is increasingly being used in national programmes. However, it would be illogical to consider the combination so long as the individual medicines had not been added to the Model List. The Committee concluded that listing of the combination at this stage would be premature, and decided to defer its decision because of the lack of information, for example, in comparison with lamivudine."

Tenofovir and emtricitabine are listed in current WHO treatment guidelines for adults (*18*) as one option for first-line combination treatment as part of the NRTI backbone, and as an alternative to abacavir (ABC).

Expert reviews of the application were prepared by: Mr Andy Gray and Dr Lenita Wannmacher.[1]

The evidence for comparative effectiveness and safety in this application consists of trials that were the basis of the USA's regulatory approval of the FDC and two studies of bioequivalence and pharmacokinetics. It is not clear that any of the large trials used the proposed FDC. Safety data based on the use of the components individually and in combination, not as an FDC, is as presented in the applications for the single components. There is no evidence of use of this combination in resource-poor settings. The Committee noted that differential pricing of the FDC is proposed through an access programme: 30 days supply for US$ 26.25. No formal cost-effectiveness evaluation was provided.

The Committee noted that this combination is one of several proposed in the WHO treatment guidelines, and is one combination for first-line treatment. The combination can be used in adult HIV patients but not children; there is limited information about its use in pregnant women. It is specifically recommended for use in patients co-infected with hepatitis B virus (HBV). One product of adequate quality exists, containing appropriate doses of the components, and there have been clinical studies using the components of the FDC at the same doses, but no clinical studies of the use of the FDC; there are also bioequivalence and pharmacokinetic studies. There is limited experience of use of this product in resource-poor settings.

The Committee therefore decided to add the combination of tenofovir and emtricitabine to the core list, noting particularly its utility in patients with HBV co-infection and with an accompanying note that 3TC is an acceptable alternative to FTC, based on knowledge of the pharmacology, the resistance patterns and clinical trials of ARVs.

[1] Dr Lenita Wannmacher, Department of Clinical Pharmacology, School of Medicine, University of Passo Fundo, Teixeira Soares, Rio Grande do Sul, Brazil, is a Member of the Expert Committee.

4.5.4.5 Addition of efavirenz, emtricitabine and tenofovir disoproxil fumarate FDC tablet

A new application for a new FDC medicine, tablets containing 600 mg efavirenz, 200 mg emtricitabine and 300 mg tenofovir, to be listed in section 6.4.2 Antiretrovirals, as a combination of NRTIs and NNRTIs has been submitted by Merck Sharp & Dohme, France. The Committee received the letter from Merck as a late paper.

Efavirenz, tenofovir and emtricitabine are listed in current WHO treatment guidelines for adults (*18*) as one option for first-line combination treatment. As stated in the application, the triple combination has so far been registered in the USA only, although other regulatory approvals are being sought.

Expert reviews of the application were prepared by: Dr Lenita Wannmacher. Additional supporting statements were received from the Access to Essential Medicines Campaign, Médecins Sans Frontières.

The evidence for comparative effectiveness and safety in this application consisted of two studies: Study 934, published by Gallant et al. 2006 (*36*) and an observational study, ANRS 1207 in 40 subjects (presented as a poster only). Neither study used the proposed FDC. Gallant et al. compared treatment with the three components given separately with a FDC of AZT/3TC plus efavirenz, and the observational study appears to have used the individual components. Evidence of safety was based on the use of the components individually and in combination, not as an FDC, and is as presented in the other applications. Postmarketing safety reports from the use of the FDC were also provided but they reported adverse events only amd were unquantified. Causality in relation to use of the FDC was not assessed. There was no evidence of use of this combination in resource-poor settings. The Committee noted that differential pricing of the FDC is proposed through an access programme, although the details were not provided in the application.

The Committee noted that this combination is one of several proposed in the WHO treatment guidelines, and is one combination for first-line treatment. The combination can be used in adult HIV patients but not children; efavirenz should not be used in pregnant women. It is specifically recommended for use in patients co-infected with HBV. One product of adequate quality exists, containing appropriate doses of the components and there has been one clinical study using the components of the FDC at the same doses and a small observational study using this FDC.

The Committee therefore decided this FDC should be added to the core list, noting particularly its utility in patients with HBV co-infection.

4.6 New section under 6.4.3: Addition of new section and medicine ribavirin

An application has been received from the Department of Epidemic and Pandemic Alert and Response (CDS/EPR) at WHO for the inclusion of ribavirin on the Model List for the treatment of viral haemorrhagic fevers (VHF) particularly Lassa fever (LF), Argentine haemorrhagic fever (AHF), Crimean-Congo haemorrhagic fever (CCHF) and haemorrhagic fever with renal syndrome (HFRS). The listing is as an individual medicine.

Expert reviews of the application were prepared by: Dr Lisa Bero.[1] Additional statements were received from Médecins Sans Frontières.

The Committee noted that the application provides a comprehensive review of the available clinical data on the use of ribavirin for the nominated haemorrhagic fevers. Most of the evidence is derived from case series and there have been few randomized or placebo controlled studies to assess the efficacy of ribavirin. The data generally suggest that ribavirin shortens the course of illness and reduces mortality rates from LF, CCHF and HFRS. While it has been suggested that further studies are required to establish the effectiveness of ribavirin, haemorrhagic fevers are associated with high morbidity and mortality, and there are few treatment options. The application notes a wide range of prices for ribavirin.

Given the potential benefits of treatment and the manageable side-effect profile of ribavirin, the Committee agreed to list ribavirin tablets and injection on the Model List. The Committee noted that even at the nominated prices, access in some country settings would remain a problem.

4.7 Late item: antiviral medicines for pandemic influenza

Dr Noël Cranswick[2] and Dr Thamizhanban Pillay[3] excused themselves during discussion of this item.

The Committee noted the memo from the WHO Global Influenza Programme: GIP, "Possibility of inclusion of influenza-specific antivirals to the Model List" and acknowledged the problem stated in the paper. The Committee noted that this situation highlights the need for a process for making decisions between meetings and would welcome applications for antivirals for pandemic situations.

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[1] Dr Lisa Bero, University of California, San Francisco, USA, is a Member of the Expert Committee.

[2] Dr Noël Cranswick, Clinical Pharmacology Department, Royal Children's Hospital, Parkville, Victoria, Australia, is a Member of the Expert Committee.

[3] Dr Thamizhanban Pillay, Pharmaceutical Economic Evaluation, National Department of Health, Pretoria, South Africa, participated as Temporary Adviser to the Expert Committee.

4.8 Section 6.5.2: Antileishmaniasis: addition of paromomycin

Medicines for treating leishmaniasis have been on the Model List since its first edition and the currently listed medicines are meglumine antimoniate (core list) and pentamidine and amphotericin B (complementary list). The Institute for OneWorld Health, San Francisco, USA, has submitted a new application for a new medicine to be listed for leishmanias, paromomycin. The dosage form and strength proposed is a solution for intramuscular injection containing 375 mg/ml paromomycin base as a 2-ml ampoule (750 mg of paromomycin base present as the sulfate). Paromomycin is an aminoglycoside antibiotic identical to aminosidine (*37*) which was first shown to have antileishmanial activity in the early 1960s.

The application provided a summary of the evidence based primarily on the phase III clinical trial (*38*), but as noted by the Committee, did not cover all published literature. In the Phase III trial, paromomycin (11 mg/kg paromomycin base for 21 days) was shown to be comparable with amphotericin B (1 mg/kg intravenously every other day for 30 days). The final cure rate in patients treated with paromomycin was equivalent to that of patients treated with amphotericin B. In another study, paromomycin was shown to be more effective that sodium stibogluconate (final cure rates of 93%–97% versus 63%) (*39*). Combinations of paromomycin with antimony compounds were found to be highly efficacious (*40–42*).

The application provided a review of safety information. Overall, ototoxicity, nephrotoxicity and elevations of liver enzymes are noted, but do not appear to be clinically relevant and may be reversible. Nephrotoxicity was shown to be less of a problem with paromomycin than with amphotericin B. Currently, a post-approval Phase IV trial is being conducted in India.

In summary, paromomycin has been found to be effective in terms of effect on standard end-points, such as initial and final cure, for the treatment of visceral leishmaniasis in children and adults. The Committee considered the additional evidence supporting safety and efficacy that was not included in the application, as noted above. The safety profile is well-characterized in randomized trials and during the period of approximately 40 years of its use for treating various bacterial and protozoal infections, including leishmaniasis. Once daily intramuscular administration for 21 days offers greater suitability than sodium stibogluconate (30 days) and amphotericin B (intravenous, 30 days). Paromomycin appears to be the most cost-effective treatment among all available alternatives. Leishmaniasis is a neglected disease. The Committee therefore recommended adding paromomycin to the core Model List.

4.9 Section 6.5.3: Antimalarial medicines

4.9.1 *Review of section 6.5.3: Antimalarial medicines*

Expert reviews of the application were prepared by: Dr Eva M.A. Ombaka and Mr Andy Gray.

The WHO Malaria treatment guidelines (*43*) were published in early 2006. The main change to the treatment recommended in those guidelines was the recommendation that first-line treatment for malaria should be with combinations of medicines rather than monotherapy. Artemisinin combinations were recommended as first-line treatment although other combinations were also noted to be more effective than monotherapy.

The Global Malaria Programme, WHO, has therefore proposed several changes to the current Model List of medicines for malaria, to align it with the treatment guidelines. The following combinations are proposed as additions to the core list, for treatment of uncomplicated malaria:

— artesunate plus amodiaquine, co-packaged 50 mg + 153 mg
— artesunate plus mefloquine, co-packaged 50 mg + 250 mg
— artesunate plus sulfadoxine–pyramethamine, co-packaged 50 mg + 250 mg.

The addition of two new artesunate formulations for emergency use in severe malaria: intravenous artesunate (ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution) and rectal artesunate (capsules containing 100 mg or 400 mg sodium artesunate) was also considered, see Section 4.8.2.

The malaria treatment guidelines were based on a number of comprehensive systematic reviews of clinical evidence in relation to treatment of malaria, and these reviews formed the basis of this application.

The Committee noted that the evidence in the application had not been updated to include studies published in the last 18 months and that this recent evidence was comprehensively summarized in one of the expert reviews. In summary, the clinical evidence showed that:

- Combination therapy for uncomplicated malaria is superior to monotherapy (odds ratio (OR) 0.30, 95% CI, 0.26–0.36).
- Artemisinin-containing combination therapy (ACTs) may be superior to other combinations such as amodiaquine plus sulfadoxine–pyramethamine (OR 0.49, 95% CI, 0.27–0.87).
- Currently, there do not appear to be any differences in effectiveness between the different ACTs.
- 6-dose regimens are superior to 4-dose regimens (based on polymerase-chain-reaction-adjusted cure at 28 days).

The guidelines also include recommendations about treatment of pregnant women and children with ACTs, based on reviews of observational and pharmacokinetic studies. ACTs are recommended as effective and safe in the second and third trimester of pregnancy, and artemether–lumefantrine can be used in children with a body weight > 5 kg rather than > 10 kg.

The main safety issues relate to the adverse effects of amodiaquine and mefloquine; the adverse effects of both products have been well characterized. It is also important to note that the concerns about adverse effects of these products arose when they were being used for prophylaxis. However, there are continuing reports of adverse reactions with both amodiaquine and mefloquine.

The regulatory status of the products proposed for addition was unclear. The Committee noted that the application was primarily for co-blistered packaged preparations and no true FDCs currently exist. The Committee also considered several other changes to the list of antimalarial medicines that would be required to ensure consistency of listing with the treatment guidelines, that were not considered in the proposal from the Global Malaria Programme.

Having considered the proposal, and in the light of the policy of listing FDC products, the Committee decided to comprehensively amend the list of medicines for malaria as follows:

- To include amodiaquine, artemether + lumefantrine, mefloquine, doxycycline, primaquine, quinine and sulfadoxine + pyrimethamine oral dosage forms on the core list, with notes for each describing the appropriate combinations.
- To amend the note regarding the use of artemether + lumefantrine in pregnant women (to restrict use only in the first trimester of pregnancy) and in children (to note that use is possible in children of > 5 kg).
- To maintain chloroquine on the core list, but for use only in the treatment of *P. vivax, P. ovale* and *P. malariae* infections.
- To delete chloroquine injection, on the basis that it is no longer recommended for use in severe malaria.
- To amend the list of treatments for prophylaxis to limit the use of chloroquine to central American regions and for prophylaxis of *P. vivax, P. ovale* and *P. malariae infections.*

The Committee noted that rapid development of high-quality FDCs to meet the treatment needs for malaria would be highly desirable, and it would welcome applications for such products, once they exist. In addition, the Committee recommended rigorous trials of these FDCs as well as noting the potential advice available for drug development and regulatory approvals through existing regulatory procedures such as Article 58 of Regulation (EC) No 726/2004 1.

4.9.2 *Addition of artesunate (injectable and suppositories)*

Expert reviews of the application were prepared by: Dr Youping Li and Mr Andy Gray. Comments on the application were received from Dr John McEwen, Member of the WHO Expert Advisory Panel on Drug Evaluation. Additional statements were received from Médecins Sans Frontières and UNICEF.

Artemisinin derivatives – artesunate and artemether – were added to the complementary section of the Model List of Essential Medicines in 2002. Following the publication of the WHO treatment guidelines for malaria (*43*), the Global Malaria Programme proposed the addition of two new artesunate formulations for emergency use in severe malaria: intravenous artesunate (ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution) and rectal artesunate (capsules containing 100 mg or 400 mg sodium artesunate).

The application provides a short summary of the clinical evidence of effectiveness of intravenous and rectal artesunate compared to intravenous quinine for treatment of severe and moderate-to-severe malaria, but did not include all relevant published studies. Importantly, the application did not refer to the systematic review of artemisinin derivatives in severe malaria published in 2000, although additional trials were cited. The Cochrane systematic review included 16 trials comparing artemisinin derivatives with quinine although not all the derivatives were artesunate. Five of the trials, involving 458 participants, reported effects of intravenous artesunate (*44*).

Intravenous artesunate: The application refers to two randomized trials comparing intravenous artesunate with intravenous quinine. One was conducted in Thailand, in 113 adults with severe malaria, and did not find a significant difference in mortality (RR 0.53, 95% CI, 0.23–1.26) after 300 hours (*45*). The second study was a large multicentre randomized clinical trial (*46*), involving 1461 participants with severe malaria, in Bangladesh, India, Indonesia and Myanmar. It found a significantly lower mortality rate in the group treated with artesunate than in the group that received quinine: RR 0.69, 95% CI, 0.54–0.83. The risk difference was 7.8% (95% CI, 3.8–11.8%), number needed to treat, 13. Including these results with those from the pooled trials in the review gives an overall effect size of RR 0.61 (95% CI, 0.50–0.75), RD 0.11 (95% CI, 0.17–0.05), favouring artesunate.

Evidence of the effectiveness of intravenous artesunate in children as presented in the application is limited. One additional small randomized trial (*47*) was identified which found that intravenous artesunate significantly reduced time to parasite and fever clearance and coma recovery although there was no statistically significant effect on mortality.

Rectal artesunate: The application referred to a study (*48*) that directly compared the responses to rectally administered artesunate and intravenous quinine in 144 people with moderately severe malaria: 109 children in Malawi and 35 adults in South Africa. It found that in children, artesunate significantly reduced fever clearance time and parasite clearance time compared with quinine. In adults, there was no significant difference in fever clearance time and parasite clearance time. An additional randomized study identified by the expert reviewer, compared rectal artesunate and intramuscular artemether in 79 children in Papua New Guinea. There were statistically significant differences in parasite clearance time with the rectally administered artesunate but this small study did not find differences in clinical outcomes (*49*).

Evidence on safety of rectal and intravenous artesunate was provided. Generally, particularly in the context of severe malaria, artesunate preparations are well tolerated.

The Committee noted the potential value of rectal dosage formulations and overall the evidence provided in the application supports the public health need, effectiveness and safety of artesunate formulations for emergency use in adults and children for treating severe malaria. However, the Committee noted that the regulatory status of the products, particularly the rectal capsule, was unclear. The Committee therefore recommended that artesunate ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution be added to the core list of the 15th WHO Model List with the note: "for use in the management of severe malaria". The Committee decided, given the uncertainty about currently available rectal products, to refer review of the rectal form to the paediatric subcommittee meeting and recommended further research on rectal dosage forms.

4.10 Review of section 6.5.5: Antitrypanosomal medicines

Expert reviews of the application were prepared by: Dr Marcus M. Reidenberg. Additional statements were received from Dr Carmen Pérez-Casas, Access to Essential Medicines Campaign, Médecins Sans Frontières.

The Department of Control of Neglected Tropical Diseases, WHO, submitted a proposal for restructuring Section 6.5.5.1 of the Model List by moving pentamidine and eflornithine to the core list. Pentamidine was added to the core list in 1977, and moved to the complementary list in 2003, when the review of core versus complementary listing of medicines was undertaken. Suramin was added to the core list in 1979. Melarsoprol was added to the core list in 1977 for use only in the second (neurological) phase of *Trypanosoma brucei* disease. Eflornithine was added to the complementary

list in 1992 as second-line therapy for late stage African trypanosomiasis due to *Trypanosoma brucei gambiense* (*T .b. g.*) and as second-line treatment for those not responding to melarsoprol for treatment of meningoencephalopathy due to *T. b. g*. Pentamidine, melarsoprol and eflornithine are produced and donated to WHO by Sanofi-aventis. Pentamidine iseothionate, 300-mg vials are also registered by the US Food and Drug Administration. Suramin is produced and donated by Bayer HealthCare.

The Committee noted that there is relatively little high-quality evidence to establish the effectiveness and safety of these medicines, but they have been in use for many years. Two drugs, pentamidine and suramin, have been used for more than 60 years for the treatment of first-stage disease. Treatment of second-stage disease is with melarsoprol and eflornithine, as these medicines reach therapeutic levels in the central nervous system – these medicines have also been used for many years. All four medicines are given by injection, although pentamidine is administered intramuscularly rather than intravenously. All have significant side-effects.

With respect to treatment of first-stage disease, the Committee considered the resistance data provided in the application and the additional clinical evidence summarized by the Secretariat. Pentamidine is used preferentially for *T. b. g.* infections. Drug resistance in the field has (up to now) had no significant consequences for the treatment, but, owing to a naturally lower susceptibility, it is not used to treat *Trypanosoma brucei rhodesiense* (*T. b. r.*) infections. There is no resistance to suramin, which is the medicine of choice for *T. b. r.* infections (*50*).

The clinical evidence to support the use of these products is limited. The most persuasive evidence is the report of results of the first 5 years (1996–2001) of a Human African trypanosomiasis (HAT) control programme in northern Angola, run by a nongovernmental organization (*51*). Thirteen thousand four hundred and twenty-six patients were screened for HAT. Pentamidine isethionate was administered as seven intramuscular injections at a dose of 4 mg/kg body weight every day for patients in stage I. Patients in stage II were treated with melarsoprol, and in cases of relapse after melarsoprol treatment, with eflornithine (400 mg/kg body weight, given as intravenous infusion at 6-hour intervals over a period of 2 weeks – the second-line treatment). Relapse was defined as trypanosomes detected in blood or cerebrospinal fluid (CSF) within the first year after completion of treatment. Relapse and clinical resistance to melarsoprol reached levels of 25% in M'banza Congo, and remained below 3% in the other study sites. Overall mortality rate of patients in stage II fell from 7.5% to 2.9%. The study demonstrated the efficiency of a national control programme, and although an observational study, it supports the efficacy of pentamidine, melarsoprol and eflornithine.

The application describes adverse effects of pentamidine and suramin noted in several reviews (*50, 52, 53*). Pentamidine is much better tolerated than suramin. The major adverse reactions to pentamidine are hypotension and hypoglycaemia. Nausea and vomiting, local reactions at the site of injection including pain, pruritus and rash; tachycardia; hypocalcaemia and abnormal findings in liver function have also been reported. Suramin causes severe adverse effects, including anaphylactic shock, severe cutaneous, neurotoxic reactions and renal failure. Polyneuropathy and stomatitis have also been described.

With respect to treatment of second-stage disease, the application provides a summary of failure rates for treatment of *T.b.g.* infection with melarsoprol and eflornithine, based mainly on observational studies. The failure rates appear to be similar. In addition three studies (*54–56*), that compared the efficacy of treatment with eflornithine and melarsoprol in patients with the second stage of *T. b.g.*, including one randomized trial, were also considered. The trial showed that eflornithine was an effective treatment for the second stage of Gambian trypanosomiasis and the results of the two comparative studies of eflornithine versus melarsoprol suggest that eflornithine is no worse than melarsoprol, and may in fact be less toxic.

Based on the clinical information provided, the Committee agreed that pentamidine is the drug of choice for treatment of the first stage of *T.b.g.* infection, which constitutes 95% of all HAT cases. It is much safer than suramin, is easier to use and the demand for pentamidine is nearly five times greater than that for suramin. The requirements for skills and monitoring for safe and effective use are the same. Cost is not a consideration given that all products are donated to control programmes.

Eflornithine has been demonstrated to be similar to melarsoprol in its efficacy for treating second-stage HAT in adults and children and to be safer than melarsoprol. Eflornithine is currently recommended as an alternative first-line treatment strategy particularly in view of increasing resistance to melarsoprol. The requirements for special skills or monitoring for safe and effective use of eflornithine and melarsoprol are essentially the same, although the availability of skilled personnel and equipment for both may be problematic in remote resource-poor rural areas. Recognizing the public health importance of supporting access to the few treatments available for sleeping sickness, the Committee recommended that all four products should be included on the core list, with notes indicating their appropriate indications.

4.11 Section 7: Antimigraine medicines

4.11.1 *Addition of sumatriptan*

Expert reviews of the application were prepared by: Dr Liliana de Lima and Dr Rohini Fernandopulle. Comments in support of the application

were received from Dr Benedetto Saraceno, Director, Mental Health and Substance Abuse, WHO.

During its meeting in 2005, the Committee recommended that ergotamine be deleted from the Model List because of lack of evidence of efficacy and the availability of effective and safe alternatives and, that a full application for inclusion of a 5HT1 agonist (triptan) for migraine be submitted at its next meeting in 2007. An application for inclusion of sumatriptan 50-mg tablet was received from the Global Campaign to Reduce the Burden of Headache Worldwide: Lifting the Burden.

The Committee noted that the application was generally of poor quality and provided only a limited review of the evidence. Although medicines for managing migraine are on the Model List, the information provided did not establish the public health need for an additional medicine. As noted by the expert reviewers, there is high-quality clinical evidence from a Cochrane review (*57*) that supports the superiority of sumatriptan for the acute management of migraine, compared with placebo. However, there have been few trials comparing sumatriptan with standard management (aspirin and metoclopramide, or caffeine and ergotamine). In these studies, sumatriptan was found to be superior in effectiveness to caffeine and ergotamine although it caused more adverse events. When compared with aspirin and metoclopramide, sumatriptan was superior for only one outcome (pain relief at 2 hours) and also caused more adverse events. The Committee noted that it would be helpful to have updated Cochrane reviews to confirm these findings. Some studies have found that the 50 mg dose of sumatriptan is as effective as the 100 mg dose.

Despite the availability of some generic preparations, the current cost of sumatriptan is substantially higher than that of aspirin and metoclopramide. No valid cost-effectiveness evidence was provided.

Overall the evidence provided in the application did not support the public health need or comparative effectiveness, safety and cost-effectiveness of sumatriptan. The Committee therefore recommended that sumatriptan not be added to the Model List and will seek high-quality national treatment guidelines to guide a full review of Section 7, Antimigraine Medicines.

4.11.2 *Deletion of paracetamol*

Expert reviews of the application were prepared by: Dr Liliana de Lima and Dr Rohini Fernandopulle. Comments in support of the application were received from Dr Benedetto Saraceno, Director, Mental Health and Substance Abuse, WHO. After review the Committee decided to retain paracetamol on the Model List.

During its meeting in 2005, the Committee recommended that ergotamine be deleted from the Model List because of lack of evidence of efficacy and

the availability of effective and safe alternatives. A proposal for deletion of paracetamol as a medicine for treatment of acute attack of migraine was received from the Global Campaign to Reduce the Burden of Headache Worldwide: Lifting the Burden.

The Committee noted that the application was of poor quality, with limited presentation of evidence for the lack of efficacy of paracetamol. As noted by one of the expert reviewers, a recent systematic review on efficacy of paracetamol in treating migraine (Damen, 2005) (*58*) and important studies on comparative effectiveness of paracetamol combinations versus sumatriptan were not included. The additional evidence identified was: one trial that showed paracetamol to be superior to placebo in treatment of acute migraine attack in children (RR 1.5, 95% CI, 1.0–2.1: 1 trial; 106 participants) and two studies comparing paracetamol (combined with other medicines) with sumatriptan, which showed equal or better efficacy of paracetamol combinations than of sumatriptan 50 mg (ASSET trial) (*59*) or 100 mg (Freitag, 2001) (*60*). The study cited in the application (Lipton, 2000) (*61*) showed the efficacy of oral paracetamol (100 mg) in treatment of acute migraine attack when compared to placebo. The only study (Leinisch, 2005) (*62*) which did not show benefits of intravenous paracetamol over placebo was small (n = 60) and could not be used alone to support lack of efficacy of paracetamol.

Overall the evidence provided in the application was selective and did not support the claim of lack of efficacy of paracetamol. Paracetamol may be a useful alternative in children. No significant toxicity was identified, and no evidence for better alternatives was provided. The Committee therefore recommended that paracetamol be retained on the Model List.

4.12 Section 8.2: Cytotoxic drugs

4.12.1 *Section 8.2: Cytotoxic medicines*

The expert review of the application was prepared by: Dr Alar Irs.

The Committee welcomed the contribution of the International Network for Cancer Treatment and Research (INCTR) to the review of the cytotoxic drugs for the Model List and noted the letter from Dr Ian McGrath (December 2006) outlining the continuing commitment of the INCTR to the review of the cytotoxic medicines. It is expected that the Network will contribute formal proposals for deletions and additions to the Model List for consideration at subsequent Expert Committee meetings. Two proposals were submitted for consideration at the 15th meeting of the Expert Committee – proposals for deletion of chlormethine (mustine) and levamisole.

4.12.2 *Deletion of chlormethine*

Comments on the proposal were received from: Adamos Adamou, Chairman of the ESMO task force for developing countries; Professor T. Eden; Ben

Anderson and Alex Eniu, The Breast Health Global Initiative; and Professor Ian Olver.

The Committee noted that chlormethine (mustine or nitrogen mustard) has been used for the treatment of various lymphomas for more than 50 years, mostly in combination with other agents. The side-effects of the earlier combination therapies (secondary malignancies and infertility) have led to the identification of other, more effective treatment combinations, such that chlormethine is now rarely used in clinical practice. It is not a component of standard therapy for any tumour in current clinical practice. In addition, chlormethine is a vesicant and can cause severe tissue damage and ulceration if it leaks at the site of intravenous administration. Topical mustine has also been replaced by other agents for the treatment mycosis fungoides. Given the availability of more effective and less toxic alternatives, the Committee recommended that chlormethine be deleted from the Model List (Section 8.2 Cytotoxic Medicines).

4.12.3 Deletion of levamisole as an anticancer medicine

The Committee noted that levamisole was developed originally as an anthelminthic. It was subsequently recommended for use as adjuvant therapy in colon cancer. However, more recent evidence from large randomized controlled trials has failed to show any benefit of levamisole in this situation. Levamisole has no place in the treatment of metastatic colon disease, nor is it used in clinical practice in the treatment of other cancers, including melanoma. Therefore, as levamisole has no clearly identified role in the treatment of cancers, the Committee recommended that levamisole be deleted from the section listing cytotoxic medicines (Section 8.2 Cytotoxic Medicines).

4.13 Review of section 8.4: Medicines used in palliative care

Expert reviews of the application were prepared by: Dr Eva Ombaka and Dr Abdelkader Helali.

The 14th Model List of Essential Medicines lists medicines for palliative care by reference to two WHO treatment guidelines for pain and palliative care (*63, 64*), which have not been updated since they were published in 1996 and 1998, respectively. Both contain a number of recommendations that would now be regarded as obsolete, as well as not referring to more recently available medicines.

In 2005, the International Association for Hospice and Palliative Care (IAHPC), in response to a request from WHO, developed a list of essential medicines for palliative care, in collaboration with other organizations. This was a consensus-based process, and for the first step, the group identified the most common symptoms in palliative care. Based on the symptoms, and

using a Delphi process, the group then listed possible essential medicines. The resulting list of 33 medicines has been announced as the IAHPC List of Essential Medicines. Of the 33 IAHPC essential medicines, 14 are already on the WHO Model List for several indications. Two medicines were added at the present meeting (prolonged-release morphine (Section 2.2) and fluoxetine (Section 24.2.1).

