

# The Selection and Use of Essential Medicines

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Report of the WHO Expert Committee, 2013  
(including the 18th WHO Model List of Essential Medicines  
and the 4th WHO Model List of Essential Medicines for Children)



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## Executive summary

The 19th meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines took place in Geneva, Switzerland, from 8 to 12 April 2013. The report was approved by the Committee on 1 October 2013. The purpose of the meeting was to review and update the 17th WHO Model List of Essential Medicines (EML) and the 3rd WHO Model List of Essential Medicines for Children (EMLc). The Expert Committee members and temporary advisers who participated in the meeting are listed in the report, together with their declarations of interest.

In accordance with its approved procedures<sup>1</sup> the Expert Committee evaluated the scientific evidence on the comparative effectiveness, safety and cost-effectiveness of medicines to update the EML and the EMLc. The Expert Committee considered 52 applications and 15 reviews and:

- approved the addition of 17 new medicines to the EML (10 to the core list and seven to the complementary list);
- approved the deletion of one medicine from the EML;
- approved new indications for three medicines already listed on the EML;
- approved the addition of a new dosage form or strength for four medicines already on the EML;
- approved the moving of two medicines from the complementary list to the core list, and one from the core list to the complementary list;
- rejected nine applications for the addition of medicines to the EML and deferred a decision in the case of a further two applications;
- approved two medicines for neonatal care.

The following are some of the main recommendations in order of their appearance on the Model List.

Section 2. Analgesics, antipyretics, non-steroidal anti-inflammatory medicines (NSAIDs), medicines used to treat gout, and disease-modifying agents in rheumatoid disorders (DMARDs): The section was renamed “Medicines for pain and palliative care” to emphasize the importance of the medicines used in palliative care. The Expert Committee recognized the importance of palliative care not only in cancer but also in HIV/AIDS, multidrug-resistant tuberculosis and severe congenital diseases. Therefore it moved these medicines from Section 8 (Antineoplastic, immunosuppressives and medicines used in palliative

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<sup>1</sup> See: [http://www.who.int/selection\\_medicines/committees/subcommittee/2/eeb1098%5b1%5d.pdf](http://www.who.int/selection_medicines/committees/subcommittee/2/eeb1098%5b1%5d.pdf).

care) to Section 2 in both the EML and the EMLc. Medicines needed for the treatment of other common symptoms in palliative care – such as anorexia, nausea, constipation and diarrhoea – were also included in Section 2. A new section on “Medicines for diseases of joints” (Section 30) was created to list the treatments for gout and the disease-modifying agents used in rheumatoid disorders and juvenile joint diseases that were deleted from Section 2.

Section 6.4. Antiviral medicines: The Expert Committee considered the applications submitted for addition, deletion and modification of antiretrovirals and noted the ongoing work on *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach* scheduled for publication in June 2013. In consultation with the relevant departments in WHO, the Expert Committee decided to defer the applications until the guidelines had been published.

Section 6.4.3. Other antivirals: Pegylated interferon alpha (2a or 2b) was added for the treatment of hepatitis C (in combination with ribavirin), for obtaining a sustainable virological response. Although this combination is now being used with direct-acting antivirals in some countries, the Expert Committee noted the high level of expertise and specialized facilities needed for safe and effective use of interferons, as well as the high cost, and therefore included it in the complementary list.

In the same section, the Expert Committee considered the application for deletion of oseltamivir. The Expert Committee reviewed all the evidence available to it and decided to retain oseltamivir in the list, with only the restricted indication of treatment of potentially severe or complicated illness due to confirmed or suspected influenza virus infection, in accordance with WHO treatment guidelines.

Section 6.5.3.1. Antimalarial medicines, curative treatment: The Expert Committee added artesunate + mefloquine fixed-dose combination tablets for the treatment of malaria in adults and children in line with current WHO treatment guidelines. In making its decision, the Expert Committee noted that both medicines were listed separately in the EML and the EMLc, and that evaluation in clinical trials had shown similar comparative efficacy of the separate tablets and the combination. Some products containing the fixed-dose combination have been approved by the United Nations prequalification programme administered by WHO. With this addition, three of the five fixed-dose combinations recommended by WHO for the treatment of malaria are included in the core list.

Section 8.2. Cytotoxic and adjuvant medicines: After considering the applications for the addition of imatinib and trastuzumab, the Expert Committee decided that an urgent review of this subsection was needed, using a process and structure

similar to that used for the same section in the EMLc. This process would require identification in adults of the treatable tumours of public health relevance and identification of the medicines required to treat those tumours, within the context of a stepwise development of cancer care systems in the overall context of health system development. The Expert Committee considered the two applications in detail and noted the high quality of evidence showing relevant clinical benefits in support of both imatinib and trastuzumab but deferred the final specifications of the medicines and their inclusion until the review of the section of cytotoxics is completed.

Section 11. Blood products and plasma substitutes: After considering the application for the addition of whole blood and red blood cells, the Expert Committee decided to restructure this section. The heading was changed to “Blood products of human origin and plasma substitutes”. Subsection 11.1 was retitled “Blood and blood components” to include fresh–frozen plasma, red blood cells, platelets and whole blood. Subsection 11.2 was renamed “Plasma-derived medicinal products” with a Subsection 11.2.1 on “Human immunoglobulins” and a Subsection 11.2.2 on “Blood coagulation factors”. The title of Subsection 11.3 was changed to “Plasma substitutes”.

Section 21. Ophthalmological preparations: Bevacizumab injection was added to the complementary list in a new section of the EML (Section 21.6: Anti-vascular endothelial growth factor (VEGF) preparations). Neovascular age-related macular degeneration is a leading cause of blindness in persons over 50 years of age and bevacizumab has been shown to be effective with an acceptable risk profile. The Expert Committee recommended the addition of bevacizumab, while noting the precautions needed for intravitreal administration.

Section 22.1. Oxytocics: The application for deletion of misoprostol was based on interpretation of the data presented to the previous meeting of the Expert Committee. After considering the available evidence, the Expert Committee decided to retain misoprostol, restating that it was for the prevention of postpartum haemorrhage where oxytocin is not available or cannot be safely used.

Section 24.1. Medicines used in psychotic disorders: Risperidone was added to the core list as an alternative to chlorpromazine or haloperidol, and clozapine was added to the complementary list. The Expert Committee considered the application for risperidone and decided to list this second-generation antipsychotic on the basis of its efficacy, adverse effects, availability and cost. Clozapine was added to the complementary list for individuals with psychosis who do not respond to other antipsychotics, provided that laboratory facilities are available for regular monitoring of white blood cells.

Section 29. Specific medicines for neonatal care: Chlorhexidine 7.1% solution or gel delivering 4% was added to the core list for use in umbilical cord care in community settings. A new subsection (Section 29.2: Medicines administered to the mother) was added. Dexamethasone was included for accelerated fetal lung maturation in anticipated preterm birth; the efficacy of steroids for this condition had been conclusively demonstrated. While alternative steroids with similar efficacy were available, dexamethasone was considered the most appropriate product in terms of availability and cost.

Other medicines added were: loperamide, loratadine (for adults only in the context of palliative care), hyoscine butyl bromide, gliclazide (to replace glibenclamide), azithromycin eye drops, latanoprost eye drops and ofloxacin eye drops, which were