The IAHPC list is based on a holistic approach to treatment of patients with advanced, incurable and progressive diseases. The medicines in this section are included for the treatment of symptoms, not the underlying conditions.

The Committee welcomed this initiative and recognized the need for a comprehensive Palliative Care section that lists specific medicines. However, there are still a number of unresolved issues. The guidelines remain unchanged, and although WHO is planning to update them, this is still in the preliminary stages. Ideally, the guidelines should be updated first and then changes to the Model List could be proposed.

The Committee noted that the consensus process cannot replace consideration of evidence for comparative effectiveness and safety, even allowing for possible evidence gaps, given the difficulties of carrying out trials in palliative care settings, and that, based on a review of evidence, some of the recommendations may change.

For this reason, the Committee decided not to specify any medicines in the Palliative Care Section at this time. In addition, the Committee amended the note in this section to read: "The Committee expects applications for medicines essential in palliative care to be submitted for the next meeting."

4.14 Section 12.6: Lipid-lowering drugs: addition of simvastatin

Expert reviews of the application were prepared by: Dr Alar Irs and Professor Hany Abdel-Aleem.[1] Comments in support of the application were received from Dr Shanthi Mendis, Senior Adviser, Cardiovascular Diseases, Chronic Diseases Prevention and Management, WHO.

During its meeting in 1997, the Committee added the section on lipid-lowering medicines to the Model List. At that time, no specific medicine was recommended at the global level, although it was recommended that the choice should be made at the national level and the class of medicines, "statins" (β-hydroxy-β-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors) was suggested. The following statement has been included in the Model List since that meeting (with minor variations):

[1] Professor Hany Abdel-Aleem, Department of Obstetrics and Gynecology, Assiut University Hospital, Assiut, Egypt, participated as Temporary Adviser to the Expert Committee.

"The WHO Expert Committee on the Selection and Use of Essential Medicines recognizes the value of lipid-lowering drugs in treating patients with hyperlipidaemia. HMG-CoA reductase inhibitors, often referred to as "statins", are a family of potent and effective lipid-lowering drugs with a good tolerability profile. Several of these drugs have been shown to reduce the incidence of fatal and non-fatal 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 drug has been shown to be significantly more effective or less expensive than others in the group, none is included in the Model List; the choice of drug for use in patients at highest risk should be decided at the national level."

An application for inclusion of simvastatin 5, 10, 20 and 40-mg tablet was submitted by the NHS Centre for the Evaluation of Effectiveness of Health Care (CeVEAS), Local Health Unit, Modena, Italy and Universities Allied for Essential Medicines (UAEM). The proposal is to list simvastatin with a square box, with pravastatin, fluvastatin, atorvastatin and lovastatin as named alternatives.

The Committee noted that the application was of high quality and provided a comprehensive review of the existing evidence regarding the effectiveness and safety of statins used for secondary prevention of cardiovascular disease. The public health need for inclusion of a statin on the Model List was fully substantiated. As noted by the expert reviewers, there is high-quality clinical evidence from many large randomized trials and systematic reviews that establish the benefits of statins, in conjunction with lifestyle modification, for secondary prevention of cardiovascular disease. For example, the estimates of benefit in the UK National Institute for Clinical Excellence (NICE) systematic review (*65*) are RR 0.80 (95% CI, 0.71–0.90) for all-cause mortality and RR 0.75 (95% CI, 0.68–0.83) for cardiovascular mortality. These results are consistent with those of the other studies presented.

The Committee noted that statins are generally well tolerated (*66*). However, some of the rare adverse effects of statins are potentially very serious, including rhabdomyolysis. For the statins included in the application, there is no evidence of a difference in adverse effect profiles although adverse effects appear to be dose-related. The Committee noted that one medicine in the statin class, cerivastatin, had been withdrawn from the market due to unacceptably high rates of adverse reactions. Ideally, regular monitoring of liver function should be available if patients are taking long-term statin treatment, but it is also possible to assess safety on the basis of clinical assessment of muscle symptoms such as pain and fatigue. In general the

benefits of statins in preventing cardiovascular deaths outweigh the risk of the rare adverse effects.

Generic preparations of simvastatin are available worldwide; the current cost of simvastatin is reasonable and its inclusion on the Model List would potentially contribute to further reductions in prices. The application provided a review of the evidence on cost-effectiveness of long-term statin therapy for secondary prevention. The Committee noted that the cost-effectiveness of statin treatment is closely related to the absolute risk for coronary heart disease. There have been many cost-effectiveness analyses of use of statins in developed countries, but few in developing countries. The study by Murray et al. (*67*) provided modelled estimates of the average cost per disability-adjusted life year (DALY) of statins for secondary prevention in developing countries and suggested that, using the threshold of gross national income per capita, the products are acceptably cost-effective.

Overall the evidence provided in the application supports the public health need, effectiveness, safety and cost-effectiveness of simvastatin as an example statin. The Committee therefore recommended that simvastatin be added to the Model List for risk reduction in high-risk populations with a square box symbol denoting pravastatin, lovastatin, fluvastatin and atorvastatin as possible alternatives, with the choice to be made at the national level. These alternatives were identified on the basis of availability of comparable clinical outcome data.

4.15 Section 18.3: Contraceptives

4.15.1 *Review of section 18.03.00.00: Contraceptives*

Expert reviews of the application were prepared by: Dr Lenita Wannmacher and Mr Dinesh Mehta.[1] Comments in support of the application were received from Dr Catherine d'Arcangues, Reproductive Health and Research (RHR), WHO. Additional supporting statements were received from Dr Lindsay Edouard, Senior Adviser, Reproductive Health Branch, United Nations Population Fund, New York, USA.

The Section on Contraceptives was noted for review at the 14th Meeting of the Expert Committee on the Selection and Use of Essential Medicines, as the Committee declined to list several contraceptive medicines. In the discussion of the applications, the Committee noted that the approach to provision of contraceptives was a philosophy of choice and therefore required a wide range of options and that this was in contrast to the principles of drug selection applied for the Model List, i.e. the approach is one of identifying the minimum needed to provide health care.

[1] Mr Dinesh Mehta, British National Formulary, Royal Pharmaceutical Society of Great Britain, London, England, is a Member of the Expert Committee.

A review of the available evidence was commissioned to provide a stronger evidentiary basis upon which the Committee could make its recommendations. This review sought to answer the question: "Does a policy of providing a wide range of contraceptive methods, as opposed to a limited range, improve health outcomes including contraceptive uptake, acceptability, adherence, continuation and satisfaction, reduction of unintended pregnancy and improved maternal health and well-being?"

The review provided was comprehensive, and concluded that based on a limited literature: "It supports the contention that increased choice is associated with increased uptake and with better health outcomes (such as lower pregnancy rates and fewer STIs), and that women given a choice exercise it and continue use of their chosen contraceptives to a greater degree than those denied their choices. There is no evidence to the contrary. Nonetheless, a commitment to expanded choice is pervasive in the literature and has informed global and national policies. Such an approach is consistent with a Human Rights and Essential Medicines approach" (Executive Summary, page 5). However the literature is not particularly helpful in answering a question that has both biosocial and biomedical aspects. Therefore the Committee will need to decide the principles upon which drug selection for contraceptives for the Model List should be based. Should acceptability and suitability be considered, as well as the standard criteria used in identifying medicines for inclusion in the Model List of comparative efficacy, namely, comparative safety and comparative cost? The competing arguments can be summarized in part as follows:

> Family planning cannot and should not be considered in the same ways as curative medicine. Data regarding behavioural and psychosocial outcomes such as satisfaction with contraceptive method, persistence with contraceptive choice and desire to try other therapy options are crucial for family planning services.
>
> Different methods can be defined in a variety of ways, including route of administration, duration, components (e.g., progesterone only versus combined), or perception of the person using the contraceptive.

The Department of Reproductive Health and Research in part challenges the commissioned review on the perspective taken, arguing that the review considers the biomedical view, whereas the biosocial science point of view is more relevant to this question. These perspectives frame the questions in different ways. The biomedical view asks whether there is evidence that an increased range of treatment options improves outcomes (health, satisfaction), whereas the biosocial science point of view asks whether limited choices of contraceptive methods act as a barrier to achieving high levels of contraceptive use. The Programme of Action of the International Conference on Population and Development held in Cairo in 1994 recommended the provision of a wide range of contraceptive options.

The approaches adopted by the Expert Committee to the selection of contraceptives are based on the definition and selection criteria defined in the procedures for the Expert Committee 2002, which defines essential medicines as those that satisfy the priority health care needs of the population and where medicines are selected with due regard to disease prevalence, evidence on efficacy and safety, and comparative cost-effectiveness. Implicit in these criteria is an approach based on parsimonious choice, i.e. a limited list of drugs targeting priority health care needs.

After discussion of the review and considering the various arguments, the Committee confirmed that it would take an evidence-based approach to listing contraceptives. The Committee will assess new products on a case-by-case basis using the accepted criteria of comparative efficacy, comparative safety and comparative cost, as well as suitability and acceptability.

4.15.2 *Addition of levonorgestrel implants*

In 2005, the Expert Committee rejected the application for two implantable contraceptives (levonorgestrel- and etonogestrel-releasing implants) after consideration of the balance of benefits, harm, suitability, the need for the additional choice and the relatively high cost. In particular, the disadvantages noted included the special training required for insertion and removal of the implant and the relatively high cost. A revised application was submitted for the present meeting by The Geneva Foundation for Medical Education and Research, but this time only for inclusion of a two-rod levonorgestrel-releasing implant, each rod containing 75 mg of levonorgestrel (150 mg total).

Expert reviews of the application were prepared by: Dr Lenita Wannmacher and Mr Dinesh Mehta.

The Committee noted that the application provided an updated review of the existing evidence for the comparative effectiveness and safety of levonorgestrel-releasing implants for reversible contraception. There are reports from studies of four different products:

(1) two silastic rods containing levonorgestrel, 70 mg, with contraceptive life of up to 3 years (marketed as Norplant-2®);
(2) 6-capsule implant containing 36 mg of levonorgestrel each with a contraceptive life of up to 5 years (marketed as Norplant®);
(3 and 4) the proposed formulations (Jadelle® and Sino-implant No. 2).
The studies distinguish the different products by brand name.

Two trials comparing the proposed formulation of 2-rod implants with the 6-capsule implant have established contraceptive efficacy (*68, 69*). The cumulative 5-year pregnancy rate in these studies was 0.7–1 per 100 users for the 2-rod implant versus 0–0.7 per 100 users. For comparison with other methods of contraception, the application referred to a Cochrane systematic

review (*70*). One randomized controlled trial in family planning clinics in China (*71*) compared Norplant-2 with intrauterine systems impregnated with levonorgestrel (LNG-20 IUS). Both methods were found to be equally effective in preventing pregnancy, with pregnancy rates of 1/3098 women-months in the group using LNG-20 IUS versus 0/3093 women-months in the group using Norplant-2. The rates for continuation, expulsion and formation of ovarian cysts showed no difference between the two contraception methods. The use of 2-rod levonorgestrel-releasing implants (Norplant-2) was associated with less amenorrhoea and oligomenorrhoea, although there were more reports of spotting and prolonged bleeding.

The Committee noted that levonorgestrel-releasing implants are recommended in a number of WHO documents (*72, 73*) and that there are advantages of implantable contraceptives for women with risk factors for pelvic inflammatory disease and in cases of problems with adherence to other contraceptive methods. There is now at least one generic preparation and the cost has been reduced substantially.

As the evidence provided in the application supports the effectiveness, safety and cost-effectiveness of 2-rod levonorgestrel-releasing implants, the Committee recommended that a 2-rod levonorgestrel-releasing implant, each rod containing 75 mg of levonorgestrel (150 mg total) be added to the core Model List for long-term reversible contraception.

4.15.3 *Addition of medroxyprogesterone acetate plus estradiol cypionate*

Expert reviews of the application were prepared by: Dr Lenita Wannmacher and Mr Dinesh Mehta.

In 2005, the Expert Committee rejected the application for two combination injectable contraceptives (medroxyprogesterone acetate plus estradiol cypionate and norethisterone enanthate plus estradiol valerate), questioning the public health need for these preparations in view of the lack of compelling evidence of better efficacy, convenience and safety. A revised application for inclusion of medroxyprogesterone acetate 25 mg plus estradiol cypionate 5 mg was submitted by the Geneva Foundation for Medical Education and Research.

The new application presented the same evidence for comparative effectiveness and safety from a Cochrane systematic review (*74*) and additional results for comparative safety based on three observational studies. The systematic review included two multicentre studies that directly compared the proposed combination with medroxyprogesterone-only injection. Comparative contraceptive efficacy was not reported in the review although other evidence from the same systematic review shows that the proposed product is an effective contraceptive. In terms of potential advantages of the proposed combination, the results of the review suggest less menstrual disturbance, better control of bleeding and greater intention to continue contraception

with the combination injectable contraceptive (medroxyprogesterone acetate plus estradiol cypionate) than with medroxyprogesterone-only injections.

To address the concerns raised at the previous meeting, the application presented new information from three observational studies (*75–77*) all of 1 year's duration. The studies were designed to measure changes in surrogate biochemical markers, but not in cardiovascular events or fracture outcomes. The results generally showed that the injectable combined contraceptive did not have deleterious effects on lipid metabolism, coagulation or bone mineral density. The studies were of insufficient duration to identify any effects on clinical outcomes such as cardiovascular events or fractures. Importantly, although the application acknowledged the need for a sterile injection technique for administration of this product, it did not provide an assessment of the possible risks associated with a monthly injection regimen. The application did not provide information on the cost-effectiveness of the combination injectable contraceptive. Based on the information provided, the acquisition cost of the product would appear to be substantially more than that of the alternatives.

The Committee noted that combination injectable medroxyprogesterone acetate/estradiol cypionate is recommended in WHO guidelines (the WHO Medical eligibility criteria for contraceptive use (*78*); and the Selected practice recommendations for contraceptive use (*73*)), although there are currently no such products on the Model List.

Notwithstanding the previous inclusion of progestagen-only injectable contraceptives (POIC), and the similarity in contraceptive effectiveness between them and the combined injectable contraceptive (CIC), the differences in safety profile and convenience may serve to increase tolerance and continuation rates in women with different organic conditions and preferences. The Committee therefore decided to add medroxyprogesterone acetate plus estradiol cypionate 25 mg + 5 mg combination injectable contraceptive to the Model List of Essential Medicines as a new section, 18.3.5. The Committee also recommended that the Uppsala Collaborating Centre for Drug Monitoring be requested to monitor reports of adverse events in relation to use of this product.

4.16 Section 19.2: Sera and immunoglobulins

4.16.1 *Application for antivenom serum: equine immunoglobulin F(ab')2 fragment*

Expert reviews of the application were prepared by: Dr Estrella Paje-Villar[1] and Dr Noël Cranswick. Additional supporting statements were received from Dr José Manuel Gutiérrez.

[1] Dr Estrella Paje-Villar is Professor of Paediatrics and Pharmacology, Faculty of Medicine, University of Sto. Tomas, Sampaloc, Manila, Philippines, and participated as a Temporary Adviser to the Expert Committee.

An application was received from Sanofi Pasteur SA Lyon, France Equine F(ab')2 antivenoms for the inclusion of four polyvalent antivenoms on the Model List as individual medicines. These are FAVAFRICA for the management of snake bites in sub-saharan Africa, FAVIREPT for the management of snake bites in the Middle-East, VIPERFAV for snake bites in Europe, and SCORPIFAV for scorpion bites in the Middle East. The core Model List (2005) includes antivenom serum, but provides no further specification on type of product beyond a comment that the exact type needs to be defined locally.

The application from Sanofi Pasteur provides a possible short-term solution for ongoing supply problems identified in Africa and the Middle East for region-specific polyvalent antivenoms, and the Committee agreed to add antivenom immunoglobulins to the core list. The Committee decided that it was not appropriate to specifically include the individual products as nominated above on the Model List. At its next meeting, the Committee anticipates a full review of this section.

4.16.2 *Immunoglobulin*

Expert reviews of the application were prepared by: Dr Albert Figueras and Dr Noël Cranswick. Comments in support of the application were received from: Dr Neelam Dhingra, Coordinator, Blood Transfusion Safety, Essential Health Technologies, WHO, Dr Ana Maria Padilla Marroquin, Quality and Safety of Plasma Derivatives and Related Substances, WHO and Dr H. Goubran, from Egypt. The Committee acknowledged the receipt of additional supporting statements from the general public and professional organizations.

An application was received from the International Union of Immunological Societies (IUIS) and International Patient Organisation for Primary Immunodeficiencies (IPOPI) for the inclusion of polyvalent human immunoglobulins on the Model List. Human immunoglobulins were listed in Section 19.2 Sera and immunoglobulins, of the Model List in 2002, but deleted by the Expert Committee in 2003. The application seeks listing of polyvalent human immunoglobulins in several places in the Model List: Section 19.2 Sera and immunglobulins; Section 11.2 Plasma fractions for specific use; and Section 8.1 Immunosuppressive therapies, under the new subsection 8.1.1 Medicines used in immunomodulation.

The Committee noted that the evidence presented in the application does support the claims of efficacy and safety, and extensive clinical experience underpins the specific clinical recommendations to use these products. The costs of these products were noted as a concern. The Committee noted that cost-effectiveness has been assessed, but that this was done in a developed country setting and not found to be cost-effective for all indications.

Two of the specific issues that underpinned the decision to remove the product in 2003 were not directly addressed in the application; i.e. that human polyvalent immunoglobulins are not included in any Standard Treatment Guidelines (STGs), and that quality control of the blood product poses a problem. The application does state that improvements in manufacturing practice have reduced infusion-related adverse events, but ensuring that quality products are available in all settings may pose difficulties. No STGs were identified that included IVIg therapy.

The Committee considered that the products may not be cost-effective in many jurisdictions. In addition, however, the Committee considered that these products were part of the blood fractionation process that would yield other blood products for human use. Therefore the products could be seen as part of a package to encourage good manufacturing of plasma-derived products.

Because of potential infusion-related adverse events, IVIg would need to be administered in hospital settings where adequate specialist supervision was available. The Committee therefore agreed to list polyvalent human immunoglobulins on the complementary list in Section 11.2, Plasma fractions for specific use, in the following forms:

— human normal immunoglobulin for intramuscular administration: 16% protein solution; and
— human normal immunoglobulin for intravenous administration: 5%, 10% protein solution.

However, the Committee noted that unless the prices of the products were substantially reduced, access in developing countries would remain a problem. Countries are advised to acquire human immunoglobulins for specific disorders, such as primary immunodeficiency, Guillain-Barré syndrome and Kawasaki disease.

4.17 Review of section 19.3: Vaccines

The Model List of Essential Medicines currently lists vaccines based on the component antigens. This section has not been updated since 1999, when the List was modified to specify antigens rather than vaccines. In reviewing the text for the 2006 WHO Model Formulary, it was noted that several of the vaccine recommendations were out of date and several vaccines that are now recommended by WHO were not listed.

The option of undertaking a comprehensive update of the section was considered. In discussions with the Department of Immunization, Vaccines and Biologicals, WHO, however, it was pointed out that there is a separate expert group, the Strategic Advisory Group of Experts (SAGE) that now makes recommendations to the Director-General of WHO on the work of

the Department. A Global Advisory Group of Experts provides scientific advice to SAGE on the safety of vaccines. There is also an Expert Committee on Biological Standardization to define standards for prequalification of vaccines. It might be argued therefore that there is already sufficient WHO advice available to Member States on norms and standards for vaccines, including what vaccines to use. However, although there are several reference sources provided, none of them appear to contain an equivalent to an "essential list of vaccines".

The Committee was advised by Dr David Salisbury, Chair of the SAGE, that there are several problems with the current list and with potentially listing vaccines in the Model List:

- The current list is incomplete and out of date.
- The current division of the list into vaccines for universal and specific use is incorrect.
- The recommendations of SAGE and the vaccines listed in the Model List could be inconsistent. The List would need to be continuously updated to keep SAGE recommendations and the Model List harmonized. Countries that use the Model List to guide procurement may not purchase vaccines that are recommended by SAGE. If a vaccine is not listed on the Model List, this can be a disincentive to a country to purchase it.
- In making recommendations, SAGE considers trials, studies of safety and efficacy from industrialized countries, and experience of use in developing countries. An expert subgroup is convened to review this evidence to examine epidemiology of disease, availability of the vaccine, and cost-effectiveness data on the vaccine; this is presented as a WHO position paper on vaccines.

One proposed solution discussed was to remove specific vaccines from the Model List and refer people to the SAGE recommendations which include a list of pre-qualified vaccines that is updated weekly. This list does not specify which vaccines are universally recommended; it is not a list of "essential" vaccines. Countries could select vaccines from this list based on the epidemiology of disease in that country.

Another solution considered was that a procedure for updating the Model List between meetings could be linked to the SAGE process. Thus, the Model List could be updated as the SAGE recommendations are updated.

The Secretariat sought comments from regions and countries on the proposal and was advised that the vaccine list should be maintained as part of the Model List.

Recognizing that there are several other expert groups that consider vaccines, it would seem unnecessary for the Expert Committee on Selection and Use of Essential Medicines to expect a full application for new vaccines.

However, the other sources of information do not seem to completely replace the function of the Model List. The Committee decided to list all the vaccines for which the SAGE group has a position paper, with a link to the relevant web site. The preamble to the section has been revised to indicate that:

> Selection of vaccines from the Model List will need to be determined by each country after consideration of international recommendations, epidemiology and national priorities. The list below details the vaccines for which there is either a recommendation from the Strategic Advisory Group of Experts on Immunization (SAGE): (http://www.who.int/immunization/sage_conclusions/en/index.html) and/or a WHO position paper: (http://www.who.int/immunization/documents/positionpapers/en/index.html). This site will be updated as new position papers are published and contains the most recent information and recommendations. All vaccines should comply with the WHO Requirements for Biological Substances.

4.18 Section 21.1: Ophthalmological preparations – Anti-infective agents

4.18.1 *Review of section 21: Ophthalmological preparations*

Expert reviews of the application were prepared by: Dr Lisa Bero and Dr Usha Gupta.

In 2006, Sightsavers International, representing the VISION 2020 Technology Working Group approached the Department of Medicines Policies and Standards, WHO, with proposals to review and update the list of medicines for ophthalmic conditions. As the Expert Committee had recommended this in 2005, the proposal was welcomed. The justification for the proposal also notes the WHA resolutions on prevention of blindness, which urge Member States to make available essential medicines for eye care, and the importance of the Model List in influencing procurement and tax policies. This proposal was the initial submission, with suggested additional changes requiring applications and/or systematic reviews.

The public health importance of providing adequate treatment for the prevention of blindness is clearly established. The major causes of blindness are cataract (in adults and children), viral and fungal infections and glaucoma. All are potentially treatable. The Committee noted that no current WHO treatment guidelines are identified. A "standard list" (*79*) for a vision service unit exists, which specifies medicines, equipment, instruments, optical supplies and educational resources needed for effective eye care.

As noted in the proposal, several systematic reviews are currently in progress to assess the comparative effectiveness and safety of the additional

medicines suggested. There have been preliminary discussions with WHO about a possible joint grant proposal with the Cochrane group to seek funding to support these reviews.

The Committee noted the potential usefulness of the VISION 2020 list, but decided not to add a note to the Model List referring to it until further assessment of the comparative effectiveness and safety of the medicines included on it could be carried out. The Committee expects applications for additional medicines for the Ophthamological preparations section.

4.18.2 *Addition of aciclovir and deletion of idoxuridine*

Expert reviews of the application were prepared by: Dr Lisa Bero and Dr Usha Gupta.

In 2005 the Expert Committee requested a review of Section 21 of the WHO Model List of Essential Medicines Ophthalmological preparations. As part of the review, undertaken by Sight Savers International and the VISION 2020 Technology Working Group, an application for inclusion of a new formulation of aciclovir (ophthalmological preparation) and a proposal to delete the listed antiviral ophthalmological medicine idoxuridine was submitted. The proposal was to list aciclovir ointment 3% W/W as a new formulation replacing idoxuridine solution (eye drops), 0.1% and eye ointment, 0.2%.

The Committee noted that the application provided a review of the existing evidence for the comparative effectiveness of ophthalmological aciclovir compared to idoxuridine and other topical antivirals for treating epithelial keratitis caused by herpes simplex virus. The public health need for inclusion of a new formulation of aciclovir on the Model List was fully demonstrated. As noted by the expert reviewers, the clinical evidence, based on systematic reviews (*80*), shows that aciclovir ointment is superior to idoxuridine in both adult and child populations, based on improved healing at 7 days (RR 2.10, 95% CI, 1.27–3.47) and healing at 14 days (RR 1.21, 95% CI, 1.05–1.40). The Cochrane review found that aciclovir appeared to be equivalent to other nucleoside antiviral agents (trifluridine). The Committee noted that aciclovir was well tolerated.

The Committee noted that aciclovir ointment has been approved by several stringent regulatory authorities and is available as a generic preparation, while idoxuridine has largely been removed from the market. The current cost of aciclovir ointment is variable (from US$ 0.25 to US$ 23.00 per tube) and its inclusion on the Model List may lead to further reductions in price.

As the evidence provided in the application supports the public health need, effectiveness and safety of aciclovir ophthalmological formulation, the Committee recommended that aciclovir ointment 3% W/W be added to the core Model List for treatment of ocular surface disease caused by herpes simplex virus.

4.19 Section 24: Psychotherapeutic medicines – 24.2.1: Medicines used in depressive disorders

4.19.1 *Addition of fluoxetine hydrochloride*

Expert reviews of the application were prepared by: Dr Liliana de Lima and Dr Rohini Fernandopulle.

The antidepressant amitriptyline has been on the Model List since its first edition and is currently listed in Section 24.2.1 Medicines used in depressive disorders: amitriptyline tablet, 25 mg (hydrochloride). Following a Delphi process among it members in 2005–2006, the International Association of Hospice and Palliative Care suggested fluoxetine be considered for addition to the Model List for use in the context of palliative care as well as in treating depression. An application for inclusion of fluoxetine 20 mg tablet was prepared for the Department of Medicines Policy and Standards (PSM) by the WHO Collaborating Centre for Research and Training in Mental Health, University of Verona, Italy. The proposal is to list fluoxetine with a square box as an example selective serotonin reuptake inhibitor (SSRI).

The Committee noted that the application was of good quality and provided a comprehensive review of the existing evidence regarding the effectiveness and safety of SSRIs used for acute-phase treatment of moderate-to-severe depression. The public health need for inclusion of an SSRI on the Model List was fully substantiated. As noted by the expert reviewers, there is abundant clinical evidence from many randomized trials and systematic reviews that establish the benefits of SSRIs for short-term treatment of depressive disorders. Results from a considerable body of evidence, including a Cochrane Systematic Review (*81*), show that fluoxetine is as effective as amitriptyline and may have fewer side-effects.

The Committee noted that the major concern with the use of the SSRIs is the potential stimulation of suicidal ideation in high-risk depressive patients, particularly in patients aged 8–18 years. Many studies have attempted to quantify this risk over the past 15–20 years and there is an increased risk of suicidal ideation, but no increased risk of completed suicide. Most recent reviews support the view that the risk is likely to be real, but there is uncertainty about its magnitude, although it appears most likely to be a problem in young, severely depressed patients. This is reflected in the current labelling of fluoxetine preparations by the EMEA and FDA, among others.

Very recent estimates from the USA suggest that overdose with an SSRI is associated with lower mortality and morbidity than overdose with tricyclic antidepressants (TCAs) (*82*).

Generic preparations of fluoxetine are available worldwide. The application provided a review of the evidence on cost-effectiveness of SSRI use in

the treatment of depressive disorders which suggested that there are no differences in terms of cost-effectiveness between SSRIs and tricyclics.

Overall, the evidence provided in the application supports the public health need, comparable effectiveness and generally more favourable tolerability profile than amitriptyline. The Committee therefore recommended that fluoxetine be added to the core Model List for short-term treatment of depressive disorders. A square box was not included, because there may be significant within-class differences in relation to safety.

5. Paediatric medicines

5.1 Section 5: Anticonvulsants/antiepileptics

5.1.1 *Carbamazepine – addition of new dosage form*

An application was prepared by the University of Liverpool, England, at the request of the Department of Medicines, Policy and Standards, WHO, for the addition of carbamazepine oral suspension (100 mg/5 ml) and 100 mg, 200 mg chewable tablets to the Model List for the treatment of childhood epilepsy. The listing is as an individual medicine.

Expert reviews of the application were prepared by: Dr Susan Walters.[1] Comments in support of the application were received from Dr Benedetto Saraceno, Director, Mental Health and Substance Abuse, WHO. Additional supporting statements were received from DRA.

The Committee noted that several Cochrane reviews (*83–86*) and other randomized controlled trials (*87–91*) were cited in the application to support the efficacy and safety of carbamazepine in both adults and children. While there is not a substantial body of clinical trial data to establish the superior efficacy and safety of carbamazepine over other antiepileptic medicines, there are differences in tolerability and side-effects between available agents and there is a need for a range of antiepileptic drugs for different seizure types.

The need for both suspension and chewable tablet formulations is not addressed in the application. There may however be a preference for chewable tablets over syrup formulations because of the additional costs associated with liquid paediatric formulations. The costs for these dosage formulations compared to 100 mg carbamazepine tablets, which are currently included in the Model List, were not provided in the application.

The Committee recommended inclusion of carbamazepine suspension 100 mg/5 ml on the core Model List of drugs for the treatment of generalized tonic–clonic and partial seizures. The Committee was concerned that chewable tablets can be expensive and that the stability of liquid forms can

[1] Dr Susan Walters is a Member of the Expert Committee.

be problematic. Where a crushable tablet may be specified, a dispersable one may be acceptable. Where an oral liquid is specified, it is possible to make granules. The Committee noted that this may be an issue for the subcommittee on children's medicines to consider further.

5.1.2 *Phenobarbital: addition of new dosage form*

An application was received from Professor Josemir W. Sander, WHO Collaborating Centre for Research and Training in Neurosciences, London, England, for inclusion of phenobarbital 200 mg/ml injection on the Model List for second-line treatment for status epilepticus refractory to initial treatment with benzodiazepines in both adults and children. Listing is as an individual medicine and formulation.

Expert reviews of the application were prepared by: Dr Noël Cranswick and Dr Marcus M. Reidenberg. Comments in support of the application were received from Dr Benedetto Saraceno, Director, Mental Health and Substance Abuse, WHO.

The Committee noted that the efficacy and safety data were derived from a small number of trials, but generally supported the view that phenobarbital injection is both effective and safe for use in status epilepticus. In the largest trial (Treiman et al., 1998) (*92*), treatment with lorazepam was successful in 64.9% of subjects with overt generalized convulsive status epilepticus, phenobarbital in 58.2%, diazepam plus phenytoin in 55.8%, and phenytoin in 43.6% of subjects. There was no statistically significant difference in the risk of non-cessation of seizures between lorazepam IV and phenobarbital IV (34/97 versus 38/91 participants) or adverse effects (42/97 versus 46/91 participants).

The side-effects of phenobarbital such as respiratory and cardiac depression are serious. However, it is not clear whether these side-effects relate to the treatment or to the condition being managed; the evidence suggests that complications occur no more frequently with phenobarbital than other agents.

The application suggests second-line listing for status epilepticus refractory to initial treatment with benzodiazepines in both adults and children. Wilmshurst and Newton (2005) (*93*) suggest third-line use in status epilepticus and that it can be and is used at all levels of hospital care.

The Committee recommended inclusion of phenobarbital injection 200 mg/ml on the core Model List as second-line treatment for status epilepticus refractory to initial treatment with benzodiazepines in both adults and children. The Committee had some concerns about availability across countries and anticipated that listing would stimulate production of these dosage forms and strengths, and thus improve availability.

5.1.3 *Phenytoin oral liquid and chewable tablets: addition of new dosage form*

An application was prepared by the University of Liverpool at the request of the PSM Department, for the addition of phenytoin base syrup (30 mg/5 ml) and 50-mg chewable tablets to the Model List for the treatment of childhood epilepsy. Listing is as an individual medicine.

Expert reviews of the application were prepared by: Dr Susan Walters and Dr Marcus M. Reidenberg. Comments in support of the application were received from Dr B. Saraceno, Director, Mental Health and Substance Abuse (MSD). Additional supporting statements were received from DRA.

The Committee noted that several Cochrane reviews (*85, 94– 96*) and other randomized controlled trials (*97, 98*) were cited in the application to support the efficacy and safety of phenytoin in both adults and children. While there is not a substantial body of clinical trial data to establish the superior efficacy and safety of phenytoin over other antiepileptic medicines, there are differences in tolerability and side-effects between available agents and there is a need for a range of antiepileptic drugs for different seizure types.

The need for both suspension and chewable tablet formulations is not addressed in the application. There may however be a preference for chewable tablets over syrup formulations because of the additional costs associated with liquid paediatric formulations. The comparative costs for these dosage formulations were not provided in the application.

The Committee recommended inclusion of phenytoin suspension 30 mg/5 ml and the chewable tablet on the core Model List.

5.1.4 *Valproic acid (sodium valproate): addition of new dosage form*

An application was prepared by the University of Liverpool, England, at the request of the PSM Department for the addition of valproic acid oral liquid (200 mg/5 ml) and 100 mg crushable tablets to the Model List for the treatment of childhood epilepsy. Listing is as an individual medicine.

Expert reviews of the application were prepared by: Dr Susan Walters. Comments in support of the application were received from Dr B. Saraceno, Director, Mental Health and Substance Abuse (MSD). Additional supporting statements were received from DRA.

The Committee noted that several Cochrane reviews (*84, 95, 97–99*) and other randomized controlled trials were cited in the application to support the efficacy and safety of valproic acid (*91, 100, 101*) in both adults and children. No clinical data are presented on use of valproic acid in children younger than 3 years. While there is not a substantial body of clinical trial data to establish the superior efficacy and safety of valproic acid over other

antiepileptic medicines, there are differences in tolerability and side-effects between available agents, and a need for a range of antiepileptic drugs for different seizure types.

Valproic acid has a product licence in Europe and the USA for the treatment of generalized, partial and other seizures in adults and children. No lower age limit is specified for its use as monotherapy or adjunctive therapy. However, because of the risk of liver damage it is not recommended as first-line therapy for children younger than 2 years, in whom its use is reserved for difficult cases of epilepsy.

The need for both suspension and chewable tablet formulations is not addressed in the application. There may however be a preference for chewable tablets over syrup formulations because of the additional costs associated with liquid paediatric formulations. The comparative costs for the crushable tablet formulation were not provided in the application.

The Committee recommended inclusion of valproic acid oral liquid (200 mg/5 ml) and the crushable tablet on the core Model List.

5.2 Section 6.2.4: Antituberculosis medicines

5.2.1 *Isoniazid: addition of new dosage form*

An application was received from the Global Drug Facility (GDF), Stop TB (STB) and the TB Partnership (TBP) for inclusion of isoniazid 50 mg scored tablets on the Model List for the prevention and treatment of tuberculosis in children. Listing is as an individual medicine.

Expert reviews of the application were prepared by: Dr Estrella Paje-Villar. Additional supporting statements were received from DRA.

The Committee noted that there had been few recent studies of the efficacy and safety of isoniazid for the treatment of TB in children. However it has been used effectively for many decades and is recommended in the WHO Treatment Guidelines (*15*). There is recent evidence on the benefit of isoniazid prophylaxis in HIV-positive adults and children (*102–106*), and HIV-negative but at-risk adults and children (*107–109*) in reducing the development of TB. At present, the lack of an appropriate paediatric formulation means that tablets have to be broken and fractionated to approximate intended doses. An appropriate paediatric formulation would minimize these problems. Limited information was provided on potential suppliers of a quality-assured 50 mg isoniazid product.

The Committee recommended inclusion of isoniazid 50 mg scored tablets on the core Model List for treatment and chemoprophylaxis of tuberculosis in paediatric populations with concurrent HIV infection or at risk of HIV infection, or others with increased risk of contracting the disease.

5.2.2 *Pyrazinamide: addition of new dosage form*

An application was received from the Global Drug Facility (GDF), Stop TB (STB) and the TB Partnership (TBP) for inclusion of pyrazinamide 150 mg dispersible and scored tablets on the Model List for the treatment of tuberculosis in children. Listing is as an individual medicine.

Expert reviews of the application were prepared by: Dr Estrella Paje-Villar. Additional supporting statements were received from DRAs, Japan.

The Committee noted that the efficacy and safety data were derived from a small number of studies (*110–112*), but generally supported the view that pyrazinamide is safe and effective in children. It has been widely used in children and is recommended in the WHO Treatment Guidelines (*15*). There have been a small number of studies (*113–115*) of the pharmacokinetics of pyrazinamide in children, with conflicting results on the clearance and half-life of the drug in children compared to adults. Further work is required to establish whether higher doses of pyrazinamide are needed in children. At present, the lack of an appropriate paediatric formulation means that tablets have to be broken and fractionated to approximate intended doses. Limited information was provided on potential suppliers of a quality-assured 150 mg pyrazinamide product.

The Committee recommended inclusion of pyrazinamide 150 mg dispersible and scored tablets on the core Model List.

5.3 Section 6.5.3: Antimalarial medicines

5.3.1 *Artemether/lumefantrine: addition of new dosage form*

An application was received from Dafra Pharma (Belgium) for a powder for paediatric suspension of artemether/lumefantrine to be included in the Model List. The powder for suspension contains 7.9 mg β-artemether/47.4 mg lumefantrine per gram. After reconstitution with water the mixture delivers:

— *60 ml* fixed-dose combination of 180 mg β-artemether and 1080 mg lumefantrine;
— *12 ml* fixed-dose combination of 360 mg β-artemether and 2160 mg lumefantrine, i.e. the same 1:6 ratio as is included in the tablet formulation. The recommended dosage schedule delivers artemether in a daily dosage of approximately 4 mg/kg/day for 3 days.

Expert reviews of the application were prepared by Dr Susan Walters and Dr Noël Cranswick. Comments on the application were received from Dr Peter Olumese, Global Malaria Programme. Additional statements were received from DRAs, Japan.

The Committee noted that while the application identifies a need for a paediatric formulation suitable for children with a body weight of less than

10 kg, the current *WHO Guidelines for the treatment of malaria, 2006* suggest that tablets can be used for children who weigh ≥ 5 kg. The Committee also expressed some concerns about the recommended doses. For children who weigh 5–10 kg, the population most likely to be prescribed the suspension, the recommended doses of suspension were substantially lower than the currently recommended doses of the tablet formulation. Limited clinical trial data were presented in the application to demonstrate the efficacy and safety of the suspension at this dose, and these were short-term studies in small numbers of children. None were rigorous randomized controlled trials comparing the combination suspension with the drugs administered in tablet form in the same populations of patients. While the application states that registration has been achieved in 19 countries and is pending in a further eight, none of these are stringent regulatory authorities.

The Committee noted the comments from the Global Malaria Programme (WHO), which concluded it could not support the application as the doses for specific age groups, the dosage regimen (single daily dose), and dosage ratio recommended in the submitted dossier are at variance with the current recommended WHO schedules (*WHO Guidelines for the treatment of malaria, 2006*). No evidence was provided to the Global Malaria Programme, nor was there evidence available on the safety and efficacy of the dosages and regimen recommended in this submission.

Although the Committee recognized the need for a suspension formulation for paediatric use, given the uncertainty about the dose, the Committee decided not to include the artemether/lumefantrine suspension on the Model List.

5.5 Section 25: Medicines acting on the respiratory tract

5.5.1 *Addition of caffeine citrate*

Expert reviews of the application were prepared by: Dr Estrella Paje-Villar.

During its meeting in 2005, the Committee deferred a decision on listing caffeine citrate for apnoea of prematurity on the Model List because of limited evidence of efficacy and the lack of longer-term safety data. The Committee was waiting for the results of a large randomized controlled trial then underway. A second application for the inclusion of caffeine citrate was received from the Royal Children's Hospital, Melbourne, Australia.

The Committee noted that the efficacy data were largely unchanged from those in the previous application and that the long-term safety results of the large randomized controlled trial were still not available. As noted by the expert reviewers, data from two Cochrane reviews (*116, 117*) are available. Although they are based on small numbers of trials and patients, they support the efficacy of methylxanthines in managing apnoea in preterm

infants and suggest that while it had similar efficacy, caffeine citrate was associated with fewer adverse events than theophylline. Limited safety data are provided in these reviews. Schmidt et al. 2006 (*118*) reported short-term, secondary safety outcomes in the large Caffeine for Apnoea of Prematurity trial. No differences were noted between caffeine citrate and placebo in the incidence of retinopathy of prematurity, necrotizing enterocolitis or ultrasonographic signs of brain injury. However data on the primary study outcome (a composite of death, cerebral palsy, cognitive delay, deafness, or blindness at a corrected age of 18–21 months) are not yet available. The inclusion criteria of the study may have excluded the most vulnerable infants from evaluation i.e. the smallest infants on ventilation for long periods of time. The efficacy of caffeine in this population remains uncertain.

The *WHO Pocket book of hospital care for children* (2005, p. 55) states that caffeine citrate and aminophylline prevent and treat apnoea in premature babies. Caffeine is preferred if it is available. Dosing recommendations are consistent with this application.

No valid cost-effectiveness data were provided and limited cost comparisons are possible for caffeine citrate, aminophylline and theophylline. Neither aminophylline nor theophylline is currently on the Model list.

Based on the evidence for efficacy and safety, the Committee decided to include caffeine citrate on the Model List.

5.6 Section 27: Vitamins and minerals

5.6.1 *Vitamin A (retinol palmitate): addition of new dosage strength*

Expert reviews of the application were prepared by: Dr Estrella Paje-Villar. Additional supporting statements were received from: Dr J. Wiley, Therapeutic Goods Administration, Australia; DRA; Dr K. Misawa, Director, Pharmaceuticals and Medical Devices Agency, Japan; and Mr M. Goddard, Information Centre, Medicines and Healthcare Products Regulatory Agency, London, England.

Retinol (vitamin A) was added to the UK Model List in 1987 as 10 000 IU tablets, 200 000 IU capsules and other forms that have not been reviewed since then. Vitamin A is widely promoted as supplementation for prophylaxis and treatment of deficiency in children including infants of 12 months of age and younger. However, the dose used in younger children is 50–100 000 IU, currently supplied to some extent by UNICEF as 100 000 IU capsules. An application for inclusion of retinol (as palmitate) 50 000 to 100 000 IU per capsule was received from the Clinical Pharmacology Unit, General Medicine, Royal Children's Hospital, Melbourne, Australia; and the Centre for International Child Health, Department of Pediatrics, University of Melbourne, Australia.

The Committee noted that the application provided a comprehensive review of the evidence of effectiveness of vitamin A supplementation for prophylaxis and treatment of deficiency in children, including infants of 12 months of age and younger. The public health need for an additional formulation is fully justified. As noted by the expert reviewers, there is high-quality clinical evidence from the Cochrane systematic review (*119*) involving more than one million very low-birth-weight infants that proved the benefits of retinol supplementation in reducing deaths or oxygen use at one month of age (RR 0.93, 95% CI, 0.88–0.99). Additional evidence shows a reduction in death from measles pneumonia in children given supplementary vitamin A (*120*) and a reduction in all-cause mortality (*121*). The tolerability of oral retinol in infants is excellent, with no evidence of any permanent or long-term sequelae (*122–124*). This intervention has been estimated as one of the most cost-effective of all health interventions (*125*).

Overall the evidence provided in the application supports the public health need, effectiveness, safety and cost-effectiveness of retinol lower-strength capsules for infants of 12 months of age and younger. The Committee therefore recommended that retinol 50 000 IU capsule and 100 000 IU capsule be added to the core list of the 15th WHO Model List.

6. Summary of recommendations – additions, changes and deletions to the Model List

1. The Committee updated the following explanatory notes and made the following changes to Sections:
   The term "oral liquid" was clarified and used to replace "syrup", "oral elixir", "oral suspension" and similar terms throughout the Model List.
   Section 4: The Committee noted that there was no need for a review of Section 4 (Antidotes and other substances used in poisoning) at this time.
   Section 6.4.2: The note on antiretrovirals was revised.
   Section 6.4.2.3: The note on protease inhibitors was revised with the section marked for review at the next meeting of the Expert Committee.
   Section 6.5.3: Antimalarial medicines. The Committee edited the note for antimalarial medicines for curative treatment and comprehensively updated the section to reflect current treatment guidelines. Artemether injection 80 mg/ml, artesunate tablet 50 mg, doxycycline 100 mg tablets or capsules, mefloquine 250 mg tablets and sulfadoxine + pyrimethamine tablets 500 mg + 25 mg were moved from the complementary to the core list. This means there is now no complementary list for antimalarials.
   Section 6.5.5.1: African trypanosomiasis. All medicines are now included in the core list; eflornithine injection 200 mg and pentamidine powder for injection 200 mg were moved from the complementary list to the core list.

Section 8.2: Cytotoxic medicines were marked for review at the next meeting of the Expert Committee.
Section 8.4: The note on medicines used in palliative care was updated.
Section 19.3: The Committee revised the note on the selection of vaccines and updated the Model List to include all vaccines for which there is a SAGE recommendation or a WHO position paper.
Section 21: This section on ophthalmological preparations was noted for review at the next meeting of the Expert Committee.

2. The Committee recommended the following additions to the Model List:
Section 2.2: Addition of prolonged-release morphine tablets 10 mg, 30 mg, 60 mg.
Section 5: Addition of carbamazepine chewable tablets 100 mg, 200 mg and oral liquid 100 mg/5 ml.
Addition of phenobarbital sodium injection 200 mg/ml.
Addition of phenytoin chewable tablet 50 mg and oral liquid 25–30 mg/5 ml with a note advising against having both strengths available in the same market.
Addition of valproic acid (sodium valproate) crushable 100-mg tablets and oral liquid 200 mg/5 ml.
Section 6.2.1: Addition of cefazolin powder for injection 1 gram (as sodium salt) with a note on use in surgical prophylaxis.
Section 6.2.4: Addition of isoniazid scored tablet 50 mg.
Addition of pyrazinamide dispersible tablets 150 mg and scored tablets 150 mg.
Addition of fixed-dose combination of rifampicin + isoniazid + ethambutol tablets 150 mg + 75 mg + 275 mg.
Addition of footnote to ofloxacin that levofloxacin may be an alternative for use in multidrug-resistant TB.
Section 6.4.2.1: Addition of emtricitabine capsules 200 mg and oral liquid 10 mg/ml with a note that FTC is an acceptable alternative.
Addition of footnote to stavudine 40 mg marking it for review for possible deletion at the next meeting of the Expert Committee.
Section 6.4.2.2: Addition of efavirenz tablet 600 mg.
Section 6.4.2.3: Addition of tenofovir capsule 300 mg.
Addition of the following fixed-dose combinations of antiretrovirals, as a new unnumbered section:
Emtricitabine + tenofovir tablets 200 mg + 300 mg, with a note that FTC is an acceptable alternative to 3TC.
Efavirenz + emtricitabine + tenofovir tablets 600 mg + 200 mg + 300 mg, with a note that FTC is an acceptable alternative to 3TC.
Stavudine + lamivudine + nevirapine tablets 30 mg + 150 mg + 200 mg.
Zidovudine + lamivudine tablets 300 mg + 150 mg.

Zidovudine + lamivudine + nevirapine tablets 300 mg + 150 mg + 200 mg.
Section 6.4.3: Addition of new section "Other antivirals".
Addition of ribavirin injection for intravenous administration 1000 mg, 800 mg in 10 ml phosphate buffer solution; oral solid dosage form 200 mg, 400 mg, 600 mg.
Section 6.5.2: Addition of paromomycin solution for intramuscular injection 750 mg (present as the sulfate).
Section 6.5.3.1: Addition of artesunate injection 60 mg.
Section 11.2: Plasma fractions for specific use. *Complementary list*: Addition of human normal immunoglobulin for intravenous administration 5%, 10% protein solution; for intramuscular administration 16% protein solution.
Section 12.6: Addition of simvastatin tablets or capsules 5 mg, 10 mg, 20 mg, 40 mg with a note on use in high-risk patients and a square box indicating that atorvastatin, fluvastatin, lovastatin and pravastatin are suitable alternatives depending on local availability and cost.
Section 18.3.2: Addition of injectable contraceptive medroxyprogesterone acetate + estradiol cypionate 25 mg + 5 mg.
Section 18.3.5: Addition of new section called "Implantable contraceptives". Addition of levonorgestrel-releasing implant, two-rod, each containing 75 mg levonorgestrel.
Section 19.3: Addition of cholera, hepatitis A, *Haemophilus influenzae* type b, Japanese encephalitis, pneumococcal, rotavirus and varicella vaccines.
Section 21.1: Addition of acyclovir ointment 3%.
Section 24.2.1: Addition of fluoxetine tablets or capsules 20 mg.
Section 25.2: Addition of new section called "Other medicines acting on the respiratory tract".
Addition of caffeine citrate injection 20 mg/ml and oral liquid 20 mg/ml.
Section 27: Addition of retinol 50 000 IU and 100 000 IU (as palmitate) per capsule.

3. The Committee recommended that the following listings for medicines be amended to correct dosage strength and form:
Section 12.2: Injection of epinephrine (adrenalin) corrected to 100 mcg/ml in 10-ml ampoules.
Section 13.2: Corrected strength of neomycin and bacitracin ointment to show neomycin sulfate 5 mg + 250 IU bacitracin zinc/g.
Section 13.4: Strength of aluminium acetate solution changed to 5%.
Section 19.2: Modification of antivenom sera to read antivenom immunoglobulin.

4. The Committee considered proposals for the following medicines but rejected their inclusion in the Model List:
Section 6.2.1: Cefalexin oral capsules, oral liquid – rejected on the grounds of concern about appropriate indications for use, relatively lower quality of evidence and potential for irrational use.

Section 6.4.2.3: Fixed-dose combination antiretroviral containing stavudine + lamivudine + nevirapine 40 mg + 150 mg + 200 mg – rejected on the basis of safety concerns with 40 mg stavudine.
Section 6.5.3: Artemether/lumefantrine powder for suspension – rejected on the grounds of inadequate evidence of clinical efficacy at the dose and schedule of administration proposed for the suspension.
Section 7.1: Sumatriptan 50 mg tablets – rejected on the basis of inadequate evidence of clinical superiority or safety over existing therapies and the substantially higher cost.
Section 19.2: Antivenom serum: equine immunoglobulin F(ab')2 fragments rejected on the grounds that the specific product could be included in the modification of antivenom sera to read antivenom immunoglobulin.

5. The Committee considered proposals for deletion, but recommended that the following medicines be retained on the Model List:
Section 6.1.1: Levamisole 50 mg, 150 mg tablets as anthelminthic, but will review safety data at the next meeting of the Expert Committee.
Section 7.1: Paracetamol tablets 300–500 mg for treatment of acute attacks of migraine.

6. The Committee recommended that the following medicines should be deleted from the Model List:
Section 6.2.4: Deletion of individual listing of ciprofloxacin and levofloxacin for multidrug-resistant TB, on the grounds that ofloxacin is the preferred medicine and levofloxacin is now noted as an alternative.
Section 6.5.3.1: Deletion of chloroquine injection 40 mg/5 ml, on the grounds that it is not recommended for use in severe malaria.
Section 6.5.5.1: Deletion of pentamidine injection 300 mg as it is not provided in this strength for treatment of trypanosomiasis.
Section 8.2: Deletion of chlormethine powder for injection 10 mg, as it is no longer recommended for use in any oncology treatment protocol.
Section 8.2: Deletion of levamisole tablet 50 mg, as it is no longer recommended for use in any oncology treatment protocol.
Section 14.2: Deletion of iopanoic acid tablets 500 mg, as an obsolete diagnostic agent.
Deletion of propyliodone oily suspension 500–600 mg/20 ml ampoules as an obsolete diagnostic agent.
Section 21.1: Deletion of idoxuridine ointment 0.2% and solution 0.1%, as aciclovir ointment is superior.

7. The Committee considered the following application but recommended it be deferred to the first meeting of the Subcommittee on Essential Medicines for Children:

Artesunate rectal capsules 100 mg and 400 mg, on the grounds of uncertainty about the availability of the proposed products.

8. The Committee made the following recommendations in relation to two of the policy items considered:
   1. Recommendation for the establishment of a Subcommittee to examine the specific issues relating to paediatric medicines and to draft the first Essential Medicines List for Children.
   2. Recommendation to strongly support the resolution on Rational Use of Medicines to be presented to the World Health Assembly in May 2007 and the need to establish a Steering Group to guide work on rational use of medicines. The Steering Group would not be a subgroup of the Expert Committee, but overlapping membership would ensure the engagement of the Expert Committee in its work.

References

1. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report.* Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929).
2. Connor J, Rafter N, Rodgers A. Do fixed combination pills or unit-of-use packaging improve adherence? A systematic review. *Bulletin of the World Health Organization,* 2004, **82**:935–939.
3. Heneghan CJ, Glasziou P, Perera R. Reminder packaging for improving adherence to self-administered long-term medications. *Cochrane Database of Systematic Reviews,* 2006, Issue 1. Art. No.: CD005025. DOI: 10.1002/14651858.CD005025.pub2.
4. Stolk P, Willemen MJ, Leufkens HG. Rare essentials: drugs for rare diseases as essential medicines. *Bulletin of the World Health Organization*, 2006, **84**:745–751.
5. Reidenberg MM. Are drugs for rare diseases "essential"? *Bulletin of the World Health Organization*, 2006, **84**:686.
6. Henry DA, Hill SR, Harris A. Drug prices and value for money: the Australian Pharmaceutical Benefits Scheme. *Journal of the American Medical Association*, 2005, **294**:2630–2632.
7. *Antimicrobial resistance: a threat to global health security: rational use of medicines by prescribers and patients, A58/14.* Geneva, World Health Organization (http://www.who.int/gb/ebwha/pdf_files/WHA58/A58_14-en.pdf).
8. *Rational use of medicines: progress in implementing the WHO medicines strategy, EB118/6.* Geneva, World Health Organization (http://www.who.int/gb/ebwha/pdf_files/EB118/B118_6-en.pdf).
9. Wiffen PJ et al. Oral morphine for cancer pain. *Cochrane Database of Systematic Reviews,* 2003, Issue 4. Art. No.: CD003868. DOI: 10.1002/14651858.CD003868.
10. *Preventive chemotherapy in human helminthiasis.* Geneva, World Health Organization, 2006.

11. Hopkins L, Smaill F. Antibiotic prophylaxis regimens and drugs for cesarean section. *Cochrane Database of Systematic Reviews,* 1999, Issue 2. Art. No.: CD001136. DOI: 10.1002/14651858.CD001136.

12. Stewart A, Eyers PS, Earnshaw JJ. Prevention of infection in arterial reconstruction. *Cochrane Database of Systematic Reviews*, 2006, Issue 3. Art. No.: CD003073.pub2. DOI: 10.1002/14651858.CD003073.pub2.

13. Koning S et al. Interventions for impetigo. *Cochrane Database of Systematic Reviews*, 2003, Issue 2. Art. No.: CD003261.pub2. DOI: 10.1002/14651858.CD003261.pub2.

14. Parish LC et al. Moxifloxacin versus cefalexin in the treatment of uncomplicated skin infections. *International Journal of Clinical Practice*, 2000, **54**:497–503.

15. *Treatment of tuberculosis: guidelines for national programmes,* 3rd ed. Geneva, World Health Organization, 2003 (http://whqlibdoc.who.int/hq/2003/WHO_CDS_TB_2003.313_eng.pdf).

16. Yew WW et al. Comparative roles of levofloxacin and ofloxacin in the treatment of multidrug-resistant tuberculosis: preliminary results of a retrospective study from Hong Kong. *Chest*, 2003, **124**:1476–1481.

17. Ziganshina LE, Vizel AA, Squire SB. Fluoroquinolones for treating tuberculosis. *Cochrane Database of Systematic Reviews*, 2005, Issue 3. Art. No.: CD004795. DOI: 10.1002/14651858.CD004795.pub2.

18. *Antiretroviral therapy for HIV infection in adults and adolescents in resource-limited settings: toward universal access. Recommendations for a public health approach – 2006 revision.* Geneva, Switzerland, World Health Organization, 2006 (http://www.who.int/hiv/pub/guidelines/adult/en/index.html).

19. *Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access.* Geneva, World Health Organization (http://www.who.int/hiv/pub/guidelines/art/en/index.html).

20. Landman R et al. Once-a-day highly active antiretroviral therapy in treatment-naive HIV-1-infected adults in Senegal. *AIDS*, 2003, **17**:1017–1022.

21. Staszewski S et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. *New England Journal of Medicine*, 1999, **341**:1865–1873.

22. Albrecht MA et al. Nelfinavir, efavirenz, or both after the failure of nucleoside treatment of HIV infection. *New England Journal of Medicine*, 2001, **345**:398–407.

23. Siegfried NL et al. Stavudine, lamivudine and nevirapine combination therapy for treatment of HIV infection and AIDS in adults. *Cochrane Database of Systematic Reviews*, 2006, Issue 2. Art. No.: CD004535.pub2. DOI: 10.1002/14651858.CD004535.pub2.

24. *Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: towards universal access. Recommendations for a public health approach.* Geneva, World Health Organization, 2006 (http://www.who.int/hiv/pub/guidelines/pmtctguidelines2.pdf).

25. Rutherford GW, Saganai PR, Kennedy GE. Three-or-four-versus two –drug antiretroviral maintenance regimens for HIV infection. Cochrane Database of Systematic Reviews, 2003, Issue 4. Art No.: DOI: 10.1002/1465858.CD002037.

26. Jordan R et al. Systematic review and meta-analysis of evidence for increasing numbers of drugs in antiretroviral combination therapy. *British Medical Journal*, 2002, **324**:1–10.

27. Legoreta A et al. Adherence to combined lamivudine + zidovudine versus individual components: a community-based retrospective medicaid claims analysis. *AIDS Care,* 2005, **17**:938–948.

28. Eron JJ et al. Efficacy, safety and adherence with a twice daily combination lamivudine/zidovudine tablet formulation, plus a protease inhibitor, in HIV infection. *AIDS*, 2000, **14**:671–681.

29. Pujari SN et al. Effectiveness of generic fixed-dose combinations of highly active antiretroviral therapy for treatment of HIV infection in India. *Journal of Acquired Immune Deficiency Syndrome*, 2004, **37**:1566–1569.

30. French M et al. Randomized, open-label, comparative trial to evaluate the efficacy and safety of three antiretroviral drug combinations including two nucleoside analogues and nevirapine for previously untreated HIV-1 infection: the OzCombo 2 study. *HIV Clinical Trials,* 2002, **3**:177–185.

31. Podzamczer D et al. A randomised clinical trial comparing nelfinavir or nevirapine associated to zidovudine/lamivudine in HIV-infected naïve patients (the Combine Study). *Antiviral Therapy*, 2002, **7**:81–90.

32. Casado A et al. Health-related quality of life in HIV-infected naïve patients treated with nelfinavir or nevirapine associated with AZT/3TC (the Combine QoL Substudy). *HIV Clinical Trials,* 2004, **5**:132–139.

33. Plana M et al. Immune restoration in HIV-positive, antiretroviral-naïve patients after 1 year of zidovudine/lamivudine plus nelfinavir or nevirapine. *Antiviral Therapy*, 2004, **9**:197–204.

34. Bonjoch A et al. Antiretroviral treatment simplification with 3 NRTIs or 2 NRTIs plus nevirapine in HIV-1-infected patients treated with successful first-line HAART. *Journal of Acquired Immune Deficiency Syndrome,* 2005, **39**:313–316.

35. Calmy A et al. Generic fixed-dose combination antiretroviral treatment in resource-poor settings: multicentric observational cohort. *AIDS,* 2006, **20**:1163–1169.

36. Gallant JE et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *New England Journal of Medicine*, 2006, **354**:251–260.

37. Schilling RT, Schaffner CP. Differentiation of catenulin-neomycin antibiotics: identity of catenulin, paromomycin, hydroxymycin and aminosidin. *Antimicrobial Agents Chemotherapy*, 1961, **4**: 274–285.

38. Sundar S et al. Injectable paromomycin for visceral leishmaniasis in India. *New England Journal of Medicine*, 2007, **356**: 2571–2581.

39. Jha TK et al. Randomised controlled trial of aminosidine (paromomycin) v sodium stibogluconate for treating visceral leishmaniasis in North Bihar, India. *British Medical Journal*, 1998, **16**:1200–1205.

40. Seaman J et al. Epidemic visceral leishmaniasis in Sudan: a randomized trial of aminosidine plus sodium stibogluconate versus sodium stibogluconate alone. *Journal of Infectious Diseases*, 1993, **168**:715–720.

41. Thakur CP et al. Aminosidine plus sodium stibogluconate for the treatment of Indian kala-azar: a randomized dose-finding clinical trial. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1995, **89**:219–223.

42. Thakur CP et al. A prospective randomized, comparative, open-label trial of the safety and efficacy of paromomycin (aminosidine) plus sodium stibogluconate versus sodium stibogluconate alone for the treatment of visceral leishmaniasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 2000, **94**:429–431.

43. *WHO Guidelines for the treatment of malaria.* Geneva, World Health Organization, 2006 (www.who.int/malaria/docs/TreatmentGuidelines2006.pdf).

44. McIntosh HM, Olliaro P. Artemisinin derivatives for treating severe malaria. *Cochrane Database of Systematic Reviews,* 2000, Issue 2. Art. No.: CD000527. DOI: 10.1002/14651858. CD000527

45. Newton PN et al. Randomized comparison of artesunate and quinine in the treatment of severe falciparum malaria. *Clinical Infectious Diseases*, 2003, **37**:7–16.

46. South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group. Artesunate versus quinine for treatment of severe falciparum malaria: a randomized Trial. *Lancet,* 2005, **366**:717–725.

47. Mohanty AK et al. Randomized control trial of quinine and artesunate in complicated malaria. *Indian Journal of Pediatrics,* 2004, **71**:291–295.

48. Barnes KI et al. Efficacy of rectal artesunate compared with parenteral quinine in initial treatment of moderately severe malaria in African children and adults: a randomised study. *Lancet,* 2004, **363**:1598–1605.

49. Harin A et al. Artesunate suppositories versus intramuscular artemether for treatment of severe malaria in children in Papua New Guinea *Antimicrobial Agents and Chemotherapy*, 2006, **50**:968–974.

50. Docampo R, Moreno SNJ. Current chemotherapy of human African trypanosomiasis. *Parasitology Research,* 2003, **90**:10–13.

51. Abel PM et al. Retaking sleeping sickness control in Angola. *Tropical Medicine and International Health*, 2004, **9**:141–148. Erratum in: *Tropical Medicine and International Health*, 2004, **9** (2):314.

52. Legros D et al. Treatment of human African trypanosomiasis—present situation and needs for research and development. *Lancet Infectious Diseases,* 2002, **2**:437–440.

53. Pépin J, Milord F. The treatment of human African trypanosomiasis. *Advances in Parasitology*, 1994, **33**:1–47.

54. Pépin J et al. Short-course eflornithine in Gambian trypanosomiasis: a multicentre randomized controlled trial. *Bulletin of the World Health Organization,* 2000, **78**:1284–1295.

55. Chappuis F et al. Eflornithine is safer than melarsoprol for the treatment of second-stage Trypanosoma brucei gambiense human African trypanosomiasis. *Clinical Infectious Diseases*, 2005, **41**:748–751.

56. Balasegaram M et al. Melarsoprol versus eflornithine for treating late-stage Gambian trypanosomiasis in the Republic of the Congo. *Bulletin of the World Health Organization,* 2006, **84**:783–791.

57. McCrory DC, Gray RN. Oral sumatriptan for acute migraine. *Cochrane Database of Systematic Reviews*, 2003, Issue 3. Art. No.: CD002915. DOI: 10.1002/14651858.CD002915.

58. Damen L et al. Symptomatic treatment of migraine in children: a systematic review of medication trials. *Pediatrics*, 2005, **116**:e295–302.

59. Goldstein J. et al. Acetaminophen, aspirin, and caffeine versus sumatriptan succinate in the early treatment of migraine: results from the ASSET trial. *Headache*, 2005, **45**:973–982.

60. Freitag FG et al. Comparative study of a combination of isometheptene mucate, dichloralphenazone with acetaminophen and sumatriptan succinate in the treatment of migraine. *Headache*, 2001, **41**:391–398.

61. Lipton RB et al. Efficacy and safety of acetaminophen in the treatment of migraine: results of a randomized, double blind, placebo controlled, population based study. *Archives of Internal Medicine*, 2000, **160**:3486–3492.

62. Leinisch E et al. Evaluation of the efficacy of intravenous acetaminophen in the treatment of acute migraine attacks: a double blind, placebo controlled parallel group multicenter study. *Pain*, 2005, **117**:396–400.

63. *Cancer pain relief, with a guide to opioid availability*, 2nd ed. Geneva, World Health Organization, 1996.

64. *Cancer pain relief and palliative care in children*. Geneva, World Health Organization, 1998.

65. *Statins for the prevention of coronary events – technology assessment report commissioned to ScHARR by the NICE HTA Programme.* London, National Institute for Health and Clinical Excellence, 2005.

66. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density, lipoprotein cholesterol, ischaemic heart disease and stroke: systematic review and meta-analysis. *British Medical Journal*, 2003, **326**:1423–1432.

67. Murray CJL et al. Effectiveness and cost of interventions to lower systolic blood pressure and cholesterol: a global and regional analysis on reduction of cardiovascular-disease risk. *Lancet*, 2003, **361**:717–725.

68. Sivin I et al. The performance of levonorgestrel rod and norplant contraceptive implants: a 5-year randomized study. *Human Reproduction*, 1998, **13**:3371–3378.

69. Fan HM et al. A multicenter comparative study of Sino-levonorgestrel-releasing implants – No. I and No. II with Norplant. *Journal of Reproduction & Contraception*, 2004, **15**:101–107.

70. French R et al. Hormonally impregnated intrauterine systems (IUSs) versus other forms of reversible contraceptives as effective methods of preventing pregnancy (Cochrane Review). In: *The Cochrane Library, Issue 3.* Chichester, John Wiley & Sons, Ltd., 2004.

71. Wang SL et al. Three years' experience with levonorgestrel-releasing intrauterine device and Norplant-2 implants: a randomized comparative study. *Advances in Contraception*, 1992, **8**:105–114.

72. *WHO medical eligibility criteria for contraceptive use.* Geneva, World Health Organization, 2004 (http://www.who.int/reproductive-health/publications/MEC_3/mec.pdf).

73. *Selected practice recommendations for contraceptive use*. Geneva, World Health Organization, 2004 (http://www.who.int/reproductive-health/publications/spr/spr.pdf).

74. Gallo MF et al. Combination injectables for contraception. In: *The Cochrane Library.* Chichester, John Wiley & Sons, Ltd., 2006.

75. United Nations Development Programme/United Nations Population Fund/World Health Organization/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, Task Force on Long-acting Systemic Agents for Fertility Regulation. Comparative study of the effects of two once-a-month injectable contraceptives (Cyclofem and Mesigyna) and one oral contraceptive (Ortho-Novum 1/35) on coagulation and fibrinolysis. *Contraception*, 2003, **68**:159–176.

76. United Nations Development Programme/United Nations Population Fund/ World Health Organization/World Bank, Special Programme of Research, Development and Research Training in Human Reproduction. Comparative study of the effects of two once-a-month injectable steroidal contraceptives (Mesigyna and Cyclofem) on lipid and lipoprotein metabolism. *Contraception*, 1997, **56**:193–207.

77. United Nations Development Programme/United Population Fund/World Health Organization/World Bank, Special Programme of Research, Development and Research Training in Human Reproduction, Task Force on Long-acting Systemic Agents for Fertility Regulation. Comparative study of the effects of two once-a-month injectable steroidal contraceptives (Mesigyna and Cyclofem) on glucose metabolism and liver function. *Contraception,* 1998, **57**:71–81.

78. Bahamondes L et al. Bone mineral density in users of two kinds of once-a-month combined injectable contraceptives. *Contraception*, 2006, **74**:259–263.

79. *Technology guidelines for a district eye care programme*. London, Vision 2020, 2006.

80. Wilhelmus KR. Interventions for herpes simplex virus epithelial keratitis. *Cochrane Database of Systematic Reviews,* 2003, Issue 2. Art. No.: CD002898. DOI: 10.1002/14651858.CD002898.

81. Cipriani A et al. Fluoxetine versus other types of pharmacotherapy for depression. *Cochrane Database of Systematic Reviews,* 2005, Issue 4. Art. No.: CD004185.pub2. DOI: 10.1002/14651858.CD004185.pub2.

82. McKenzie MS, McFarland BH. Trends in antidepressant overdoses. *Pharmacoepidemiology and Drug Safety,* 2007, 67, 513–523.

83. Tudur Smith C, Marson AG, Williamson PR. Carbamazepine versus phenobarbitone monotherapy for epilepsy. *Cochrane Database of Systematic Reviews*, 2003, Issue 1. Art. No.: CD001904. DOI: 10.1002/14651858. CD001904.

84. Marson AG et al., on behalf of the epilepsy monotherapy trialists. Carbamazepine versus valproate monotherapy for epilepsy. *Cochrane Database of Systematic Reviews*, 2000, Issue 3. Art. No.: CD001030. DOI: 10.1002/14651858.CD001030.

85. Tudur Smith C et al. Carbamazepine versus phenytoin monotherapy for epilepsy. *Cochrane Database of Systematic Reviews*, 2002, Issue 2. Art. No.: CD001911. DOI: 10.1002/14651858.CD001911.

86. Gamble CL, Williamson PR, Marson AG. Lamotrigine versus carbamazepine monotherapy for epilepsy. *Cochrane Database of Systematic Reviews*, 2006, Issue 1. Art. No.: CD001031. DOI: 10.1002/14651858.CD001031.pub2.

87. de Silva M et al. Randomised comparative monotherapy trial of phenobarbitone, phenytoin, carbamazepine, or sodium valproate for newly diagnosed childhood epilepsy. *Lancet*, 1996, **347**:709–713.

88. Verity CM, Hosking G, Easter DJ. A multicentre comparative trial of sodium valproate and carbamazepine in paediatric epilepsy. The Paediatric EPITEG Collaborative Group. *Developmental Medicine and Child Neurology*, 1995, **37**:97–108.

89. Brodie MJ, Richens A, Yuen AW. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. UK Lamotrigine/ Carbamazepine Monotherapy Trial Group. *Lancet*, 1995, **345**:476–479.

90. Chadwick D. Safety and efficacy of vigabatrin and carbamazepine in newly diagnosed epilepsy: a multicentre randomized double-blind study. *Lancet*, 1999, **354**:13–19.

91. Wheless JW, Neto W, Wang S, EPMN-105 Study Group. Topiramate, carbamazepine, and valproate monotherapy: double-blind comparison in children with newly diagnosed epilepsy. *Journal of Child Neurology,* 2004, **9**:135–141.

92. Treiman DM et al. A comparison of four treatments for generalized convulsive status epilepticus. *New England Journal of Medicine*, 1998, **339**:792–798.

93. Wilmshurst JM, Newton CRJC. Withdrawal of older anticonvulsants for management of status epilepticus: implications for resource-poor countries. *Developmental Medicine and Child Neurology*, 2005, **2005**:219.

94. Taylor S et al. Phenobarbitone versus phenytoin monotherapy for partial onset seizures and generalized onset tonic-clonic seizures. *Cochrane Database of Systematic Reviews,* 2003, Issue 2. Art. No.: CD002217. DOI: 10.1002/14651858.CD002217.

95. Tudur Smith C, Marson AG, Williamson PR. Phenytoin versus valproate monotherapy for partial onset seizures and generalized onset tonic-clonic seizures. *Cochrane Database of Systematic Reviews* 2001, Issue 4. Art. No.: CD001769. DOI: 10.1002/14651858.CD001769.

96. Muller M, Marson AG, Williamson PR. Oxcarbazepine versus phenytoin monotherapy for epilepsy. *Cochrane Database of Systematic Reviews,* 2006, Issue 2. Art. No.: CD003615. DOI: 10.1002/14651858.CD003615.pub2.

97. Callaghan N et al. A prospective study between carbamazepine, phenytoin and sodium valproate as monotherapy in previously untreated and recently diagnosed patients with epilepsy. *Journal of Neurology, Neurosurgery and Psychiatry,* 1985, **48**:639–644.

98. Forsythe I et al. Cognitive impairment in new cases of epilepsy randomly assigned to carbamazepine, phenytoin and sodium valproate. *Developmental Medicine and Child Neurology,* 1991, **33**:524–534.

99. Posner EB, Mohamed K, Marson AG. Ethosuximide, sodium valproate or lamotrigine for absence seizures in children and adolescents. *Cochrane Database of Systematic Reviews,* 2005, Issue 4. Art. No.: CD003032. DOI: 10.1002/14651858.CD003032.pub2.

100. Steinhoff BJ et al., LAM-SAFE Study Group. The LAM-SAFE Study: lamotrigine versus carbamazepine or valproic acid in newly diagnosed focal and generalised epilepsies in adolescents and adults. *Seizure*, 2005, **14**:597–605.

101. Coppola G et al. Lamotrigine versus valproic acid as first-line monotherapy in newly diagnosed typical absence seizures: an open-label, randomized, parallel-group study. *Epilepsia,.* 2004, **45**:1049–1053.

102. Woldehanna S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database of Systematic Reviews,* 2004, Issue 1. Art. No.: CD000171. DOI: 10.1002/14651858.CD000171.pub2.

103. Zar HJ et al. Effect of isoniazid prophylaxis on mortality and incidence of tuberculosis in children with HIV: randomised controlled trial. *British Medical Journal*, 2007, **334**:136.

104. Colebunders R et al. Tuberculosis in resource-poor countries (editorial). *British Medical Journal,* 2007, **334**:105–106.

105. Golub JE et al. Tuberculosis (TB) incidence by HAART and isoniazid prophylactic therapy (IPT) in HIV-infected patients in Rio de Janeiro, Brazil [abstract]. XVI International AIDS Conference, 13–16 August 2006: MOPE0395.

106. Wilkinson D, Squire DB, Garner P. Effect of preventive treatment for tuberculosis in adults infected with HIV: systematic review of randomised placebo controlled trials. *British Medical Journal*, 1998, **317**:625–629.

107. Smieja MJ et al. Isoniazid for preventing tuberculosis in non-HIV infected persons. *Cochrane Database of Systematic Reviews*, 1999, Issue 1. Art. No.: CD001363. DOI: 10.1002/14651858.CD001363.

108. Marais BJ et al. Adherence to isoniazid preventive chemotherapy: a prospective community based study. *Archives of Disease in Childhood*, 2006, **91**:762–765.

109. Schaaf HS et al. Evaluation of young children in contact with adult multidrug-resistant pulmonary tuberculosis: a 30-month follow-up. *Pediatrics*, 2002,**109**:765–771.

110. Swaminathan S et al. Short-course chemotherapy for paediatric respiratory tuberculosis: 5-year report. *The International Journal of Tuberculosis and Lung Disease,* 2005, **9**:693–696.

111. Sanchez-Albisua I et al. Tolerance of pyrazinamide in short course chemotherapy for pulmonary tuberculosis in children. *Pediatric Infectious Disease Journal,* 1997, **16**:760–763.

112. Corrigan D, Paton J. Hepatic enzyme abnormalities in children on triple therapy for tuberculosis. *Pediatric Pulmonology,* 1999, **27**:37–42.

113. Zhu M et al. Population pharmacokinetic modeling of pyrazinamide in children and adults with tuberculosis. *Pharmacotherapy*, 2002, **22**:686–695.

114. Roy V, Tekur U, Chopra K. Pharmacokinetics of pyrazinamide in children suffering from pulmonary tuberculosis. *The International Journal of Tuberculosis and Lung Disease*, 1999, **3**:133–137.

115. Graham SM et al. Low levels of pyrazinamide and ethambutol in children with tuberculosis and impact of age, nutritional status, and human immunodeficiency virus infection. *Antimicrobial Agents and Chemotherapy*, 2006, **50**:407–413.

116. Steer PA, Henderson-Smart DJ. Caffeine versus theophylline for apnea in preterm infants. *Cochrane Database of Systematic Reviews*, 1998, Issue 2. Art. No.: CD000273. DOI: 10.1002/14651858.CD000273 (most recent amendment February 1998).

117. Henderson-Smart DJ, Steer P. Methylxanthine treatment for apnea in preterm infants. *Cochrane Database of Systematic Reviews*, 2001, Issue 3. Art. No.: CD000140. DOI: 10.1002/14651858.CD000140 (most recent amendment April 2001).

118. Schmidt B et al. Caffeine therapy for apnea of prematurity. *New England Journal of Medicine*, 2006, **354**:2112.

119. Darlow BA, Graham P. Vitamin A supplementation for preventing morbidity and mortality in very low birth weight infants (Review). *Cochrane Database of Systematic Reviews*, 2006(4).

120. Huiming Y, Chaomin W, Meng M. Vitamin A for treating measles in children (review). *Cochrane Database of Systematic Reviews,* 2005(4).

121. Ching P et al. Childhood mortality impact and costs of integrating vitamin A supplementation into immunizing campaigns. *American Journal of Public Health,* 2000, **90**:1526.

122. West K et al. Tolerance of young infants to single, large dose of vitamin A: a randomised community trial in Nepal. *Bulletin of the World Health Organization,* 1992, **70**:733–739.

123. D'Souza RM, D'Souza R. Vitamin A for the treatment of children with measles: a systematic review. *Journal of Tropical Pediatrics,* 2002, **48**:323–327.

124. Stephensen CB et al. Adverse effects of high-dose vitamin A supplements in children hospitalised with pneumonia. *Pediatrics,* 1998, **101**:E3.

125. World Bank. *World development report 1993: investing in health.* New York, Oxford University Press, 1993.

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Annex 1
Declaration of interests of Committee Members

The Members of the Committee reported the following:

Dr Noël Cranswick reported being an investigator on trials for GlaxoSmithKline, Quintiles, Uriach and BioMarin, but not any products or products being considered at the meeting or related to them, and also reported holding shares in Biota. He therefore excluded himself from discussion of the late item on antivirals.

Mr Dinesh Mehta reported being an employee of the British National Formulary, whose organization carries out editorial work on the WHO Model Formulary.

Dr Marcus M. Reidenberg reported having been a consultant for Roche about drug research and development and is currently a member of a data safety and monitoring board for them; receiving royalties through the National Institutes of Health (NIH) on the use of gossypol for cancer; and being a consultant to several start-up companies none of which have products on the market.

Dr Rohini Fernandopulle reported having been a consultant for GlaxoSmith-Kline. Dr Susan Walters reported having been a consultant for solicitors acting for a generics company, and manufacturer of over-the-counter (OTC) preparations, and having received travel support from Novartis to present a training course to the Brazilian regulatory authority.

Dr Lisa Bero, Dr Anwar-ul Hassan Gilani, Dr Usha Gupta, Dr Abdelkader Helali, Dr Alar Irs, Dr Youping Li, Dr Liliana de Lima, Dr Sri Suryawati, and Dr Lenita Wannmacher reported no conflict of interest.

The Temporary Advisers reported the following:

Dr Albert Figueras reported a family member being an employee of Merck, Sharpe and Dohme, Brazil. He therefore excluded himself from review or discussion of the product applications from Merck on this agenda.

Mr Andy Gray reported having accepted travel support from AstraZeneca, Aspen Pharmacare, Alphapharm to attend conferences; research support from the Merck Foundation 5 years ago, and being a study pharmacist for the International Clinical Trials Unit and Center for the AIDS Programme of Research in South Africa in KwaZulu-Natal, and also being a director of a government funding agency for biotechnology.

Dr Thamizhanban Pillay reported a family member being an employee of Roche Pharmaceuticals. He therefore excluded himself from discussion of the late item on antivirals.

Professor Hany Abde-Aleem and Dr Estrella Paje-Villar reported no conflict of interests.

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Annex 2

The 15th 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.

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 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. The Model List has since been revised and updated at intervals of approximately two years. 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 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 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 2003, 156 Member States had official essential medicines lists, of which 99 had been updated in the previous five 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 Office of the United Nations High Commissioner for Refugees (UNHCR), the United Nations Children's Fund (UNICEF) and the United Nations Population Fund (UNFPA), 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 under way 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 relevant WHO clinical guidelines, systematic reviews, key references and indicative cost information is being made available via the WHO web site as the WHO Essential Medicines Library. 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.

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. 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.

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 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 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.

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.

Drug and therapeutics committees

Drug and therapeutics 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 drug and therapeutics committees and prescribers in guideline development can contribute to improved prescribing behaviour.

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). 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 consistent higher costs or less attractive cost-effectiveness in a variety of settings.

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

Therapeutic equivalence is 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 listed in alphabetical order, within sections.

The presence of an entry on the Essential Medicines List carries no assurance as to pharmaceutical quality. It is the responsibility of each local regulatory

authority to ensure that each brand is of appropriate pharmaceutical quality (including stability) and that, when relevant, different brands are interchangeable.

Dosage forms of medicines are listed in alphabetical order and there is no implication of preference for one form over another. Standard treatment guidelines should be consulted for information on appropriate dosage forms.

Entries of the type *oral liquid* are intended to permit any solution, suspension or other form of liquid. Granules for reconstitution as an oral liquid may substitute for oral liquids, and typically carry benefits in the form of better stability and lower transport costs. If more than one type of oral liquid is available on the same market (e.g. solution, suspension, granules for reconstitution), they may be interchanged and in such cases should be bioequivalent. It is preferable that oral liquids do not contain sugar and that solutions for children do not contain alcohol.

Entries of the type *tablet* are intended to allow various forms of immediate-release tablet such as uncoated, film-coated, crushable, chewable, dispersible etc. Enteric coating, on the other hand, modifies drug release, and enteric-coated products are a modified-release dosage form. Crushable, chewable and dispersible tablets may be easier to administer to paediatric populations and to the elderly.

1. Anaesthetics

1.1 *General anaesthetics and oxygen*

□ 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)	Dental cartridge: 2% (hydrochloride) + epinephrine 1:80 000. Injection: 1%; 2% (hydrochloride) + epinephrine 1:200 000 in vial.
Complementary List	
ephedrine	Injection: 30 mg (hydrochloride)/ml in 1-ml ampoule. (For use in spinal anaesthesia during delivery, to prevent hypotension).

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.
morphine	Injection: 10 mg (sulfate or hydrochloride) in 1-ml ampoule.
promethazine	Oral liquid: 5 mg (hydrochloride)/5 ml.

2. Analgesics, antipyretics, non-steroidal anti-inflammatory medicines (NSAIMs), medicines used to treat gout and disease modifying agents in rheumatoid disorders (DMARDs)

2.1 *Non-opioids and non-steroidal anti-inflammatory medicines (NSAIMs)*

acetylsalicylic acid	Suppository: 50-150 mg. Tablet: 100-500 mg.
ibuprofen	Tablet: 200 mg; 400 mg.
paracetamol*	Oral liquid: 125 mg/5 ml. Suppository: 100 mg. Tablet: 100-500 mg. * Not recommended for anti-inflammatory use due to lack of proven benefit to that effect.

2.2 *Opioid analgesics*

codeine	Tablet: 30 mg (phosphate).
morphine	Injection: 10 mg (morphine hydrochloride or morphine sulfate) in 1-ml ampoule. Oral liquid: 10 mg (morphine hydrochloride or morphine sulfate)/5 ml. Tablet: 10 mg (morphine sulfate). Tablet (prolonged release): 10 mg; 30 mg; 60 mg (morphine sulfate).

2.3 *Medicines used to treat gout*

allopurinol	Tablet: 100 mg.

2.4 *Disease modifying agents used in rheumatoid disorders (DMARDs)*

chloroquine	Tablet: 100 mg; 150 mg (as phosphate or sulfate).
Complementary List	
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	Injection: 10 mg (hydrogen maleate) in 1-ml ampoule. Tablet: 4 mg (hydrogen maleate).
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.

3. Antiallergics and medicines used in anaphylaxis *(continued)*

hydrocortisone	Powder for injection: 100 mg (as sodium succinate) in vial.
□ prednisolone*	Tablet: 5 mg; 25 mg * There is no evidence for complete clinical similarity between prednisolone and dexamethasone at high doses.

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.
methylthioninium chloride (methylene blue)	Injection: 10 mg/ml in 10-ml ampoule.
naloxone	Injection: 400 micrograms (hydrochloride) in 1-ml ampoule.
penicillamine	Capsule or tablet: 250 mg.
potassium ferric hexacyano-ferrate(II) $-2H_20$ (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	Oral liquid: 100 mg/5 ml. Tablet (chewable): 100 mg; 200 mg. Tablet (scored): 100 mg; 200 mg.
□ diazepam	Injection: 5 mg/ml in 2-ml ampoule (intravenous or rectal).
magnesium sulfate*	Injection: 500 mg/ml in 2-ml ampoule; 500 mg/ml in 10-ml ampoule. * For use in eclampsia and severe pre-eclampsia and not for other convulsant disorders.

5. Anticonvulsants/antiepileptics *(continued)*

phenobarbital	Injection: 200 mg/ml (phenobarbital sodium). Oral liquid: 15 mg/5 ml (as phenobarbital or phenobarbital sodium). Tablet: 15-100 mg (phenobarbital).
phenytoin	Capsule: 25 mg; 50 mg; 100 mg (sodium salt). Injection: 50 mg/ml in 5-ml vial (sodium salt). Oral liquid: 25-30 mg/5 ml.* Tablet: 25 mg; 50 mg; 100 mg (sodium salt). Tablet (chewable): 50 mg. * The presence of both 25 mg/5 ml and 30 mg/5 ml strengths on the same market would cause confusion in prescribing and dispensing and should be avoided.
valproic acid	Oral liquid: 200 mg/5 ml. Tablet (crushable): 100 mg. Tablet (enteric-coated): 200 mg; 500 mg (sodium valproate).
Complementary List	
ethosuximide	Capsule: 250 mg. Oral liquid: 250 mg/5 ml.

6. Anti-infective medicines

6.1 *Anthelminthics*

6.1.1 *Intestinal anthelminthics*

albendazole	Tablet (chewable): 400 mg.
levamisole	Tablet: 50 mg; 150 mg (as hydrochloride).
□ mebendazole	Tablet (chewable): 100 mg; 500 mg.
niclosamide*	Tablet (chewable): 500 mg. * Niclosamide is listed for use when praziquantel treatment fails.
praziquantel	Tablet: 150 mg; 600 mg.
pyrantel	Oral liquid: 50 mg (as embonate)/ml. Tablet (chewable): 250 mg (as embonate).

6.1.2 *Antifilarials*

ivermectin	Tablet (scored): 3 mg; 6 mg.
Complementary List	
diethylcarbamazine	Tablet: 50 mg; 100 mg (dihydrogen citrate).
suramin sodium	Powder for injection: 1 g in vial.

6. Anti-infective medicines *(continued)*

6.1.3 *Antischistosomals and antitrematode medicine*

praziquantel	Tablet: 600 mg.
triclabendazole	Tablet: 250 mg.
Complementary List	
*oxamniquine**	Capsule: 250 mg. Oral liquid: 250 mg/5 ml. * Oxamniquine is listed for use when praziquantel treatment fails.

6.2 Antibacterials

6.2.1 *Beta lactam medicines*

amoxicillin	Capsule or tablet: 250 mg; 500 mg (anhydrous). Powder for oral liquid: 125 mg (anhydrous)/5 ml.
amoxicillin + clavulanic acid	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.
cefazolin*	Powder for injection: 1 g (as sodium salt) in vial. * For surgical prophylaxis.
cefixime*	Capsule: 400 mg. * Only listed for single-dose treatment of uncomplicated ano-genital gonorrhoea.
□ cloxacillin	Capsule: 500 mg; 1 g (as sodium salt). Powder for injection: 500 mg (as sodium salt) in vial. Powder for oral liquid: 125 mg (as sodium salt)/5 ml.
phenoxymethylpenicillin	Powder for oral liquid: 250 mg (as potassium salt)/5 ml. Tablet: 250 mg (as potassium salt).
procaine benzylpenicillin	Powder for injection: 1 g (= 1 million IU); 3 g (= 3 million IU) in vial.

Complementary List

ceftazidime	Powder for injection: 250 mg (as pentahydrate) in vial.
□ *ceftriaxone*	Powder for injection: 250 mg, 1 g (as sodium salt) in vial.
imipenem + cilastatin**	Powder for injection: 250 mg (as monohydrate) + 250 mg (as sodium salt); 500 mg (as monohydrate) + 500 mg (as sodium salt) in vial. * Only listed for the treatment of life-threatening hospital-based infection due to suspected or proven multidrug-resistant infection.

6.2.2 *Other antibacterials*

azithromycin*	Capsule: 250 mg or 500 mg. Oral liquid: 200 mg/5 ml. * Only listed for single-dose treatment of genital *Chlamydia trachomatis* and of trachoma.
chloramphenicol	Capsule: 250 mg. Oily suspension for injection: 0.5 g (as sodium succinate)/ml in 2-ml ampoule. Oral liquid: 150 mg (as palmitate)/5 ml. Powder for injection: 1 g (sodium succinate) in vial.
□ ciprofloxacin*	Tablet: 250 mg (as hydrochloride). * Final selection depends on indication for use.
doxycycline*	Capsule or tablet: 100 mg (hydrochloride). * Final selection depends on indication for use.
□ erythromycin	Capsule or tablet: 250 mg (as stearate or ethyl succinate). Powder for injection: 500 mg (as lactobionate) in vial. Powder for oral liquid: 125 mg/5 ml (as stearate or ethyl succinate).
□ gentamicin*	Injection: 10 mg; 40 mg (as sulfate)/ml in 2-ml vial. * Final selection depends on indication for use.
□ metronidazole	Injection: 500 mg in 100-ml vial. Oral liquid: 200 mg (as benzoate)/5 ml. Suppository: 500 mg; 1 g. Tablet: 200-500 mg.
nitrofurantoin	Tablet: 100 mg.
spectinomycin	Powder for injection: 2 g (as hydrochloride) in vial.

sulfamethoxazole + trimethoprim	Injection: 80 mg + 16 mg/ml in 5-ml and 10-ml ampoules. Oral liquid: 200 mg + 40 mg/5 ml. Tablet: 100 mg + 20 mg; 400 mg + 80 mg.
trimethoprim	Tablet: 100 mg; 200 mg.
Complementary List	
clindamycin	Capsule: 150 mg. Injection: 150 mg (as phosphate)/ml.
sulfadiazine	Injection: 250 mg (sodium salt) in 4-ml ampoule. Tablet: 500 mg.
vancomycin	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. 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).
isoniazid	Tablet: 100-300 mg. Tablet (scored): 50 mg.
isoniazid + ethambutol	Tablet: 150 mg + 400 mg.
pyrazinamide	Tablet: 400 mg. Tablet (dispersible): 150 mg. Tablet (scored): 150 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 (For intermittent use three times weekly). 150 mg + 150 mg (For intermittent use three times weekly).
rifampicin + isoniazid + ethambutol	Tablet: 150 mg + 75 mg + 275 mg.

6. Anti-infective medicines *(continued)*

rifampicin + isoniazid + pyrazinamide	Tablet: 60 mg + 30 mg + 150 mg; 150 mg + 75 mg + 400 mg. 150 mg + 150 mg + 500 mg (For intermittent use three times weekly).
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

Reserve second-line drugs for the treatment of multidrug-resistant tuberculosis (MDR-TB) should be used in specialized centres adhering to WHO standards for TB control.

amikacin	Powder for injection: 1000 mg in vial.
p-aminosalicylic acid	Granules: 4 g in sachet. Tablet: 500 mg.
capreomycin	Powder for injection: 1000 mg in vial.
cycloserine	Capsule or tablet: 250 mg.
ethionamide	Tablet: 125 mg; 250 mg.
kanamycin	Powder for injection: 1000 mg in vial.
*ofloxacin**	Tablet: 200 mg; 400 mg. * Levofloxacin may be an alternative based on availability and programme considerations.

6.3 Antifungal medicines

clotrimazole	Vaginal cream: 1%; 10%. Vaginal tablet: 100 mg; 500 mg.
□ fluconazole	Capsule: 50 mg. Injection: 2 mg/ml in vial. Oral liquid: 50 mg/5 ml.
griseofulvin	Capsule or tablet: 125 mg; 250 mg.
nystatin	Lozenge: 100 000 IU. Pessary: 100 000 IU. Tablet: 100 000 IU; 500 000 IU.

Complementary List

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	Powder for injection: 250 mg (as sodium salt) in vial. Tablet: 200 mg.

6.4.2 Antiretrovirals

Based on current evidence and experience of use, medicines in the following three classes of antiretrovirals are included as essential medicines for treatment and prevention of HIV (prevention of mother-to-child transmission and post exposure prophylaxis). The Committee emphasizes the importance of using these products in accordance with global and national guidelines. The Committee recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms with assured pharmaceutical quality.

6.4.2.1 Nucleoside/Nucleotide reverse transcriptase inhibitors

abacavir (ABC)	Oral liquid: 100 mg (as sulfate)/5 ml. Tablet: 300 mg (as sulfate).
didanosine (ddI)	Buffered powder for oral liquid: 100 mg; 167 mg; 250 mg packets. Capsule (unbuffered enteric-coated): 125 mg; 200 mg; 250 mg; 400 mg. Tablet (buffered chewable, dispersible): 25 mg; 50 mg; 100 mg; 150 mg; 200 mg.
emtricitabine (FTC)*	Capsule: 200 mg. Oral liquid: 10 mg/ml. * FTC is an acceptable alternative to 3TC, based on knowledge of the pharmacology, the resistance patterns and clinical trials of antiretrovirals.
lamivudine (3TC)	Oral liquid: 50 mg/5 ml. Tablet: 150 mg.
stavudine (d4T)	Capsule: 15 mg; 20 mg; 30 mg; 40 mg.* * The Committee expects this dosage form to be reviewed for possible deletion at the next meeting. Powder for oral liquid: 5 mg/5 ml.
tenofovir disoproxil fumarate (TDF)	Tablet: 300 mg (tenofovir disoproxil fumarate - equivalent to 245 mg tenofovir disoproxil).
zidovudine (ZDV or AZT)	Capsule: 100 mg; 250 mg. Oral liquid: 50 mg/5 ml. Solution for IV infusion injection: 10 mg/ml in 20-ml vial. Tablet: 300 mg.

6.4.2.2 Non-nucleoside reverse transcriptase inhibitors

efavirenz (EFV or EFZ)	Capsule: 50 mg; 100 mg; 200 mg. Oral liquid: 150 mg/5 ml. Tablet: 600 mg.
nevirapine (NVP)	Oral liquid: 50 mg/5 ml. Tablet: 200 mg.

6.4.2.3 Protease inhibitors

Selection of protease inhibitor(s) from the Model List will need to be determined by each country after consideration of international and national treatment guidelines and experience. Ritonavir is recommended for use in combination as a pharmacological booster, and not as an antiretroviral in its own right.

This section will be reviewed by the Committee as a priority at its next meeting. It is expected that application for a heat stable tablet formulation containing 200/50 mg lopinavir + ritonavir will be submitted for the next meeting.

indinavir (IDV)	Capsule: 200 mg; 333 mg; 400 mg (as sulfate).
lopinavir + ritonavir (LPV/r)	Capsule: 133.3 mg + 33.3 mg. Oral liquid: 400 mg + 100 mg/5 ml.
nelfinavir (NFV)	Oral powder: 50 mg/g. Tablet: 250 mg (as mesilate).
ritonavir	Oral liquid: 400 mg/5 ml. Oral solid dosage form: 100 mg.
saquinavir (SQV)	Capsule: 200 mg.

Fixed-dose combinations

efavirenz + emtricitabine* + tenofovir	Tablet: 600 mg + 200 mg + 300 mg. * FTC is an acceptable alternative to 3TC, based on knowledge of the pharmacology, the resistance patterns and clinical trials of antiretrovirals.
emtricitabine* + tenofovir	Tablet: 200 mg + 300 mg. * FTC is an acceptable alternative to 3TC, based on knowledge of the pharmacology, the resistance patterns and clinical trials of antiretrovirals.
stavudine + lamivudine + nevirapine	Tablet: 30 mg + 150 mg + 200 mg.
zidovudine + lamivudine	Tablet: 300 mg + 150 mg.
zidovudine + lamivudine + nevirapine	Tablet: 300 mg + 150 mg + 200 mg.

6.4.3 *Other antivirals*

ribavirin	Injection for intravenous administration: 1000 mg and 800 mg in 10-ml phosphate buffer solution. Oral solid dosage forms: 200 mg; 400 mg; 600 mg.

6. Anti-infective medicines *(continued)*

6.5 Antiprotozoal medicines

6.5.1 *Antiamoebic and antigiardiasis medicines*

diloxanide	Tablet: 500 mg (furoate).
□ metronidazole	Injection: 500 mg in 100-ml vial. Oral liquid: 200 mg (as benzoate)/5 ml. Tablet: 200-500 mg.

6.5.2 *Antileishmaniasis medicines*

□ meglumine antimoniate	Injection, 30%, equivalent to approximately 8.1% antimony in 5-ml ampoule.
paromomycin	Solution for intramuscular injection: 750 mg of paromomycin base present as the sulfate.
Complementary List	
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*

6.5.3.1 For curative treatment

Medicines for the treatment of *P. falciparum* malaria cases should be used in combination. The list currently recommends combinations according to treatment guidelines. The Committee recognizes that not all of these FDCs exist and encourages their development and rigorous testing. The Committee also encourages development and testing of rectal dosage formulations.

amodiaquine*	Tablet: 153 mg or 200 mg (as hydrochloride). * To be used (a) in combination with artesunate 50 mg OR (b) may be used alone for the treatment of *P.vivax*, *P.ovale* and *P.malariae* infections.
artemether	Oily injection: 80 mg/ml in 1-ml ampoule. For use in the management of severe malaria.
artemether + lumefantrine*	Tablet: 20 mg + 120 mg. * Not recommended in the first trimester of pregnancy or in children below 5 kg.
artesunate*	Injection: ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution. For use in the management of severe malaria. Tablet: 50 mg. * To be used in combination with either amodiaquine, mefloquine or sulfadoxine + pyrimethamine.

chloroquine*	Oral liquid: 50 mg (as phosphate or sulfate)/5 ml. Tablet: 100 mg; 150 mg (as phosphate or sulfate). * For use only for the treatment of *P.vivax* infection.
doxycycline*	Capsule: 100 mg (as hydrochloride). Tablet (dispersible): 100 mg (as monohydrate). * For use only in combination with quinine.
mefloquine*	Tablet: 250 mg (as hydrochloride). * To be used in combination with artesunate 50 mg.
primaquine*	Tablet: 7.5 mg; 15 mg (as diphosphate) * Only for use to achieve radical cure of *P.vivax* and *P.ovale* infections, given for 14 days.
quinine*	Injection: 300 mg quinine hydrochloride/ml in 2-ml ampoule. Tablet: 300 mg (quinine sulfate) or 300 mg (quinine bisulfate). * For use only in the management of severe malaria, and should be used in combination with doxycycline.
sulfadoxine + pyrimethamine*	Tablet: 500 mg + 25 mg. * Only in combination with artesunate 50 mg.

6.5.3.2 For prophylaxis

chloroquine*	Oral liquid: 50 mg (as phosphate or sulfate)/5 ml. Tablet: 150 mg (as phosphate or sulfate). * For use only in central American regions, for use for *P.vivax*.
doxycycline	Capsule or tablet: 100 mg (hydrochloride).
mefloquine	Tablet: 250 mg (as hydrochloride).
proguanil*	Tablet: 100 mg (hydrochloride). * For use only in combination with chloroquine.

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

pentamidine	Tablet: 200 mg; 300 mg.

6.5.5 *Antitrypanosomal medicines*

6.5.5.1 African trypanosomiasis

Medicines for the treatment of 1st stage African trypanosomiasis

6. Anti-infective medicines *(continued)*

pentamidine*	Powder for injection: 200 mg (pentamidine isetionate) in vial. * To be used for the treatment of *Trypanosoma brucei gambiense* infection.
suramin sodium*	Powder for injection: 1 g in vial. * To be used exclusively for the treatment of the initial phase of *Trypanosoma brucei rhodesiense* infection.

Medicines for the treatment of 2nd stage African trypanosomiasis

eflornithine	Injection: 200 mg (hydrochloride)/ml in 100-ml bottle.
melarsoprol	Injection: 3.6% solution, 5-ml ampoule (180 mg of active compound).

6.5.5.2 American trypanosomiasis

benznidazole	Tablet: 100 mg.
nifurtimox	Tablet: 30 mg; 120 mg; 250 mg.

7. Antimigraine medicines

7.1 For treatment of acute attack

acetylsalicylic acid	Tablet: 300-500 mg.
paracetamol	Tablet: 300-500 mg.

7.2 For prophylaxis

□ propranolol	Tablet: 20 mg; 40 mg (hydrochloride).

8. Antineoplastic, immunosuppressives and medicines used in palliative care

8.1 Immunosuppressive medicines

Complementary List

azathioprine	Powder for injection: 100 mg (as sodium salt) in vial. Tablet: 50 mg.
ciclosporin	Capsule: 25 mg. Concentrate for injection: 50 mg/ml in 1-ml ampoule for organ transplantation.

8.2 Cytotoxic medicines

This section is expected to be reviewed at the next meeting.

Complementary List

asparaginase	Powder for injection: 10 000 IU in vial.
bleomycin	Powder for injection: 15 mg (as sulfate) in vial.

8. Antineoplastic, immunosuppressives and medicines used in palliative care *(continued)*

calcium folinate	Injection: 3 mg/ml in 10-ml ampoule. Tablet: 15 mg.
chlorambucil	Tablet: 2 mg.
cisplatin	Powder for injection: 10 mg; 50 mg in vial.
cyclophosphamide	Powder for injection: 500 mg in vial. Tablet: 25 mg.
cytarabine	Powder for injection: 100 mg in vial.
dacarbazine	Powder for injection: 100 mg in vial.
dactinomycin	Powder for injection: 500 micrograms in vial.
daunorubicin	Powder for injection: 50 mg (as hydrochloride) in vial.
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.
mercaptopurine	Tablet: 50 mg.
methotrexate	Powder for injection: 50 mg (as sodium salt) in vial. Tablet: 2.5 mg (as sodium salt).
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

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**	Tablet: 5 mg; 25 mg. * There is no evidence for complete clinical similarity between prednisolone and dexamethasone at high doses.
tamoxifen	Tablet: 10 mg; 20 mg (as citrate).

8. Antineoplastic, immunosuppressives and medicines used in palliative care *(continued)*

8.4 Medicines used in palliative care

The WHO Expert Committee recognizes the importance of listing specific medicines in the Palliative Care Section. Some medicines currently used in palliative care are included in the relevant sections of the Model List, according to their therapeutic use, e.g. analgesics. The Guidelines for Palliative Care that were referenced in the previous list are in need of update. The Committee expects applications for medicines needed for palliative care to be submitted for the next meeting.

9. Antiparkinsonism medicines

biperiden	Injection: 5 mg (lactate) in 1-ml ampoule. Tablet: 2 mg (hydrochloride).
levodopa + □ carbidopa	Tablet: 100 mg + 10 mg; 250 mg + 25 mg.

10. Medicines affecting the blood

10.1 Antianaemia medicines

ferrous salt	Oral liquid: equivalent to 25 mg iron (as sulfate)/ml. Tablet: equivalent to 60 mg iron.
ferrous salt + folic acid	Tablet equivalent to 60 mg iron + 400 micrograms folic acid (nutritional supplement for use during pregnancy).
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, injectable solution, 3.5% is considered as equivalent.

11.2 Plasma fractions for specific use

All plasma fractions should comply with the WHO Requirements for the Collection, Processing and Quality Control of Blood, Blood Components and Plasma Derivatives (Revised 1992). (WHO Technical Report Series, No. 840, 1994, Annex 2).

11. Blood products and plasma substitutes *(continued)*

Complementary List

human normal immunoglobulin	Intramuscular administration: 16% protein solution. Intravenous administration: 5%, 10% protein solution.
□ *factor VIII concentrate*	Dried.
□ *factor IX complex (coagulation factors, II, VII, IX, X) concentrate*	Dried.

12. Cardiovascular medicines

12.1 Antianginal medicines

□ atenolol	Tablet: 50 mg; 100 mg.
glyceryl trinitrate	Tablet (sublingual): 500 micrograms.
□ isosorbide dinitrate	Tablet (sublingual): 5 mg.
verapamil	Tablet: 40 mg; 80 mg (hydrochloride).

12.2 Antiarrhythmic medicines

This subsection will be reviewed at the next meeting of the Expert Committee.

□ atenolol	Tablet: 50 mg; 100 mg.
digoxin	Injection: 250 micrograms/ml in 2-ml ampoule. Oral liquid: 50 micrograms/ml. Tablet: 62.5 micrograms; 250 micrograms.
epinephrine (adrenaline)	Injection: 100 micrograms/ml (as acid tartrate or hydrochloride) in 10-ml ampoule.
lidocaine	Injection: 20 mg (hydrochloride)/ml in 5-ml ampoule.
verapamil	Injection: 2.5 mg (hydrochloride)/ml in 2-ml ampoule. Tablet: 40 mg; 80 mg (hydrochloride).

Complementary List

□ *procainamide*	Injection: 100 mg (hydrochloride)/ml in 10-ml ampoule.
□ *quinidine*	Tablet: 200 mg (sulfate).

12.3 Antihypertensive medicines

□ amlodipine	Tablet: 5 mg.
□ atenolol	Tablet: 50 mg; 100 mg.
□ enalapril	Tablet: 2.5 mg.

12. Cardiovascular medicines *(continued)*

hydralazine*	Powder for injection: 20 mg (hydrochloride) in ampoule. Tablet: 25 mg, 50 mg (hydrochloride). * Hydralazine is listed for use in the acute management of severe 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.
□ hydrochlorothiazide	Tablet (scored): 25 mg.
methyldopa*	Tablet: 250 mg. * 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.
Complementary List	
sodium nitroprusside	Powder for infusion: 50 mg in ampoule.

12.4 Medicines used in heart failure

This subsection will be reviewed at the next meeting of the Expert Committee.

digoxin	Injection: 250 micrograms/ml in 2-ml ampoule. Oral liquid: 50 micrograms/ml. Tablet: 62.5 micrograms; 250 micrograms.
□ enalapril	Tablet: 2.5 mg.
□ furosemide	Injection: 10 mg/ml in 2-ml ampoule. Tablet: 40 mg.
□ hydrochlorothiazide	Tablet (scored): 25 mg.
Complementary List	
dopamine	Injection: 40 mg/ml (hydrochloride) in 5-ml vial.

12.5 Antithrombotic medicines

acetylsalicylic acid	Tablet: 100 mg.
Complementary List	
streptokinase	Powder for injection: 1.5 million IU in vial.

12.6 Lipid-lowering agents

□ simvastatin*	Tablet: 5 mg; 10 mg; 20 mg; 40 mg. * For use in high-risk patients.

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	
selenium sulfide	Detergent-based suspension: 2%.

13.2 Anti-infective medicines

□ methylrosanilinium chloride (gentian violet)	Aqueous solution: 0.5%. Tincture: 0.5%.
neomycin sulfate + □ bacitracin	Ointment: 5 mg neomycin sulfate + 250 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).

13.4 Astringent medicines

aluminium diacetate	Solution: 5%.

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%.

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.
barium sulfate	Aqueous suspension.
□ iohexol	Injection: 140-350 mg iodine/ml in 5-ml; 10-ml; 20-ml ampoules.
Complementary List	
□ *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	Injection: 10 mg/ml in 2-ml ampoule. Tablet: 40 mg.
□ hydrochlorothiazide	Tablet (scored): 25 mg.
mannitol	Injectable solution: 10%; 20%.
spironolactone	Tablet: 25 mg.
17. Gastrointestinal medicines	
17.1 Antacids and other antiulcer medicines	
aluminium hydroxide	Oral liquid: 320 mg/5 ml. Tablet: 500 mg.

□ ranitidine	Injection: 25 mg/ml in 2-ml ampoule. Oral liquid: 75 mg/5 ml. Tablet: 150 mg (as hydrochloride).
magnesium hydroxide	Oral liquid: equivalent to 550 mg magnesium oxide/10 ml.

17.2 Antiemetic medicines

metoclopramide	Injection: 5 mg (hydrochloride)/ml in 2-ml ampoule. Tablet: 10 mg (hydrochloride).
promethazine	Injection: 25 mg (hydrochloride)/ml in 2-ml ampoule. Oral liquid: 5 mg (hydrochloride)/5 ml. Tablet: 10 mg; 25 mg (hydrochloride).

17.3 Anti-inflammatory medicines

□ sulfasalazine	Retention enema. Suppository: 500 mg. Tablet: 500 mg.

Complementary List

□ *hydrocortisone*	Retention enema. Suppository: 25 mg (acetate). (the □ only applies to hydrocortisone retention enema).

17.4 Laxatives

□ senna	Tablet: 7.5 mg (sennosides) (or traditional dosage forms).

17.5 Medicines used in diarrhoea

17.5.1 *Oral rehydration*

oral rehydration salts*

glucose:	75 mEq
sodium:	75 mEq or mmol/l
chloride:	65 mEq or mmol/l
potassium:	20 mEq or mmol/l
citrate:	10 mmol/l
osmolarity:	245 mOsm/l
glucose:	13.5 g/l
sodium chloride:	2.6 g/l
potassium chloride:	1.5 g/l
trisodium citrate dihydrate⁺:	2.9 g/l

⁺ trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/l. However, as the stability of this latter formulation is very poor under tropical conditions, it is only recommended when manufactured for immediate use.

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

17. Gastrointestinal medicines *(continued)*

17.5.2 *Medicines for diarrhoea in children*

*zinc sulfate**	Oral liquid: in 10 mg per unit dosage forms. Tablet: in 10 mg per unit dosage forms. * In acute diarrhoea zinc sulfate should be used as an adjunct to oral rehydration salts.

17.5.3 *Antidiarrhoeal (symptomatic) medicines in adults*

codeine*	Tablet: 30 mg (phosphate). * The role of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee.

18. Hormones, other endocrine medicines and contraceptives

18.1 Adrenal hormones and synthetic substitutes

Addison's disease is a rare condition; adrenal hormones are already included in section 3.

18.2 Androgens

Complementary List

testosterone	Injection: 200 mg (enantate) in 1-ml ampoule.

18.3 Contraceptives

18.3.1 *Oral hormonal contraceptives*

□ ethinylestradiol + □ levonorgestrel	Tablet: 30 micrograms + 150 micrograms.
□ ethinylestradiol + □ norethisterone	Tablet: 35 micrograms + 1.0 mg.
levonorgestrel	Tablet: 30 micrograms; 750 micrograms (pack of two); 1.5 mg.

18.3.2 *Injectable hormonal contraceptives*

medroxyprogesterone acetate	Depot injection: 150 mg/ml in 1-ml vial.
medroxyprogesterone acetate + estradiol cypionate	Injection: 25 mg + 5 mg.
norethisterone enantate	Oily solution: 200 mg/ml in 1-ml ampoule.

18.3.3 *Intrauterine devices*

copper-containing device

18.3.4 *Barrier methods*

condoms

diaphragms

18.3.5 *Implantable contraceptives*

levonorgestrel-releasing implant	Two-rod levonorgestrel-releasing implant, each rod containing 75 mg of levonorgestrel (150 mg total).

18. Hormones, other endocrine medicines and contraceptives *(continued)*

18.4 Estrogens

□ ethinylestradiol*	Tablet: 10 micrograms; 50 micrograms. * The public health relevance and/or comparative efficacy and/or safety of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee.

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.
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

clomifene	Tablet: 50 mg (citrate).

18.7 Progestogens

norethisterone*	Tablet: 5 mg. * The public health relevance and/or comparative efficacy and/or safety of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee.

Complementary List

*medroxyprogesterone acetate**	Tablet: 5 mg. * The public health relevance and/or comparative efficacy and/or safety of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee.

18.8 Thyroid hormones and antithyroid medicines

levothyroxine	Tablet: 50 micrograms; 100 micrograms (sodium salt).
potassium iodide	Tablet: 60 mg.
□ propylthiouracil	Tablet: 50 mg.

19. Immunologicals

19.1 Diagnostic agents

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

tuberculin, purified protein derivative (PPD) Injection.

19.2 Sera and immunoglobulins

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

anti-D immunoglobulin (human)	Injection: 250 micrograms in single-dose vial.
antitetanus immunoglobulin (human)	Injection: 500 IU in vial.
antivenom immunoglobulin*	Injection. * Exact type to be defined locally.
diphtheria antitoxin	Injection: 10 000 IU; 20 000 IU in vial.
□ rabies immunoglobulin	Injection: 150 IU/ml in vial.

19.3 Vaccines

Selection of vaccines from the Model List will need to be determined by each country after consideration of international recommendations, epidemiology and national priorities. The list below details the vaccines for which there is either a recommendation from the Strategic Advisory Group of Experts on Immunization (SAGE) (http://www.who.int/immunization/sage_conclusions/en/index.html) and/or a WHO position paper (http://www.who.int/immunization/documents/positionpapers/en/index.html). This site will be updated as new position papers are published and contains the most recent information and recommendations.

All vaccines should comply with the WHO Requirements for Biological Substances.

BCG vaccine

cholera vaccine

diphtheria vaccine

hepatitis A vaccine

hepatitis B vaccine

Haemophilus influenzae type b vaccine

influenza vaccine

Japanese encephalitis vaccine

measles vaccine

meningococcal meningitis vaccine

mumps vaccine

19. Immunologicals *(continued)*

pertussis vaccine	
pneumococcal vaccine	
poliomyelitis vaccine	
rabies vaccine	
rotavirus vaccine	
rubella vaccine	
tetanus vaccine	
typhoid vaccine	
varicella vaccine	
yellow fever vaccine	

20. Muscle relaxants (peripherally-acting) and cholinesterase inhibitors

□ alcuronium	Injection: 5 mg (chloride)/ml in 2-ml ampoule.
neostigmine	Injection: 500 micrograms in 1-ml ampoule; 2.5 mg (metilsulfate) in 1-ml ampoule. Tablet: 15 mg (bromide).
suxamethonium	Injection: 50 mg (chloride)/ml in 2-ml ampoule. Powder for injection (chloride) in vial.
Complementary List	
pyridostigmine	Injection: 1 mg in 1-ml ampoule. Tablet: 60 mg (bromide).
□ *vecuronium*	Powder for injection: 10 mg (bromide) in vial.

21. Ophthalmological preparations

This section will be reviewed at the next meeting of the Expert Committee.

21.1 Anti-infective agents

aciclovir	Ointment: 3% W/W.
□ gentamicin*	Solution (eye drops): 0.3% (sulfate). * Final selection depends on indication for use.
□ tetracycline	Eye ointment: 1% (hydrochloride).

21.2 Anti-inflammatory agents

□ prednisolone	Solution (eye drops): 0.5% (sodium phosphate).

21.3 Local anaesthetics

□ tetracaine	Solution (eye drops): 0.5% (hydrochloride).

21. 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	
epinephrine (adrenaline)	Solution (eye drops): 2% (as hydrochloride).

22. Oxytocics and antioxytocics

22.1 Oxytocics

□ ergometrine	Injection: 200 micrograms (hydrogen maleate) in 1-ml ampoule.
oxytocin	Injection: 10 IU in 1-ml ampoule.
Complementary List	
misoprostol	Vaginal tablet: 25 micrograms.
mifepristone – misoprostol**	Tablet 200 mg – tablet 200 micrograms. * Requires close medical supervision.

Where permitted under national law and where culturally acceptable.

22.2 Antioxytocics (tocolytics)

nifedipine	Immediate release capsule: 10 mg.

23. Peritoneal dialysis solution

Complementary List	
intraperitoneal dialysis solution (of appropriate composition)	Parenteral solution.

24. Psychotherapeutic medicines

24.1 Medicines used in psychotic disorders

□ chlorpromazine	Injection: 25 mg (hydrochloride)/ml in 2-ml ampoule. Oral liquid: 25 mg (hydrochloride)/5 ml. Tablet: 100 mg (hydrochloride).
□ fluphenazine	Injection: 25 mg (decanoate or enantate) in 1-ml ampoule.

24. Psychotherapeutic medicines *(continued)*

□ haloperidol	Injection: 5 mg in 1-ml ampoule. Tablet: 2 mg; 5 mg.

24.2 Medicines used in mood disorders

24.2.1 *Medicines used in depressive disorders*

□ amitriptyline	Tablet: 25 mg (hydrochloride).
fluoxetine	Capsule or tablet: 20 mg (present as hydrochloride).

24.2.2 *Medicines used in bipolar disorders*

carbamazepine	Tablet (scored): 100 mg; 200 mg.
lithium carbonate	Capsule or tablet: 300 mg.
valproic acid	Tablet (enteric-coated): 200 mg; 500 mg (sodium valproate).

24.3 Medicines used in generalized anxiety and sleep disorders

□ diazepam	Tablet (scored): 2 mg; 5 mg.

24.4 Medicines used for obsessive compulsive disorders and panic attacks

clomipramine	Capsule: 10 mg; 25 mg (hydrochloride).

24.5 Medicines used in substance dependence programmes

Complementary List

□ *methadone**	Concentrate for oral liquid: 5 mg/ml; 10 mg/ml (hydrochloride). Oral liquid: 5 mg/5 ml; 10 mg/5 ml. * The square box is added to include buprenorphine. The medicines should only be used within an established support programme.

25. Medicines acting on the respiratory tract

25.1 Antiasthmatic and medicines for chronic obstructive pulmonary disease

□ beclometasone	Inhalation (aerosol): 50 micrograms per dose (dipropionate); 250 micrograms (dipropionate) per dose.
epinephrine (adrenaline)	Injection: 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule.
ipratropium bromide	Inhalation (aerosol): 20 micrograms/metered dose.

25. Medicines acting on the respiratory tract *(continued)*

□ salbutamol	Inhalation (aerosol): 100 micrograms (as sulfate) per dose. Injection: 50 micrograms (as sulfate)/ml in 5-ml ampoule. Oral liquid: 2 mg/5 ml. Respirator solution for use in nebulizers: 5 mg (as sulfate)/ml. Tablet: 2 mg; 4 mg (as sulfate).

25.2 Other medicines acting on the respiratory tract

caffeine citrate	Injection: 20 mg/ml (equivalent to 10 mg caffeine base/ml). Oral liquid: 20 mg/ml (equivalent to 10 mg caffeine base/ml).

26. Solutions correcting water, electrolyte and acid-base disturbances

26.1 Oral

oral rehydration salts	See section 17.5.1.
potassium chloride	Powder for solution.

26.2 Parenteral

glucose	Injectable solution: 5%; 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).
sodium hydrogen carbonate	Injectable solution: 1.4% isotonic (equivalent to Na+ 167 mmol/l, HCO_3- 167 mmol/l). Solution: 8.4% in 10-ml ampoule (equivalent to Na+ 1000 mmol/l, HCO_3- 1000 mmol/l).
□ sodium lactate, compound solution	Injectable solution.

26.3 Miscellaneous

water for injection	2-ml; 5-ml; 10-ml ampoules.

27. Vitamins and minerals

ascorbic acid	Tablet: 50 mg.
□ ergocalciferol	Capsule or tablet: 1.25 mg (50 000 IU). Oral liquid: 250 micrograms/ml (10 000 IU/ml).

27. Vitamins and minerals *(continued)*

iodine	Capsule: 200 mg. 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.
□ nicotinamide	Tablet: 50 mg.
pyridoxine	Tablet: 25 mg (hydrochloride).
retinol	Capsule: 50 000 IU; 100 000 IU; 200 000 IU (as palmitate). Oral oily solution: 100 000 IU (as palmitate)/ml in multidose dispenser. Tablet (sugar-coated): 10 000 IU (as palmitate). Water-miscible injection: 100 000 IU (as palmitate) in 2-ml ampoule.
riboflavin	Tablet: 5 mg.
sodium fluoride	In any appropriate topical formulation.
thiamine	Tablet: 50 mg (hydrochloride).
Complementary List	
calcium gluconate	Injection: 100 mg/ml in 10-ml ampoule.

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Annex 3

The Anatomical Therapeutic Chemical (ATC) classification system

The following list provides the corresponding Anatomical Therapeutic Chemical (ATC) classification codes for all items on the 15th WHO Model List of Essential Medicines, sorted by ATC code number.

ATC code	ATC group/medicine or item	Section
A	**ALIMENTARY TRACT AND METABOLISM**	
A02	**Drugs for acid related disorders**	
A02A	**Antacids**	
A02AA	*Magnesium compounds*	
A02AA04	magnesium hydroxide	17.1
A02AB	*Aluminium compounds*	
A02AB01	aluminium hydroxide	17.1
A02B	**Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)**	
A02BA	*H_2-receptor antagonists*	
A02BA02	ranitidine	17.1
A02BB	*Prostaglandins*	
A02BB01	misoprostol	22.1
A03	**Drugs for functional gastrointestinal disorders**	
A03B	**Belladonna and derivatives, plain**	
A03BA	*Belladonna alkaloids, tertiary amines*	
A03BA01	atropine	1.3; 4.2
A03F	**Propulsives**	
A03FA	*Propulsives*	
A03FA01	metoclopramide	17.2
A06	**Laxatives**	
A06A	**Laxatives**	
A06AB	*Contact laxatives*	
A06AB06	senna*	17.4
A07	**Antidiarrheals, intestinal antiinflammatory/antiinfective agents**	
A07A	**Intestinal antiinfectives**	
A07AA	*Antibiotics*	
A07AA02	nystatin	6.3
A07AA06	paromomycin	6.5.2

ATC code	ATC group/medicine or item	Section
A07B	**Intestinal adsorbents**	
A07BA	*Charcoal preparations*	
A07BA01	charcoal, activated*	4.1
A07C	**Electrolytes with carbohydrates**	
A07CA	*oral rehydration salts**	17.5.1; 26.1
A07E	**Intestinal antiinflammatory agents**	
A07EA	*Corticosteroids for local use*	
A07EA02	hydrocortisone	17.3
A07EC	*Aminosalicylic acid and similar agents*	
A07EC01	sulfasalazine	2.4; 17.3
A10	**Drugs used in diabetes**	
A10A	**Insulins and analogues**	
A10AB	*Insulins and analogues, fast-acting*	
A10AB	insulin injection (soluble)*	18.5
A10AC	*Insulins and analogues, intermediate-acting*	
A10AC	insulin, intermediate-acting*	18.5
A10B	**Oral blood glucose lowering drugs**	
A10BA	*Biguanides*	
A10BA02	metformin	18.5
A10BB	*Sulfonamides, urea derivatives*	
A10BB01	glibenclamide	18.5
A11	**Vitamins**	
A11C	**Vitamin A and D, incl. combinations of the two**	
A11CA	*Vitamin A, plain*	
A11CA01	retinol	27
A11CC	*Vitamin D and analogues*	
A11CC01	ergocalciferol	27
A11D	**Vitamin B_1, plain and in combination with vitamin B_6 and B_{12}**	
A11DA	*Vitamin B_1, plain*	
A11DA01	thiamine	27
A11G	**Ascorbic acid (vitamin C), incl. combinations**	
A11GA	*Ascorbic acid (vitamin C), plain*	
A11GA01	ascorbic acid	27
A11H	**Other plain vitamin preparations**	
A11HA	*Other plain vitamin preparations*	
A11HA01	nicotinamide	27
A11HA02	pyridoxine	27
A11HA04	riboflavin	27

ATC code	ATC group/medicine or item	Section
A12	**Mineral supplements**	
A12A	**Calcium**	
A12AA	*Calcium*	
A12AA03	calcium gluconate	4.2; 27
A12C	**Other mineral supplements**	
A12CB	*Zinc*	
A12CB01	zinc sulfate	17.5.2
A12CD	*Fluoride*	
A12CD01	sodium fluoride	27
A12CX	*Other mineral products*	
A12CX	iodine*	27
B	**BLOOD AND BLOOD FORMING ORGANS**	
B01	**Antithrombotic agents**	
B01A	**Antithrombotic agents**	
B01AA	*Vitamin K antagonists*	
B01AA03	warfarin	10.2
B01AB	*Heparin group*	
B01AB01	heparin sodium*	10.2
B01AC	Platelet aggregation inhibitors excl. heparin	
B01AC06	acetylsalicylic acid	12.5
B01AD	*Enzymes*	
B01AD01	streptokinase	12.5
B02	**Antihemorrhagics**	
B02B	**Vitamin K and other hemostatics**	
B02BA	*Vitamin K*	
B02BA01	phytomenadione	10.2
B02BD	*Blood coagulation factors*	
B02BD01	factor IX complex (coagulation factors II, VII, IX, X) concentrate*	11.2
B02BD02	factor VIII concentrate*	11.2
B03	**Antianemic preparations**	
B03A	ferrous salt*	10.1
B03A	**Iron preparations**	
B03AD	*Iron in combination with folic acid*	
B03AD	ferrous salt + folic acid*	10.1
B03B	**Vitamin B_{12} and folic acid**	
B03BA	Vitamin B_{12} (cyanocobalamin and analogues)	
B03BA03	hydroxocobalamin	10.1
B03BB	*Folic acid and derivatives*	
B03BB01	folic acid	10.1

ATC code	ATC group/medicine or item	Section
B05	**Blood substitutes and perfusion solutions**	
B05A	**Blood and related products**	
B05AA	*Blood substitutes and plasma protein fractions*	
B05AA05	dextran 70*	11.1
B05AA06	polygeline*	11.1
B05B	**I.V. solutions**	
B05BB	*Solutions affecting the electrolyte balance*	
B05BB01	sodium lactate, compound solution*	26.2
B05BB02	glucose with sodium chloride*	26.2
B05BC	*Solutions producing osmotic diuresis*	
B05BC01	mannitol	16
B05D	**Peritoneal dialytics**	
B05DA	*intraperitoneal dialysis solution**	*23*
B05X	**I.V. solution additives**	
B05XA	*Electrolyte solutions*	
B05XA01	potassium chloride	26.1; 26.2
B05XA02	sodium hydrogen carbonate*	26.2
B05XA03	sodium chloride	26.2
B05XA05	magnesium sulfate	5
C	**CARDIOVASCULAR SYSTEM**	
C01	**Cardiac therapy**	
C01A	**Cardiac glycosides**	
C01AA	*Digitalis glycosides*	
C01AA01	simvastatin	12.6
C01AA05	digoxin	12.2; 12.4
C01B	**Antiarrhythmics, class I and III**	
C01BA	*Antiarrhythmics, class Ia*	
C01BA01	quinidine	12.2
C01BA02	procainamide	12.2
C01BB	*Antiarrhythmics, class Ib*	
C01BB01	lidocaine	12.2
C01C	**Cardiac stimulants excl. cardiac glycosides**	
C01CA	*Adrenergic and dopaminergic agents*	
C01CA04	dopamine	12.4
C01CA24	epinephrine (adrenaline)	3; 12.2; 25.1
C01D	**Vasodilators used in cardiac diseases**	
C01DA	*Organic nitrates*	
C01DA02	glyceryl trinitrate	12.1
C01DA08	isosorbide dinitrate	12.1

ATC code	ATC group/medicine or item	Section
C02	**Antihypertensives**	
C02A	**Antiadrenergic agents, centrally acting**	
C02AB	*Methyldopa*	
C02AB01	methyldopa*	12.3
C02D	**Arteriolar smooth muscle, agents acting on**	
C02DB	*Hydrazinophthalazine derivatives*	
C02DB02	hydrazaline	12.3
C02DD	Nitroferricyanide derivatives	
C02DD01	sodium nitroprusside*	12.3
C03	**Diuretics**	
C03A	**Low-ceiling diuretics, thiazides**	
C03AA	*Thiazides, plain*	
C03AA03	hydrochlorothiazide	12.3;12.4;16
C03C	**High-ceiling diuretics**	
C03CA	*Sulfonamides, plain*	
C03CA01	furosemide	12.4; 16
C03D	**Potassium-sparing agents**	
C03DA	*Aldosterone antagonists*	
C03DA01	spironolactone	16
C03DB	*Other potassium-sparing agents*	
C03DB01	amiloride	16
C07	**Beta blocking agents**	
C07A	**Beta blocking agents**	
C07AA	*Beta blocking agents, non-selective*	
C07AA05	propranolol	7.2
C07AB	*Beta blocking agents, selective*	
C07AB03	atenolol	12.1;12.2;12.3
C08	**Calcium channel blockers**	
C08C	**Selective calcium channel blockers with mainly vascular effects**	
C08CA	*Dihydropyridine derivatives*	
C08CA01	amlodipine	12.3
C08CA05	nifedipine	22.2
C08D	**Selective calcium channel blockers with direct cardiac effects**	
C08DA	*Phenylalkylamine derivatives*	
C08DA01	verapamil	12.1;12.2
C09	**Agents acting on the renin-angiotensin system**	
C09A	**ACE inhibitors, plain**	
C09AA	*ACE inhibitors, plain*	
C09AA02	enalapril	12.3;12.4

ATC code	ATC group/medicine or item	Section
D	**DERMATOLOGICALS**	
D01	**Antifungals for dermatological use**	
D01A	**Antifungals for topical use**	
D01AA	*Antibiotics*	
D01AA01	nystatin	6.3
D01AC	*Imidazole and triazole derivatives*	
D01AC02	miconazole	13.1
D01AE	*Other antifungals for topical use*	
D01AE02	methylrosanilinium chloride (gentian violet)*	13.2
D01AE12	salicylic acid	13.5
D01AE13	selenium sulfide	13.1
D01AE20	benzoic acid + salicylic acid*	13.1
D01B	**Antifungals for systemic use**	
D01BA	*Antifungals for systemic use*	
D01BA01	griseofulvin	6.3
D02	**Emollients and protectives**	
D02A	*Emollients and protectives*	
D02AB	*Zinc products*	
D02AB	calamine lotion*	13.3
D02AE	*Carbamide products*	
D02AE01	urea*	13.5
D05	**Antipsoriatics**	
D05A	**Antipsoriatics for topical use**	
D05AA	*Tars*	
D05AA	*coal tar**	*13.5*
D05AC	Antracen derivatives	
D05AC01	dithranol	13.5
D06	**Antibiotics and chemotherapeutics for dermatological use**	
D06A	**Antibiotics for topical use**	
D06AX	*Other antibiotics for topical use*	
D06AX04	neomycin + bacitracin*	13.2
D06B	**Chemotherapeutics for topical use**	
D06BA	*Sulfonamides*	
D06BA01	silver sulfadiazine	13.2
D06BB	*Antivirals*	
D06BB04	podophyllum resin*	13.5
D07	**Corticosteroids, dermatological preparations**	
D07A	**Corticosteroids, plain**	
D07AA	Corticosteroids, weak (group I)	
D07AA02	hydrocortisone	13.3

ATC code	ATC group/medicine or item	Section
D07AC	Corticosteroids, potent (group III)	
D07AC01	betamethasone	13.3
D08	**Antiseptics and disinfectants**	
D08A	**Antiseptics and disinfectants**	
D08AC	*Biguanides and amidines*	
D08AC02	chlorhexidine	15.1
D08AE	*Phenol and derivatives*	
D08AE05	chloroxylenol	15.2
D08AG	*Iodine products*	
D08AG02	polyvidone iodine	15.1
D08AX	*Other antiseptics and disinfectants*	
D08AX	chlorine base compound*	15.2
D08AX06	potassium permanganate	13.2
D08AX08	ethanol	15.1
D10	**Anti-acne preparations**	
D10A	**Anti-acne preparations for topical use**	
D10AE	*Peroxides*	
D10AE01	benzoyl peroxide	13.5
D10AX	*Other anti-acne preparations for topical use*	
D10AX05	aluminium diacetate	13.4
G	**GENITO URINARY SYSTEM AND SEX HORMONES**	
G01	**Gynecological antiinfectives and antiseptics**	
G01A	**Antiinfectives and antiseptics, excl. combinations with corticosteroids**	
G01AA	*Antibiotics*	
G01AA01	nystatin	6.3
G01AF	*Imidazole derivatives*	
G01AF02	clotrimazole	6.3
G02	**Other gynecologicals**	
G02A	**Oxytocics**	
G02AB	*Ergot alkaloids*	
G02AB03	ergometrine	22.1
G02B	**Contraceptives for topical use**	
G02BA	*Intrauterine contraceptives*	
G02BA02	copper-containing device*	18.3.3
G02BB	*Intravaginal contraceptives*	
G02BB	diaphragms*	18.3.4

ATC code	ATC group/medicine or item	Section
G03	**Sex hormones and modulators of the genital system**	
G03A	**Hormonal contraceptives for systemic use**	
G03AA	*Progestogens and estrogens, fixed combinations*	
G03AA05	ethinylestradiol + norethisterone*	18.3.1
G03AA08	medroxyprogesterone and estrogen	18.3.1
G03AB	*Progestogens and estrogens, sequential preparations*	
G03AB03	ethinylestradiol + levonorgestrel*	18.3.1
G03AC	*Progestogens*	
G03AC01	norethisterone enantate*	18.3.2
G03AC03	levonorgestrel	18.3.1
	levonorgestrel-releasing implant	18.3.5
G03AC06	medroxyprogesterone acetate*	18.3.2; 18.7
G03B	**Androgens**	
G03BA	*3-oxoandrosten (4) derivatives*	
G03BA03	testosterone	18.2
G03C	**Estrogens**	
G03CA	*Natural and semisynthetic estrogens, plain*	
G03CA01	ethinylestradiol	18.4
G03D	**Progestogens**	
G03DC	*Estren derivatives*	
G03DC02	norethisterone	18.7
G03G	**Gonadotropins and other ovulation stimulants**	
G03GB	*Ovulation stimulants, synthetic*	
G03GB02	clomifene	18.6
G03X	**Other sex hormones and modulators of the genital system**	
G03XB	*Antiprogesterons*	
G03XB01	mifepristone	22.1
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	22.1
H02	**Corticosteroids for systemic use**	
H02A	**Corticosteroids for systemic use, plain**	
H02AB	*Glucocorticoids*	
H02AB02	dexamethasone	3; 8.3
H02AB06	prednisolone	3; 8.3
H02AB09	hydrocortisone	3; 8.3

ATC code	ATC group/medicine or item	Section
H03	**Thyroid therapy**	
H03A	**Thyroid preparations**	
H03AA	*Thyroid hormones*	
H03AA01	levothyroxine*	18.8
H03B	**Antithyroid preparations**	
H03BA	*Thiouracils*	
H03BA02	propylthiouracil	18.8
H03C	**Iodine therapy**	
H03CA	*Iodine therapy*	
H03CA	potassium iodide*	6.3; 18.8
J	**ANTIINFECTIVES FOR SYSTEMIC USE**	
J01	**Antibacterials for systemic use**	
J01A	**Tetracyclines**	
J01AA	*Tetracyclines*	
J01AA02	doxycycline	6.2.2; 6.5.3.1; 6.5.3.2
J01B	**Amphenicols**	
J01BA	*Amphenicols*	
J01BA01	chloramphenicol	6.2.2
J01C	**Beta-lactam antibacterials, penicillins**	
J01CA	*Penicillins with extended spectrum*	
J01CA01	ampicillin	6.2.1
J01CA04	amoxicillin	6.2.1
J01CE	*Beta-lactamase sensitive penicillins*	
J01CE01	benzylpenicillin	6.2.1
J01CE02	phenoxymethylpenicillin	6.2.1
J01CE08	benzathine benzylpenicillin	6.2.1
J01CE09	procaine benzylpenicillin*	6.2.1
J01CF	*Beta-lactamase resistant penicillins*	
J01CF02	cloxacillin	6.2.1
J01CR	*Combinations of penicillins, incl. beta-lactamase inhibitors*	
J01CR02	amoxicillin + clavulanic acid*	6.2.1
J01D	**Other beta-lactam antibacterials**	
J01DB	*First-generation cephalosporins*	
J01DB04	cefazolin	6.2.1
J01DD	*Third-generation cephalosporins*	
J01DD02	ceftazidime	6.2.1
J01DD04	ceftriaxone	6.2.1
J01DD08	cefixime	6.2.1
J01DH	*Carbapenems*	
J01DH51	imipenem + cilastatin*	6.2.1

ATC code	ATC group/medicine or item	Section
J01E	**Sulfonamides and trimethoprim**	
J01EA	*Trimethoprim and derivatives*	
J01EA01	trimethoprim	6.2.2
J01EC	*Intermediate-acting sulfonamides*	
J01EC02	sulfadiazine	6.2.2
J01EE	*Combinations of sulfonamides and trimethoprim, incl. derivatives*	
J01EE01	sulfamethoxazole + trimethoprim	6.2.2; 6.5.4
J01F	**Macrolides, lincosamides and streptogramins**	
J01FA	*Macrolides*	
J01FA01	erythromycin	6.2.2
J01FA10	azithromycin	6.2.2
J01FF	*Lincosamides*	
J01FF01	clindamycin	6.2.2
J01G	**Aminoglycoside antibacterials**	
J01GA	*Streptomycins*	
J01GA01	streptomycin	6.2.4
J01GB	*Other aminoglycosides*	
J01GB03	gentamicin	6.2.2
J01GB04	kanamycin	6.2.4
J01GB06	amikacin	6.2.4
J01M	**Quinolone antibacterials**	
J01MA	*Fluoroquinolones*	
J01MA01	ofloxacin	6.2.4
J01MA02	ciprofloxacin	6.2.2
J01MA12	levofloxacin	6.2.4
J01X	**Other antibacterials**	
J01XA	*Glycopeptide antibacterials*	
J01XA01	vancomycin	6.2.2
J01XD	*Imidazole derivatives*	
J01XD01	metronidazole	6.2.2
J01XE	*Nitrofuran derivatives*	
J01XE01	nitrofurantoin	6.2.2
J01XX	*Other antibacterials*	
J01XX04	spectinomycin	6.2.2
J02	**Antimycotics for systemic use**	
J02A	**Antimycotics for systemic use**	
J02AA	*Antibiotics*	
J02AA01	amphotericin B	6.3; 6.5.2

ATC code	ATC group/medicine or item	Section
J02AC	**Triazole derivatives**	
J02AC01	*fluconazole*	*6.3*
J02AX	**Other antimycotics for systemic use**	
J02AX01	flucytosine	6.3
J04	**Antimycobacterials**	
J04A	**Drugs for treatment of tuberculosis**	
J04AA	*Aminosalicylic acid and derivatives*	
J04AA01	p-aminosalicylic acid*	6.2.4
J04AB	*Antibiotics*	
J04AB01	cycloserine	6.2.4
J04AB02	rifampicin	6.2.3; 6.2.4
J04AB30	capreomycin	6.2.4
J04AC	*Hydrazides*	
J04AC01	isoniazid	6.2.4
J04AD	*Thiocarbamide derivatives*	
J04AD03	ethionamide	6.2.4
J04AK	*Other drugs for treatment of tuberculosis*	
J04AK01	pyrazinamide	6.2.4
J04AK02	ethambutol	6.2.4
J04AM	*Combinations of drugs for treatment of tuberculosis*	
J04AM02	rifampicin + isoniazid*	6.2.4
J04AM03	isoniazid + ethambutol*	6.2.4
J04AM05	rifampicin + isoniazid + pyrazinamide*	6.2.4
J04AM06	rifampicin + isoniazid + pyrazinamide + ethambutol*	6.2.4
	rifampicin + isoniazid + ethambutol	6.2.4
J04B	**Drugs for treatment of lepra**	
J04BA	*Drugs for treatment of lepra*	
J04BA01	clofazimine	6.2.3
J04BA02	dapsone	6.2.3
J05	**Antivirals for systemic use**	
J05A	**Direct acting antivirals**	
J05AB	*Nucleosides and nucleotides excl. reverse transcriptase inhibitors*	
J05AB01	aciclovir	6.4.1
J05AB04	ribavirin	6.4.3
J05AE	*Protease inhibitors*	
J05AE01	saquinavir (SQV)	6.4.2.3
J05AE02	indinavir (IDV)	6.4.2.3
J05AE03	ritonavir (r)	6.4.2.3
J05AE04	nelfinavir (NFV)	6.4.2.3
J05AE30	lopinavir + ritonavir (LPV/r)*	6.4.2.3

ATC code	ATC group/medicine or item	Section
J05AF	*Nucleoside reverse transcriptase inhibitors*	
J05AF01	zidovudine (ZDV or AZT)	6.4.2.1
J05AF02	didanosine (ddI)	6.4.2.1
J05AF04	stavudine (d4T)	6.4.2.1
J05AF05	lamivudine (3TC)	6.4.2.1
J05AF06	abacavir (ABC)	6.4.2.1
J05AF07	tenofovir	6.4.2.1
J05AF09	emtricitabine	6.4.2.1
J05AG	*Non-nucleoside reverse transcriptase inhibitors*	
J05AG01	nevirapine (NVP)	6.4.2.2
J05AG03	efavirenz (EFV or EFZ)	6.4.2.2
J05AGR		
J05AR01	zidovudine (ZDV or AZT) + lamivudine	
J05AR03	emtricitabine + tenofovir	
J05AR05	zidovudine + lamivudine + nevirapine	
J05AR06	efavirenz + emtricitabine + tenofovir	
	stavudine + lamivudine + nevirapine	
J06	**Immune sera and immunoglobulins**	
J06A	**Immune sera**	
J06AA	*Immune sera*	
J06AA01	diphtheria antitoxin	19.2
J06AA03	antivenom immunoglobulin*	19.2
J06B	**Immunoglobulins**	
J06BA	*Immunoglobulins, normal human*	
J06BA01	immunoglobulins, normal human, for extravascular adm	19.2
J06BA02	immunoglobulins, normal human, for intravascular adm	19.2
J06BB	*Specific immunoglobulins*	
J06BB01	anti-D immunoglobulin (human)	19.2
J06BB02	antitetanus immunoglobulin (human)	19.2
J06BB05	rabies immunoglobulin	19.2
J07	**Vaccines**	
J07A	**Bacterial vaccines**	
J07AE	*Cholera vaccines*	
J07AE	cholera vaccine	19.3
J07AH	*Meningococcal vaccines*	
J07AH	meningococcal meningitis vaccine*	19.3
J07AJ	*Pertussis vaccines*	
J07AJ51	diphtheria-pertussis-tetanus vaccine*	19.3
J07AM	*Tetanus vaccines*	
J07AM51	diphtheria-tetanus vaccine*	19.3

ATC code	ATC group/medicine or item	Section
J07AN	*Tuberculosis vaccines*	
J07AN01	BCG vaccine*	19.3
J07AP	*Typhoid vaccines*	
J07AP	typhoid vaccine	19.3
J07B	**Viral vaccines**	
J07BB	*Influenza vaccines*	
J07BB	influenza vaccine	19.3
J07BC	*Hepatitis vaccines*	
J07BC01	hepatitis B vaccine	19.3
J07BD	*Measles vaccine**	
J07BD52	measles-mumps-rubella vaccine*	19.3
J07BF	*poliomyelitis vaccine*	19.3
J07BG	*rabies vaccine*	19.3
J07BJ	*rubella vaccine*	19.3
J07BL	*yellow fever vaccine*	19.3
L	**ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS**	
L01	**Antineoplastic agents**	
L01A	**Alkylating agents**	
L01AA	*Nitrogen mustard analogues*	
L01AA01	cyclophosphamide	8.2
L01AA02	chlorambucil	8.2
L01AX	*Other alkylating agents*	
L01AX04	dacarbazine	8.2
L01B	**Antimetabolites**	
L01BA	*Folic acid analogues*	
L01BA01	methotrexate	2.4; 8.2
L01BB	*Purine analogues*	
L01BB02	mercaptopurine	8.2
L01BC	*Pyrimidine analogues*	
L01BC01	cytarabine	8.2
L01BC02	fluorouracil	8.2; 13.5
L01C	**Plant alkaloids and other natural products**	
L01CA	*Vinca alkaloids and analogues*	
L01CA01	vinblastine	8.2
L01CA02	vincristine	8.2
L01CB	*Podophyllotoxin derivatives*	
L01CB01	etoposide	8.2

ATC code	ATC group/medicine or item	Section
L01D	**Cytotoxic antibiotics and related substances**	
L01DA	*Actinomycines*	
L01DA01	dactinomycin	8.2
L01DB	*Anthracyclines and related substances*	
L01DB01	doxorubicin	8.2
L01DB02	daunorubicin	8.2
L01DC	*Other cytotoxic antibiotics*	
L01DC01	bleomycin	8.2
L01X	**Other antineoplastic agents**	
L01XA	*Platinum compounds*	
L01XA01	cisplatin	8.2
L01XB	*Methylhydrazines*	
L01XB01	procarbazine	8.2
L01XX	*Other antineoplastic agents*	
L01XX02	asparaginase	8.2
L02	**Endocrine therapy**	
L02B	**Hormone antagonists and related agents**	
L02BA	*Anti-estrogens*	
L02BA01	tamoxifen	8.3
L04	**Immunosuppressive agents**	
L04A	**Immunosuppressive agents**	
L04AA	*Selective immunosuppressive agents*	
L04AA01	ciclosporin	8.1
L04AX	*Other immunosuppressive agents*	
L04AX01	azathioprine	2.4; 8.1
M	**MUSCULO-SKELETAL SYSTEM**	
M01	**Antiinflammatory and antirheumatic products**	
M01A	**Antiinflammatory and antirheumatic products, non-steroids**	
M01AE	*Propionic acid derivatives*	
M01AE01	ibuprofen	2.1
M01C	**Specific antirheumatic agents**	
M01CC	*Penicillamine and similar agents*	
M01CC01	penicillamine	2.4; 4.2
M03	**Muscle relaxants**	
M03A	**Muscle relaxants, peripherally acting agents**	
M03AA	*Curare alkaloids*	
M03AA01	alcuronium	20
M03AB	*Choline derivatives*	
M03AB01	suxamethonium	20

ATC code	ATC group/medicine or item	Section
M03AC	*Other quaternary ammonium compounds*	
M03AC03	vecuronium	20
M04	**Antigout preparations**	
M04A	**Antigout preparations**	
M04AA	*Preparations inhibiting uric acid production*	
M04AA01	allopurinol	2.3
N	**NERVOUS SYSTEM**	
N01	**Anesthetics**	
N01A	**Anesthetics, general**	
N01AB	*Halogenated hydrocarbons*	
N01AB01	halothane	1.1
N01AF	*Barbiturates, plain*	
N01AF03	thiopental	1.1
N01AX	*Other general anesthetics*	
N01AX03	ketamine	1.1
N01AX13	nitrous oxide	1.1
N01B	**Anesthetics, local**	
N01BB	*Amides*	
N01BB01	bupivacaine	1.2
N01BB02	lidocaine	1.2
N01BB52	lidocaine + epinephrine (adrenaline)*	1.2
N02	**Analgesics**	
N02A	**Opioids**	
N02AA	*Natural opium alkaloids*	
N02AA01	morphine	1.3; 2.2
N02B	**Other analgesics and antipyretics**	
N02BA	*Salicylic acid and derivatives*	
N02BA01	acetylsalicylic acid	2.1; 7.1
N02BE	Anilides	
N02BE01	paracetamol	2.1; 7.1
N03	**Antiepileptics**	
N03A	**Antiepileptics**	
N03AA	*Barbiturates and derivatives*	
N03AA02	phenobarbital	5
N03AB	*Hydantoin derivatives*	
N03AB02	phenytoin	5
N03AD	*Succinimide derivatives*	
N03AD01	ethosuximide	5
N03AF	*Carboxamide derivatives*	
N03AF01	carbamazepine	5; 24.2.2

ATC code	ATC group/medicine or item	Section
N03AG	*Fatty acid derivatives*	
N03AG01	valproic acid	5; 24.2.2
N04	**Anti-parkinson drugs**	
N04A	**Anticholinergic agents**	
N04AA	*Tertiary amines*	
N04AA02	biperiden	9
N04B	**Dopaminergic agents**	
N04BA	*Dopa and dopa derivatives*	
N04BA02	levodopa + carbidopa*	9
N05	**Psycholeptics**	
N05A	**Antipsychotics**	
N05AA	*Phenothiazines with aliphatic side-chain*	
N05AA01	chlorpromazine	24.1
N05AB	*Phenothiazines with piperazine structure*	
N05AB02	fluphenazine	24.1
N05AD	**Butyrophenone derivatives**	
N05AD01	haloperidol	24.1
N05AN	*Lithium*	
N05AN01	lithium carbonate*	24.2.2
N05B	**Anxiolytics**	
N05BA	*Benzodiazepine derivatives*	
N05BA01	diazepam	1.3; 5; 24.3
N06	**Psychoanaleptics**	
N06A	**Antidepressants**	
N06AA	*Non-selective monoamine reuptake inhibitors*	
N06AA04	clomipramine	24.4
N06AA09	amitriptyline	24.2.1
N06AB	*Selective serotonin reuptake inhibitors*	
N06AB03	fluoxetine	24.2.1
N06B	**Psychostimulants, agents used for ADHD and nootropics**	
N06BC	*Xanthine derivatives*	
N06BC01	caffeine citrate	25.2
N07	**Other nervous system drugs**	
N07A	**Parasympathomimetics**	
N07AA	*Anticholinesterases*	
N07AA01	neostigmine	20
N07AA02	pyridostigmine	20
N07B	**Drugs used in addictive disorders**	
N07BC	*Drugs used in opioid dependence*	
N07BC02	methadone	24.5

ATC code	ATC group/medicine or item	Section
P	**ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS**	
P01	**Antiprotozoals**	
P01A	**Agents against amoebiasis and other protozoal diseases**	
P01AB	*Nitroimidazole derivatives*	
P01AB01	metronidazole	6.5.1
P01AC	*Dichloroacetamide derivatives*	
P01AC01	diloxanide	6.5.1
P01B	**Antimalarials**	
P01BA	*Aminoquinolines*	
P01BA01	chloroquine	2.4; 6.5.3.1; 6.5.3.2
P01BA03	primaquine	6.5.3.1
P01BA06	amodiaquine	6.5.3.1
P01BB	*Biguanides*	
P01BB01	proguanil	6.5.3.2
P01BC	*Methanolquinolines*	
P01BC01	quinine	6.5.3.1
P01BC02	mefloquine	6.5.3.1; 6.5.3.2
P01BD	*Diaminopyrimidines*	
P01BD01	pyrimethamine	6.5.4
P01BD51	sulfadoxine + pyrimethamine*	6.5.3.1
P01BE	*Artemisinin and derivatives*	
P01BE02	artemether	6.5.3.1
P01BE03	artesunate	6.5.3.1
P01BE52	artemether + lumefantrine*	6.5.3.1
P01C	**Agents against leishmaniasis and trypanosomiasis**	
P01CA	*Nitroimidazole derivatives*	
P01CA02	benznidazole	6.5.5.2
P01CB	*Antimony compounds*	
P01CB01	meglumine antimoniate	6.5.2
P01CC	*Nitrofuran derivatives*	
P01CC01	nifurtimox	6.5.5.2
P01CD	*Arsenic compounds*	
P01CD01	melarsoprol	6.5.5.1
P01CX	*Other agents against leishmaniasis and trypanosomiasis*	
P01CX01	pentamidine*	6.5.2; 6.5.4; 6.5.5.1
P01CX02	suramin sodium	6.1.2; 6.5.5.1
P01CX03	eflornithine	6.5.5.1

ATC code	ATC group/medicine or item	Section
P02	**Anthelmintics**	
P02B	**Antitrematodals**	
P02BA	*Quinoline derivatives and related substances*	
P02BA01	praziquantel	6.1.1; 6.1.3
P02BA02	oxamniquine	6.1.3
P02BX	Other antitrematodal agents	
P02BX04	triclabendazole	6.1.3
P02C	**Antinematodal agents**	
P02CA	Benzimidazole derivatives	
P02CA01	mebendazole	6.1.1
P02CA03	albendazole	6.1.1
P02CB	Piperazine and derivatives	
P02CB02	diethylcarbamazine	6.1.2
P02CC	*Tetrahydropyrimidine derivatives*	
P02CC01	pyrantel	6.1.1
P02CE	*Imidazothiazole derivatives*	
P02CE01	levamisole	6.1.1
P02CF	*Avermectines*	
P02CF01	ivermectin	6.1.2
P02D	**Anticestodals**	
P02DA	*Salicylic acid derivatives*	
P02DA01	niclosamide	6.1.1
P03	**Ectoparasiticides, incl. scabicides, insecticides and repellents**	
P03A	**Ectoparasiticides, incl. scabicides**	
P03AC	*Pyrethrines, incl. synthetic compounds*	
P03AC04	permethrin	13.6
P03AX	*Other ectoparasiticides, incl. scabicides*	
P03AX01	benzyl benzoate	13.6
R	**RESPIRATORY SYSTEM**	
R03	**Drugs for obstructive airway diseases**	
R03A	*Adrenergics, inhalants*	
R03AC	*Selective beta-2-adrenoreceptor agonists*	
R03AC02	salbutamol	25.1
R03B	**Other drugs for obstructive airway diseases, inhalants**	
R03BA	*Glucocorticoids*	
R03BA01	beclometasone	25.1
R03BB	*Anticholinergics*	
R03BB01	ipratropium bromide	25.1

ATC code	ATC group/medicine or item	Section
R03C	**Adrenergics for systemic use**	
R03CA	*Alpha- and beta-adrenoreceptor agonists*	
R03CA02	ephedrine	1.2
R03CC	*Selective beta-2-adrenoreceptor agonists*	
R03CC02	salbutamol	25.1
R05	**Cough and cold preparations**	
R05D	**Cough suppressants, excl. combinations with expectorants**	
R05DA	*Opium alkaloids and derivatives*	
R05DA04	codeine	2.2; 17.5.3
R06	**Antihistamines for systemic use**	
R06A	**Antihistamines for systemic use**	
R06AB	*Substituted alkylamines*	
R06AB04	chlorphenamine	3
R06AD	*Phenothiazine derivatives*	
R06AD02	promethazine	1.3; 17.2
S	**SENSORY ORGANS**	
S01	**Ophthalmologicals**	
S01A	**Antiinfectives**	
S01AA	*Antibiotics*	
S01AA09	tetracycline	21.1
S01AA11	gentamicin	21.1
S01AD	*Antivirals*	
S01AD03	aciclovir	21.1
S01B	**Antiinflammatory agents**	
S01BA	*Corticosteroids, plain*	
S01BA04	prednisolone	21.2
S01E	**Antiglaucoma preparations and miotics**	
S01EA	*Sympathomimetics in glaucoma therapy*	
S01EA01	epinephrine	21.5
S01EB	*Parasympathomimetics*	
S01EB01	pilocarpine	21.4
S01EC	*Carbonic anhydrase inhibitors*	
S01EC01	acetazolamide	21.4
S01ED	*Beta blocking agents*	
S01ED01	timolol	21.4
S01F	**Mydriatics and cycloplegics**	
S01FA	*Anticholinergics*	
S01FA01	atropine	21.5
S01FA06	tropicamide	14.1

ATC code	ATC group/medicine or item	Section
S01H	**Local anesthetics**	
S01HA	*Local anesthetics*	
S01HA03	tetracaine	21.3
S01J	**Diagnostic agents**	
S01JA	*Colouring agents*	
S01JA01	fluorescein	14.1
V	**VARIOUS**	
V03	**All other therapeutic products**	
V03A	**All other therapeutic products**	
V03AB	*Antidotes*	
V03AB03	sodium calcium edetate*	4.2
V03AB06	sodium thiosulfate*	4.2; 13.1
V03AB08	sodium nitrite	4.2
V03AB09	dimercaprol	4.2
V03AB14	protamine sulfate*	10.2
V03AB15	naloxone	4.2
V03AB17	methylthioninium chloride (methylene blue)	4.2
V03AB23	acetylcysteine	4.2
V03AB26	DL-methionine*	4.2
V03AB31	potassium ferric hexacyanoferrate (II) $\cdot 2H_2O$ (Prussian blue)	4.2
V03AC	*Iron chelating agents*	
V03AC01	deferoxamine	4.2
V03AF	**Detoxifying agents for antineoplastic treatment**	
V03AF03	*calcium folinate*	*8.2*
V03AN	*Medical gases*	
V03AN	oxygen	1.1
V04	**Diagnostic agents**	
V04C	**Other diagnostic agents**	
V04CF	*Tuberculosis diagnostics*	
V04CF01	tuberculin, purified protein derivative (PPD)*	19.1
V07	**All other non-therapeutic products**	
V07A	**All other non-therapeutic products**	
V07AB	*Solvents and diluting agents, incl. irrigating solutions*	
V07AB	water for injection*	26.3
V07AV	**Technical disinfectants**	
V07AV	glutaral	15.2
V08	**Contrast media**	
V08A	**X-ray contrast media, iodinated**	
V08AA	*Watersoluble, nephrotropic, high osmolar X-ray contrast media*	
V08AA01	amidotrizoate*	14.2

ATC code	ATC group/medicine or item	Section
V08AB	*Watersoluble, nephrotropic, low osmolar X-ray contrast media*	
V08AB02	iohexol	14.2
V08AC	*Watersoluble, hepatotropic X-ray contrast media*	
V08AC02	meglumine iotroxate*	14.2
V08B	**X-ray contrast media, non-iodinated**	
V08BA	*Barium sulfate containing X-ray contrast media*	
V08BA01	barium sulfate*	14.2

* Medicine or item name differs slightly from the name used.

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Annex 4

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

ATC group/medicine or item	ATC code	section
abacavir (ABC)	J05AF06	6.4.2.1
acetazolamide	S01EC01	21.4
acetylcysteine	V03AB23	4.2
acetylsalicylic acid	B01AC06	12.5
acetylsalicylic acid	N02BA01	2.1; 7.1
aciclovir	J05AB01	6.4.1
aciclovir	S01AD03	21.1
albendazole	P02CA03	6.1.1
alcuronium	M03AA01	20
allopurinol	M04AA01	2.3
aluminium diacetate	D10AX05	13.4
aluminium hydroxide	A02AB01	17.1
amidotrizoate*	V08AA01	14.2
amikacin	J01GB06	6.2.4
amiloride	C03DB01	16
amitriptyline	N06AA09	24.2.1
amlodipine	C08CA01	12.3
amodiaquine	P01BA06	6.5.3.1
amoxicillin	J01CA04	6.2.1
amoxicillin + clavulanic acid*	J01CR02	6.2.1
amphotericin B	J02AA01	6.3; 6.5.2
ampicillin	J01CA01	6.2.1
anti-D immunoglobulin (human)	J06BB01	19.2
antitetanus immunoglobulin (human)	J06BB02	19.2
antivenom immunoglobulin*	J06AA03	19.2
artemether	P01BE02	6.5.3.1
artemether + lumefantrine*	P01BE52	6.5.3.1
artesunate	P01BE03	6.5.3.1
ascorbic acid	A11GA01	27
asparaginase	L01XX02	8.2
atenolol	C07AB03	12.1;12.2;12.3
atropine	A03BA01	1.3; 4.2
atropine	S01FA01	21.5
azathioprine	L04AX01	2.4; 8.1
azithromycin	J01FA10	6.2.2
barium sulfate*	V08BA01	14.2
BCG vaccine*	J07AN01	19.3
beclometasone	R03BA01	25.1

ATC group/medicine or item	ATC code	section
benzathine benzylpenicillin	J01CE08	6.2.1
benznidazole	P01CA02	6.5.5.2
benzoic acid + salicylic acid*	D01AE20	13.1
benzoyl peroxide	D10AE01	13.5
benzyl benzoate	P03AX01	13.6
benzylpenicillin	J01CE01	6.2.1
betamethasone	D07AC01	13.3
biperiden	N04AA02	9
bleomycin	L01DC01	8.2
bupivacaine	N01BB01	1.2
caffeine citrate	N06BC01	25.2
calamine lotion*	D02AB	13.3
calcium folinate	V03AF03	8.2
calcium gluconate	A12AA03	4.2; 27
capreomycin	J04AB30	6.2.4
carbamazepine	N03AF01	5; 24.2.2
cefazolin	J01DB04	6.2.1
cefixime	J01DD08	6.2.1
ceftazidime	J01DD02	6.2.1
ceftriaxone	J01DD04	6.2.1
charcoal, activated*	A07BA01	4.1
chlorambucil	L01AA02	8.2
chloramphenicol	J01BA01	6.2.2
chlorhexidine	D08AC02	15.1
chlorine base compound*	D08AX	15.2
chloroquine	P01BA01	2.4; 6.5.3.1; 6.5.3.2
chloroxylenol	D08AE05	15.2
chlorphenamine	R06AB04	3
chlorpromazine	N05AA01	24.1
cholera vaccine	J07AE	19.3
ciclosporin	L04AA01	8.1
ciprofloxacin	J01MA02	6.2.2
cisplatin	L01XA01	8.2
clindamycin	J01FF01	6.2.2
clofazimine	J04BA01	6.2.3
clomifene	G03GB02	18.6
clomipramine	N06AA04	24.4
clotrimazole	G01AF02	6.3
cloxacillin	J01CF02	6.2.1
coal tar*	D05AA	13.5
codeine	R05DA04	2.2; 17.5.3
copper-containing device*	G02BA02	18.3.3
cyclophosphamide	L01AA01	8.2
cycloserine	J04AB01	6.2.4
cytarabine	L01BC01	8.2

ATC group/medicine or item	ATC code	section
dacarbazine	L01AX04	8.2
dactinomycin	L01DA01	8.2
dapsone	J04BA02	6.2.3
daunorubicin	L01DB02	8.2
deferoxamine	V03AC01	4.2
dexamethasone	H02AB02	3; 8.3
dextran 70*	B05AA05	11.1
diaphragms*	G02BB	18.3.4
diazepam	N05BA01	1.3; 5; 24.3
didanosine (ddI)	J05AF02	6.4.2.1
diethylcarbamazine	P02CB02	6.1.2
digoxin	C01AA05	12.2; 12.4
diloxanide	P01AC01	6.5.1
dimercaprol	V03AB09	4.2
diphtheria antitoxin	J06AA01	19.2
diphtheria-pertussis-tetanus vaccine*	J07AJ51	19.3
diphtheria-tetanus vaccine*	J07AM51	19.3
dithranol	D05AC01	13.5
DL-methionine*	V03AB26	4.2
dopamine	C01CA04	12.4
doxorubicin	L01DB01	8.2
doxycycline	J01AA02	6.2.2; 6.5.3.1; 6.5.3.2
efavirenz (EFV or EFZ)	J05AG03	6.4.2.2
efavirenz + emtricitabine + tenofovir	J05AR06	
eflornithine	P01CX03	6.5.5.1
emtricitabine	J05AF09	6.4.2.1
emtricitabine + tenofovir	J05AR03	
enalapril	C09AA02	12.3; 12.4
ephedrine	R03CA02	1.2
epinephrine	S01EA01	21.5
epinephrine (adrenaline)	C01CA24	3; 12.2; 25.1
ergocalciferol	A11CC01	27
ergometrine	G02AB03	22.1
erythromycin	J01FA01	6.2.2
ethambutol	J04AK02	6.2.4
ethanol	D08AX08	15.1
ethinylestradiol	G03CA01	18.4
ethinylestradiol + levonorgestrel*	G03AB03	18.3.1
ethinylestradiol + norethisterone*	G03AA05	18.3.1
ethionamide	J04AD03	6.2.4
ethosuximide	N03AD01	5
etoposide	L01CB01	8.2
factor IX complex (coagulation factors II, VII, IX, X) concentrate*	B02BD01	11.2

ATC group/medicine or item	ATC code	section
factor VIII concentrate*	B02BD02	11.2
ferrous salt*	B03A	10.1
ferrous salt + folic acid*	B03AD	10.1
fluconazole	J02AC01	6.3
flucytosine	J02AX01	6.3
fluorescein	S01JA01	14.1
fluorouracil	L01BC02	8.2; 13.5
fluoxetine	N06AB03	24.2.1
fluphenazine	N05AB02	24.1
folic acid	B03BB01	10.1
furosemide	C03CA01	12.4; 16
gentamicin	J01GB03	6.2.2
gentamicin	S01AA11	21.1
glibenclamide	A10BB01	18.5
glucose		26.2
glucose with sodium chloride*	B05BB02	26.2
glutaral	V07AV	15.2
glyceryl trinitrate	C01DA02	12.1
griseofulvin	D01BA01	6.3
haloperidol	N05AD01	24.1
halothane	N01AB01	1.1
heparin sodium*	B01AB01	10.2
hepatitis B vaccine	J07BC01	19.3
human normal immunoglobulin		11.2
hydrazaline	C02DB02	12.3
hydrochlorothiazide	C03AA03	12.3; 12.4; 16
hydrocortisone	A07EA02	17.3
hydrocortisone	D07AA02	13.3
hydrocortisone	H02AB09	3; 8.3
hydroxocobalamin	B03BA03	10.1
ibuprofen	M01AE01	2.1
imipenem + cilastatin*	J01DH51	6.2.1
indinavir (IDV)	J05AE02	6.4.2.3
influenza vaccine	J07BB	19.3
insulin injection (soluble)*	A10AB	18.5
insulin, intermediate-acting*	A10AC	18.5
intraperitoneal dialysis solution*	B05DA	23
iodine*	A12CX	27
iohexol	V08AB02	14.2
ipratropium bromide	R03BB01	25.1
isoniazid	J04AC01	6.2.4
isoniazid + ethambutol*	J04AM03	6.2.4
isosorbide dinitrate	C01DA08	12.1
ivermectin	P02CF01	6.1.2

ATC group/medicine or item	ATC code	section
kanamycin	J01GB04	6.2.4
ketamine	N01AX03	1.1
lamivudine (3TC)	J05AF05	6.4.2.1
levamisole	P02CE01	6.1.1
levodopa + carbidopa*	N04BA02	9
levofloxacin	J01MA12	6.2.4
levonorgestrel	G03AC03	18.3.1
levonorgestrel-releasing implant		18.3.5
levothyroxine*	H03AA01	18.8
lidocaine	C01BB01	12.2
lidocaine	N01BB02	1.2
lidocaine + epinephrine (adrenaline)*	N01BB52	1.2
lithium carbonate*	N05AN01	24.2.2
lopinavir + ritonavir (LPV/r)*	J05AE30	6.4.2.3
magnesium hydroxide	A02AA04	17.1
magnesium sulfate	B05XA05	5
mannitol	B05BC01	16
measles-mumps-rubella vaccine*	J07BD52	19.3
mebendazole	P02CA01	6.1.1
medroxyprogesterone acetate*	G03AC06	18.3.2; 18.7
medroxyprogesterone + estradiol cypionate	G03AA08	18.3.2
mefloquine	P01BC02	6.5.3.1; 6.5.3.2
meglumine antimoniate	P01CB01	6.5.2
meglumine iotroxate*	V08AC02	14.2
melarsoprol	P01CD01	6.5.5.1
meningococcal meningitis vaccine*	J07AH	19.3
mercaptopurine	L01BB02	8.2
metformin	A10BA02	18.5
methadone	N07BC02	24.5
methotrexate	L01BA01	2.4; 8.2
methyldopa*	C02AB01	12.3
methylrosanilinium chloride (gentian violet)*	D01AE02	13.2
methylthioninium chloride (methylene blue)	V03AB17	4.2
metoclopramide	A03FA01	17.2
metronidazole	J01XD01	6.2.2
metronidazole	P01AB01	6.5.1
miconazole	D01AC02	13.1
mifepristone	G03XB01	22.1
misoprostol	A02BB01	22.1
morphine	N02AA01	1.3; 2.2
naloxone	V03AB15	4.2
nelfinavir (NFV)	J05AE04	6.4.2.3
neomycin + bacitracin*	D06AX04	13.2
neostigmine	N07AA01	20
nevirapine (NVP)	J05AG01	6.4.2.2

ATC group/medicine or item	ATC code	section
niclosamide	P02DA01	6.1.1
nicotinamide	A11HA01	27
nifedipine	C08CA05	22.2
nifurtimox	P01CC01	6.5.5.2
nitrofurantoin	J01XE01	6.2.2
nitrous oxide	N01AX13	1.1
norethisterone	G03DC02	18.7
norethisterone enantate*	G03AC01	18.3.2
nystatin	A07AA02	6.3
nystatin	D01AA01	6.3
nystatin	G01AA01	6.3
ofloxacin	J01MA01	6.2.4
oral rehydration salts*	A07CA	17.5.1; 26.1
oxamniquine	P02BA02	6.1.3
oxygen	V03AN	1.1
oxytocin	H01BB02	22.1
p-aminosalicylic acid*	J04AA01	6.2.4
paracetamol	N02BE01	2.1; 7.1
paromomycin	A07AA06	6.5.2
penicillamine	M01CC01	2.4; 4.2
pentamidine*	P01CX01	6.5.2; 6.5.4; 6.5.5.1
permethrin	P03AC04	13.6
phenobarbital	N03AA02	5
phenoxymethylpenicillin	J01CE02	6.2.1
phenytoin	N03AB02	5
phytomenadione	B02BA01	10.2
pilocarpine	S01EB01	21.4
podophyllum resin*	D06BB04	13.5
poliomyelitis vaccine	J07BF	19.3
polygeline*	B05AA06	11.1
polyvidone iodine	D08AG02	15.1
potassium chloride	B05XA01	26.1; 26.2
potassium ferric hexacyanoferrate (II).2H_2O (Prussian blue)	V03AB31	4.2
potassium iodide*	H03CA	6.3; 18.8
potassium permanganate	D08AX06	13.2
praziquantel	P02BA01	6.1.1; 6.1.3
prednisolone	H02AB06	3; 8.3
prednisolone	S01BA04	21.2
primaquine	P01BA03	6.5.3.1
procainamide	C01BA02	12.2
procaine benzylpenicillin*	J01CE09	6.2.1
procarbazine	L01XB01	8.2
proguanil	P01BB01	6.5.3.2
promethazine	R06AD02	1.3; 17.2
propranolol	C07AA05	7.2

ATC group/medicine or item	ATC code	section
propylthiouracil	H03BA02	18.8
protamine sulfate*	V03AB14	10.2
pyrantel	P02CC01	6.1.1
pyrazinamide	J04AK01	6.2.4
pyridostigmine	N07AA02	20
pyridoxine	A11HA02	27
pyrimethamine	P01BD01	6.5.4
quinidine	C01BA01	12.2
quinine	P01BC01	6.5.3.1
rabies immunoglobulin	J06BB05	19.2
rabies vaccine	J07BG	19.3
ranitidine	A02BA02	17.1
retinol	A11CA01	27
ribavirin	J05AB04	6.4.3
riboflavin	A11HA04	27
rifampicin	J04AB02	6.2.3; 6.2.4
rifampicin + isoniazid*	J04AM02	6.2.4
rifampicin + isoniazid + ethambutol		6.2.4
rifampicin + isoniazid + pyrazinamide*	J04AM05	6.2.4
rifampicin + isoniazid + pyrazinamide + ethambutol*	J04AM06	6.2.4
ritonavir (r)	J05AE03	6.4.2.3
rubella vaccine	J07BJ	19.3
salbutamol	R03AC02	25.1
salbutamol	R03CC02	25.1
salicylic acid	D01AE12	13.5
saquinavir (SQV)	J05AE01	6.4.2.3
selenium sulfide	D01AE13	13.1
senna*	A06AB06	17.4
silver sulfadiazine	D06BA01	13.2
simvastatin	C01AA01	12.6
sodium calcium edetate*	V03AB03	4.2
sodium chloride	B05XA03	26.2
sodium fluoride	A12CD01	27
sodium hydrogen carbonate*	B05XA02	26.2
sodium lactate, compound solution*	B05BB01	26.2
sodium nitrite	V03AB08	4.2
sodium nitroprusside*	C02DD01	12.3
sodium thiosulfate*	V03AB06	4.2; 13.1
spectinomycin	J01XX04	6.2.2
spironolactone	C03DA01	16
stavudine (d4T)	J05AF04	6.4.2.1
stavudine + lamivudine + nevirapine		
streptokinase	B01AD01	12.5
streptomycin	J01GA01	6.2.4
sulfadiazine	J01EC02	6.2.2

ATC group/medicine or item	ATC code	section
sulfadoxine + pyrimethamine*	P01BD51	6.5.3.1
sulfamethoxazole + trimethoprim	J01EE01	6.2.2; 6.5.4
sulfasalazine	A07EC01	2.4; 17.3
suramin sodium	P01CX02	6.1.2; 6.5.5.1
suxamethonium	M03AB01	20
tamoxifen	L02BA01	8.3
tenofovir	J05AF07	6.4.2.1
testosterone	G03BA03	18.2
tetracaine	S01HA03	21.3
tetracycline	S01AA09	21.1
thiamine	A11DA01	27
thiopental	N01AF03	1.1
timolol	S01ED01	21.4
triclabendazole	P02BX04	6.1.3
trimethoprim	J01EA01	6.2.2
tropicamide	S01FA06	14.1
tuberculin, purified protein derivative (PPD)*	V04CF01	19.1
typhoid vaccine	J07AP	19.3
urea*	D02AE01	13.5
valproic acid	N03AG01	5; 24.2.2
vancomycin	J01XA01	6.2.2
vecuronium	M03AC03	20
verapamil	C08DA01	12.1; 12.2
vinblastine	L01CA01	8.2
vincristine	L01CA02	8.2
warfarin	B01AA03	10.2
water for injection*	V07AB	26.3
yellow fever vaccine	J07BL	19.3
zidovudine (ZDV or AZT)	J05AF01	6.4.2.1
zidovudine (ZDV or AZT) + lamivudine	J05AR01	
zidovudine + lamivudine + nevirapine	J05AR05	
zinc sulfate	A12CB01	17.5.2

* Medicine or item name differs slightly from the name used.

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Annex 5

Proposed procedure to update and disseminate the WHO Model List of Essential Medicines[1]

Document EB109/8 (Annex), 7 December 2001

WHO Expert Committee on the Use of Essential Drugs
Applications for inclusion, change or deletion
Review of applications and draft recommendations
Criteria for the selection of essential medicines
Presentation of recommendations, report of the Expert Committee
WHO Essential Medicines Library

WHO Expert Committee on the Use of Essential Drugs

1. The Model List is drawn up by the WHO Expert Committee on the Use of Essential Drugs, following the Regulations for Expert Advisory Panels and Committees.[2] Since 1977 the Expert Committee has been convened every two years, but could meet more often if needed.
2. The Expert Committee comprises eight to 12 members drawn from the WHO Expert Advisory Panels[3] for Drug Evaluation and for Drug Policies and Management, and, where appropriate and in consultation with the relevant department, from other expert advisory panels. Expert Committee members are selected by the Director-General to represent a wide range of geographical and professional backgrounds, including clinical pharmacology, clinical medicine, international public health, guideline development methodology, systematic literature search methods, risk-assessment and cost-effectiveness analysis.
3. Meetings of the Expert Committee are private and members are required to sign a confidentiality undertaking and complete a WHO declaration of interest form before the meeting. Observers may be invited in accordance with Regulations for Expert Advisory Panels and Committees to attend all or parts of the meetings of the Expert Committee. Patient advocacy groups and representatives of the health care industry are invited to comment on the applications and draft recommendations (see below),

[1] As part of the revised procedure for updating the Model List, the term "essential medicines" is used in preference to "essential drugs". This reflects the common use of the term "medicines" to describe pharmaceutical preparations used in clinical health care practice.
[2] *WHO Basic Documents*, 43rd ed., 2001, pp.101–109.
[3] Members of Expert Advisory Panels are proposed by WHO and, when approved by their respective government, appointed for one or more periods of up to four years.

but are not invited to attend decision-making parts of meetings of the Expert Committee.

Applications for inclusion, change or deletion

4. Applications for inclusions, changes or deletions to the Model List may be submitted to the Secretary of the Committee by relevant departments in WHO or by outside individuals or entities including, for example specialist societies, professional groups or pharmaceutical companies. If an application by an outside individual or entity has not been submitted through the relevant department in WHO, the opinion of the relevant department in WHO on any application will be obtained by the Secretary with the application and presented to the Expert Committee. The information that should be submitted with the application is summarized in Box 1. The application should be received at least four months before the meeting of the Expert Committee. Closing dates for each meeting are notified on the web site. For therapeutic categories for which no specific department exists in WHO the application can be submitted through the department of Medicines Policy and Standards. WHO must be free to make all clinical data that are cited in support of an application publicly available on the WHO web site; confidential data will not be accepted.

Box 1. Information to be included with an application for inclusion or deletion of a medicine in the WHO Model List of Essential Medicines

1. Summary statement of the proposal for inclusion, change or deletion
2. Name of the focal point in WHO submitting or supporting the application
3. Name of the organization(s) consulted and/or supporting the application, where relevant
4. International Nonproprietary Name (INN, generic name) of the medicine
5. Dosage form and strength proposed for listing; including adult and paediatric forms if appropriate
6. International availability – sources, if possible manufacturers
7. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)
8. Availability of pharmacopoieal standards (*British Pharmacopoeia, International Pharmacopoiea, United States Pharmacopeia*)
9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills)
10. Information supporting the public health relevance
11. Summary of effectiveness in a variety of clinical settings:
    - Identification of clinical evidence of effectiveness and comparative effectiveness (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)
    - Summary of available data (appraisal of quality, outcome measures, summary of results)
    - Summary of available estimates of comparative effectiveness
12. Summary of evidence on safety including:
    - Estimate of total patient exposure to date
    - Description of adverse effects/reactions
    - Identification of variation in safety due to health systems and patient factors
    - Summary of comparative safety against comparators
13. Summary of available data on comparative cost[1] and cost-effectiveness within the pharmacological class or therapeutic group:
    - range of costs of the proposed medicine
    - comparative cost-effectiveness presented as range of cost per routine outcome (e.g. cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or, if possible and relevant, cost per quality-adjusted life year gained)
14. Proposed (new/adapted) text for the *WHO Model Formulary*

[1] The information on cost and cost-effectiveness should preferably refer to average generic world market prices as listed in the *International Drug Price Indicator Guide*, an essential medicines pricing service provided by WHO and maintained by Management Sciences for Health. If this information is not available, other international sources, such as the WHO, UNICEF and Médecins sans Frontières price information service, can be used. All cost analyses should specify the source of the price information.

Review of applications and draft recommendations

5. The step-wise approach for reviewing applications and draft recommendations is summarized in Box 2. A similar process is used periodically to review whole sections of the Model List. In that case the need for review and the selection of the reviewer(s) are considered in close collaboration with the relevant department in WHO.

Box 2. Systematic review of applications

1. The secretary of the Expert Committee checks the application for completeness.
2. The application, with all supporting references, is posted on the WHO web site[1] for review and comments. Comments can be submitted by the general public (individuals and organizations) and these will be posted on the web site.
3. The application is evaluated by members of the Expert Committee and their reviews are posted on the web site. These reviews contains a draft recommendation for the Committee to consider and comments on the draft text for the *Model Formulary*.
4. Comments are provided by relevant WHO departments and are also posted on the web site for a minimum of 30 days.
5. The presenter (member of Expert Committee) reviews the comments and formulates a final text for consideration by the Expert Committee.
6. The Expert Committee reviews the application and all associated comments and provides a recommendation to the Director-General.

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

Criteria for selection[1]

6. The choice of essential medicines depends on several factors, including the disease burden and sound and adequate data on the efficacy, safety and comparative cost-effectiveness of available treatments. Stability in various conditions, the need for special diagnostic or treatment facilities and pharmacokinetic properties are also considered if appropriate. When adequate scientific evidence is not available on current treatment of a priority disease, the Expert Committee may either defer the issue until more evidence becomes available, or choose to make recommendations based on expert opinion and experience.

7. 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.

[1] Since the first meeting of the Expert Committee in 1977, criteria for selection of essential medicines have focused on disease prevalence, treatment facilities, safety, efficacy, quality, availability, and cost factors. Descriptions of selection criteria appear in the Ninth Report of the WHO Expert Committee on the Use of Essential Drugs (WHO Technical Report Series, No. 895, 2000), the Eighth Report of the WHO Expert Committee on the Use of Essential Drugs (WHO Technical Report Series, No. 882, 1998), and previous reports of the Committee.

8. In cost comparisons between medicines, the cost of the total treatment, and not only the unit cost of the medicine, is considered. Cost and cost-effectiveness comparisons may be made among alternative treatments within the same therapeutic group, but will generally not be made across therapeutic categories (for example, between treatment of tuberculosis and treatment of malaria). The absolute cost of the treatment will 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 in selecting medicines for the Model List.

9. In adapting the WHO Model List to national needs, countries often consider factors such as local demography and pattern of diseases; treatment facilities; training and experience of the available personnel; local availability of individual pharmaceutical products; financial resources; and environmental factors.

Presentation of recommendations, report of the Expert Committee

10. In its report, the Expert Committee summarizes the reasons for each recommendation with reference to the underlying evidence. The Expert Committee may grade its recommendations depending on the nature of the underlying evidence. When insufficient evidence is available, the Expert Committee specifies that its recommendations are based on expert judgment and experience. The Committee's report also refers to existing standard clinical guidelines. The Expert Committee may specifically indicate in the list medicines for which specialized health care facilities may be needed or which meet all the selection criteria and which are cost-effective within their therapeutic group, but which are not necessarily affordable for all health systems.

11. Presentation of the Model List will be recommended by the Expert Committee based on considerations of clarity and practicality. Previous model lists have been presented in various formats, including one in which medicines considered to be in the main list appear first under each therapeutic group, followed by medicines considered to be in a complementary list.

12. Immediately after the meeting and subject to final approval by the Director-General, the recommended changes to the Model List, the summary of the Expert Committee's report and other relevant information are posted on the WHO web site. The full report of the meeting is published in the WHO Technical Report Series. Translations of the report are published as soon as possible and in close collaboration with WHO regional offices.

WHO Essential Medicines Library

13. In addition to the information on whether a medicine is in the Model List or not, it is important for end-users to have access to information that supports the selection, such as summaries of relevant WHO clinical guidelines, the most important systematic reviews, important references and indicative cost information. Other information is also linked to the medicines in the Model List such as the WHO *Model Formulary* and information on nomenclature and quality-assurance standards. All this information is presented on the WHO web site as the "WHO Essential Medicines Library" and is intended to facilitate the work of national committees.

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Annex 6

Revised procedure for updating the content of the Interagency Emergency Health Kit

1. The Interagency Emergency Health Kit

1.1 Background

The agencies of the United Nations system and international and nongovernmental organizations are increasingly called upon to respond to large-scale emergencies, many of which pose a serious threat to health. Much of the assistance provided in such situations is in the form of medicines and medical devices (renewable and equipment).

During the 1980s, the World Health Organization (WHO) took up the question of how emergency response could be facilitated through effective emergency preparedness measures. The aim was to encourage the standardization of medicines and medical supplies needed in emergencies to permit a swift and effective response with medicines and medical devices using standard, pre-packed kits that could be kept in readiness to meet priority health needs in emergencies.

1.2 Introduction

The "WHO Emergency Health Kit" was the first such kit when it was launched in 1990. The second kit, "The New Emergency Health Kit 98" was the outcome of a process of revision and further harmonization by WHO in collaboration with many international and nongovernmental agencies. The third version of the kit, the "Interagency Emergency Health Kit 2006" (IEHK 2006), accommodates emergency care of AIDS, the increasing antimicrobial resistance to commonly available antimalarials and antibiotics, injection safety policy, and the experience of agencies using the emergency health kit in the field.

The content of the emergency health kit is based on the health needs of 10 000 people for a period of three months, the acute phase of an emergency. The kit is composed of ten basic units and one supplementary unit.

Over the years, the group of partners involved has grown from two in the early 1980s to more than 10 partners and suppliers in 2006.

1.2.1 *Key principles*

The key principles of the emergency health kit are:

- The kit is developed for a "worst-case scenario" where the health care system is no longer functioning and assumes the highest incidence of cases/morbidity.
- The kit is sent "blindly" to respond immediately to an emergency.
- The cost of the emergency health kit is not a criterion.
- The medicines and medical devices are selected on the basis of "keep it simple and avoid confusion" (e.g. no injectables are available in basic kits, so that they can be used by emergency staff with limited training).
- It is an enabling kit which means that when emergency staff are able to use the medicines and medical devices appropriately, they should do so, otherwise staff should not use them.

1.2.2 *Feedback*

Currently, there is no systematic feedback mechanism in place for the qualitative and quantitative monitoring of the appropriateness of the content of the emergency health kit. However, in the back of the IEHK 2006 booklet, a feedback form has been included to invite users to report on inadequacies in the content of the basic and supplementary kits, and the information provided in the kit booklet. The completed form can be faxed or the feedback can be sent by email to the IEHK Secretariat at WHO.

1.3 Current revision procedure

To date the revisions of the content of the emergency health kit were agreed by consensus by the collaborating agencies, but without any clear criteria. When necessary WHO/PSM as the IEHK Secretariat organized meetings with its partners, the IEHK Group: UNICEF, UNFPA, UNHCR, ICRC, IFRC, IOM, Médecins Sans Frontières, PSF, EPN, and Merlin. These ad-hoc meetings did not reach agreement on an official sign-off date in 2003, 2004 and 2005. Suppliers were informed about progress on the revision of the content of the IEHK.

The IEHK Group verifies whether the new content is in line with the recommendations of the WHO Model List of Essential Medicines, WHO standard treatment guidelines, specifications of medical devices defined by UNICEF, and best practices in emergencies. The content is signed off by all partners by them agreeing to the use of the logo of their respective agencies.

1.4 Need for a streamlined revision procedure

The revision of the content of the "New Emergency Health Kit 98" started in November 2002 and concluded with the endorsement of the content

of the Interagency Emergency Health Kit 2006 in February 2006. More details are provided in Box 1. One of the recommendations of the IEHK Group meeting held on 31 January 2006 was the need for a shorter, more streamlined and transparent revision procedure.

Box 1. The last update of the emergency health kit: a four-year period

The updating process started in November 2002 with a letter to all partners requesting their commitment to revising the content of the New Emergency Health Kit '98.

A proposed meeting on 16 October 2003 was postponed to 20 April 2004. During this meeting, categories of medicines and devices, including new antimalarials, post-exposure prophylaxis PEP kit and single-use syringes were reviewed. Two other meetings were held on 18 June and 25 August of that year. In July 2005, membership of the IEHK Secretariat changed due to retirement of the responsible WHO staff member. During September and December 2005, the Secretariat continued discussions by email to resolve the last outstanding issues. On 31 January 2006 an IEHK Group meeting was organized to resolve a pending issue. A web version of the IEHK 2006 booklet was posted on 28 April 2006. Printed versions of the booklet in English, French, and Spanish are in preparation.

The variations in emergencies and changing treatment regimens necessitate more frequent reviews of the content of the emergency health kit as a whole to better anticipate needs. Regular small changes to the content of the IEHK will be less problematic for the suppliers who distribute the emergency health kits.

The contents of the IEHK booklet also need to be reviewed to anticipate these regular updates.

1.5 Need for a responsive kit system

Kits developed by individual agencies for specific health conditions, such as cholera, malnutrition, reproductive health, and emergency surgical interventions, may be considered as possible complementary kits to the IEHK. This is part of the move towards a "flexible" emergency kit system.

In addition, the emerging need to develop responses to HIV and AIDS, tuberculosis and chronic conditions, such as diabetes, asthma and cardiovascular diseases can no longer be ignored in emergencies. People on long-term treatment cannot be excluded in the acute phase of emergencies.

The inclusion of formulations for children for priority diseases also needs to be considered.

The emergency health kit is a means of responding swiftly to the acute phase (first three months) of an emergency, but it is known that these kits are inappropriately used months and even years after the emergency started. As indicated in the information section of the IEHK 2006 booklet, the kit is **not** recommended for re-supplying existing health care facilities. Requirements

for further supplies should be assessed and medicines and medical devices ordered through the national supply system as soon as possible.

To respond to supply gaps for HIV, AIDS, tuberculosis, chronic conditions and emergency surgical interventions in disasters, it has been suggested that quantified lists should be developed, rather than kits to respond to acute needs.

2. Streamlined revision procedure to update the content of the IEHK

A similar procedure to the one for updating the Model List of Essential Medicines is envisaged, which will allow for wider consultation, and an evidence-based and therefore more efficient process.

2.1 Guiding principles for the new revision procedure

A new procedure for updating the IEHK will be based on major features of the revision procedure of the WHO Model List of Essential Medicines,[1] such as:

1. The *updated WHO Model List of Essential Medicines* and WHO standard treatment guidelines will be the baseline references for considering a proposed revision of the content of the IEHK. The term "essential medicines" will be used instead of "essential drugs", reflecting the common use of the term "medicines" to describe pharmaceutical preparations in clinical health care practice. Product availability is one of the criteria for inclusion of a medicine on the Model List and any comment on availability made by the Expert Committee will be taken into account.
2. A *systematic approach* will be adopted to manage proposals for the deletion, change to or inclusion of medicines and medical devices in the current IEHK.
3. A *transparent process* will be adopted for selecting and estimating medicines and medical devices to be included in the kit, including systematic analysis of effects and appropriateness of medicines and medical devices proposed for use in emergency care for different health conditions.
4. *Full involvement* of different WHO departments and other partner UN agencies and international organizations operating in emergencies will be pursued, especially during the application and review process, linking the process to clinical guidelines and essential emergency equipment

[1] WHO medicines strategy. Revised procedure for updating WHO's Model List of Essential Drugs. Report by the Secretariat. EB/109/8; 7 December 2001.

lists disseminated by WHO, medical devices specifications from UNICEF, and best practices in emergencies pursued by all departments and partners.

5. *Opportunities to react for interested parties*, including WHO's regional and country offices, relevant UN agencies, international organizations and nongovernmental organizations, will be offered with regard to both applications and draft recommendations prior to the meeting of the IEHK Review Committee. Applications and draft recommendations will be available on the WHO web site.

6. *The IEHK Review Committee* is composed of representatives of UN agencies, and international organizations and nongovernmental organizations operating in emergencies, who endorse the IEHK. Relevant WHO staff members will be invited to attend the IEHK Review Committee meeting as technical advisers.

7. *The Secretariat of the IEHK Review Committee* is the WHO Department of Medicines Policy and Standards (PSM).

8. *Membership of the IEHK Review Committee* is open to organizations which endorse the content of the IEHK and participate actively in the process of revision of the kit.

9. The list of items in the IEHK is a *core list* to which all agencies should adhere.

10. The *absolute cost of the treatment* will not constitute a reason to exclude a medicine and/or a device from the IEHK that otherwise meets the stated selection criteria.

11. The *patent status* of a medicine is not considered in selecting medicines for the IEHK.

2.2 Terms of reference of the IEHK Secretariat and Review Committee

2.2.1 *Terms of reference*

The IEHK Secretariat

The IEHK Secretariat is the WHO Department of Medicines Policy and Standards (PSM). It is responsible for instigating reviews of the content of the IEHK, developing and maintaining a specific web site, organizing meetings of the IEHK Review Committee, and collecting and sharing relevant information with IEHK partners and suppliers. The Secretariat will be responsible for the publication of the updated IEHK booklet in print and electronic versions.

The IEHK Review Committee

The IEHK Review Committee is composed of representatives of UN agencies, and representatives of technical organizations and nongovernmental organizations operating in emergencies, who endorse the IEHK. Relevant WHO staff members will be invited to attend the IEHK Review Committee meeting as technical advisers. The Committee is responsible for the regular updates of the content of the IEHK. It will guarantee adherence to the guiding principles and procedure for revision of the IEHK.

Individual Committee members will be involved in the review of applications and will draft recommendations. They will propose text for basic treatment protocols. Technical advisers may assist in the review process and contribute to consolidated recommendations.

2.2.2 *Commitment*

WHO/PSM is committed to being the Secretariat of the IEHK Review Committee. IEHK Review Committee members will represent their organization in the IEHK Review Committee for at least two years to guarantee continuity.

2.2.3 *Funding*

The Secretariat will guarantee sufficient funding for its tasks, including the publication of the IEHK booklet.

The individual members of the IEHK Review Committee will fund themselves for attendance at meetings and can allocate official time to review applications when requested.

2.3 Decision-making process by consensus

At the scheduled meeting of the IEHK Review Committee all prepared recommendations of the received applications, and relevant comments posted on the web will be reviewed. Discussion will focus on comparing efficacy, safety and suitability of products, and on reviewing the structure of the kit.

Final decisions will be made on the basis of consensus. In the case that consensus cannot be reached on a particular issue, it will be put on the agenda of the next Committee meeting and the item in the kit will not be changed.

2.4 Submission of applications for inclusion, change or deletion

Applications for inclusions, changes or deletions to the content of the IEHK are submitted by departments of WHO, other UN agencies, international organizations and nongovernmental organizations operating in emergencies, to the Secretariat of the IEHK Review Committee. The information that should be submitted with the application is summarized in Appendix 1.

The procedures for submitting and reviewing applications, for drafting recommendations and for the decision-making process for accepting or refusing recommendations are summarized in Appendix 2.

A similar process is used periodically to review the contents of the IEHK booklet. In that case the need for review and the selection of the reviewer(s) are considered in close collaboration with the IEHK Secretariat.

2.5 Principles for selection of essential medicines and medical devices

The choice of essential medicines and medical devices in emergencies depends on several sources of information, including:

— epidemiological data;
— population profiles;
— disease patterns; and
— assumptions based on experience gained by UN agencies and international organizations in emergency situations.

Factors that influence the selection of medicines and devices are:

- The most peripheral level of health care may be staffed by health care workers with limited medical training, who treat symptoms rather than diagnosed diseases using the basic units, and refer patients who need more specialized treatment to the next level of care.
- The proportion of patients presenting themselves with the more common symptoms or diseases can be predicted.
- The first referral level of health care is staffed by general doctors, experienced nurses, midwives or medical assistants, with no or limited facilities for inpatient care. They will use the supplementary unit in conjunction with one or more basic units.

The criteria for the selection of essential medicines and medical devices are as follows:

- Sound and adequate data should be available on the efficacy, safety and suitability of selected treatment regimens in the context of emergencies. WHO standard treatment guidelines and the WHO Model List of Essential Medicines are the references for the selection of medicines included in the kit.
- Stability in various conditions, the need for special diagnostic or treatment facilities and pharmacokinetic properties are also considered, if appropriate.
- Most selected medicines should be formulated as single compounds. Fixed-dose combination products are selected only when the combination has a proven advantage in therapeutic effect, safety or compliance over single compounds administered separately.

2.6 Estimation of quantities of medicines and medical devices

- Estimation of quantities of a medicine and a medical device in the kit is based on:
  - average morbidity patterns among displaced populations;
  - use of standard treatment guidelines;
  - figures and data provided by agencies with field experience.
- During emergencies, the estimate of the average number of visits for advice or treatment to such facilities by every individual is four times per year.
- Half of the population who will need assistance is under 15 years of age.
- The estimated rate of referral from the most peripheral to the next level of health care is 10%.
- Based on attendance estimates, the supplies included in one IEHK (10 basic units and 1 supplementary unit) serve the needs of a population of 10 000 people for a period of approximately 3 months.
- Each of the 10 **basic units** contains medicines, medical devices (renewable and equipment), for 1000 people for 3 months. The **supplementary unit** contains medicines, medical devices (renewable and equipment) to be used at the first referral level for 10 000 people for 3 months. To be operational, the supplementary unit should be used together with at least one basic unit.
- Estimation of need for medical devices will be complementary to estimation of need for medicines: e.g. estimation of the need for syringes is based on the number of injectable medicines included in the supplementary unit, which are to be used in accordance with the treatment guidelines provided.

2.7 Presentation of recommendations

In its meeting report, the IEHK Review Committee will summarize the reasons for each recommendation and make the reasons for its decisions explicit.

Immediately after the IEHK review meeting, the approved changes to the content of the kit and the meeting report will be posted on the WHO web site.

Appendix 1

Information to be included with an application for inclusion or change of a medicine or medical device in the IEHK

The following information should be included with an application for inclusion or change of a medicine or medical device in the IEHK:

1. Summary statement of the proposal for inclusion or change, in the context of an emergency situation.
2. Name of the responsible person and organization submitting the application.
3. Name of the organization(s) consulted and/or supporting the application.
4. Consequences for other items present in the kit (e.g. number of syringes for injectables);
5. Information requested for medicines:
   - International Nonproprietary Name (INN, generic name) of the medicine;
   - additional information on suitability for use in emergencies besides clinical information provided by the WHO Expert Committee on the Selection and Use of Essential Medicines;
   - information supporting the health emergency or public health relevance, including epidemiological information on disease burden and assessment of current use;
   - treatment details, including dosage regimen, duration; reference to existing WHO and other clinical guidelines; or treatment facilities;
   - quantities proposed, including information about the method used, if this is an application for a change or inclusion;
   - availability of suppliers, with summary of regulatory status of and quality information on the medicine.
6. Information requested for devices:
   - device name and short description from UNICEF or other suitable source;
   - for newly proposed devices, provide device name and full specifications;
   - information supporting the health emergency or public health relevance, including epidemiological information on disease burden and assessment of current use;
   - description of current use, including need for medical devices, special diagnostic or treatment facilities;
   - quantities proposed if this is an application for a change or inclusion;
   - consequences for other items present in the kit (e.g. number of syringes for injectables);
   - availability of supplier(s), with quality information.

Appendix 2

Information to be included with an application for deletion of a medicine or medical device from the IEHK

The following information should be included with an application for deletion of a medicine or medical device from the IEHK:

- summary statement of the proposal for deletion;
- name of the responsible person and organization submitting the application;
- name of the organization(s) consulted and/or supporting the application;
- consequences for other items present in the kit;
- information requested for medicines:
  - International Nonproprietary Name (INN, generic name) of the medicine;
  - information supporting the request for deletion;
- information requested for devices:
  - device name and short description from UNICEF, or other appropriate source;
  - information supporting the request for deletion.

Appendix 3

Procedures for the review of applications and for the development of recommendations

- The deadline for submitting an application will be five months prior to the meeting of the IEHK review committee for updating the content of the IEHK.
- The IEHK Secretariat will check submitted applications for completeness and verify with the relevant WHO department whether the proposed product is consistent with current standard treatment guidelines.
- Verified applications will be posted on the WHO web site for review and comments at least three months prior to the meeting; the closing date for comments will be one month prior to the meeting.
- Each verified application will be reviewed and recommendations drafted by two members of the IEHK review committee who will attend the meeting.
- The review(s), draft recommendation(s) and proposed text for the basic treatment protocol for inclusion in the IEHK booklet will be prepared by the relevant WHO departments and members of IEHK review committee. They will also be posted on the WHO web site for comments, for a minimum of 30 days.
- At the scheduled IEHK meeting, the IEHK review committee will discuss the application(s) and drafted recommendation(s) and proposed text for the basic treatment protocol, if appropriate and will finalize the recommendations for the IEHK.

SELECTED WHO PUBLICATIONS OF RELATED INTEREST

The international pharmacopoeia, fourth edition.
Volume 1: general notices; monographs for pharmaceutical substances (A–O)
Volume 2: monographs for pharmaceutical substances (P–Z); monographs for dosage forms and radiopharmaceutical preparations; methods of analysis; reagents.
2006 (1500 pages), also available in CD-ROM format

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: Good manufacturing practices and inspection.
2nd updated edition, 2007 (in press)

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

WHO Expert Committee on Specifications for Pharmaceutical Preparations
Forty-first report.
WHO Technical Report Series, No. 943, 2007 (156 pages)

International nonproprietary names (INN) for pharmaceutical substances. Cumulative list no. 11.
2004 (available in CD-ROM format only)

WHO Expert Committee on Biological Standardization
Fifty-fifth report.
WHO Technical Report Series, No. 932, 2006 (146 pages)

WHO model formulary
2006 (available in CD-ROM format only)

Further information on these and other WHO publications can be obtained from
WHO Press, World Health Organization, 1211 Geneva 27, Switzerland
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This report presents the recommendations of the WHO Expert Committee responsible for updating the WHO Model List of Essential Medicines. The first part contains a summary of the Committee's considerations and justifications for additions and changes to the Model List, including its recommendations. Annexes to the main report include the revised version of the WHO Model List of Essential Medicines (the 15th) and a list of all items on the Model List sorted according to their 5-level Anatomical Therapeutic Chemical (ATC) classification codes. Other annexes cover the proposed procedure for updating and disseminating the WHO Model List of Essential Medicines, and the revised procedure for updating the content of the Interagency Emergency Health Kit.

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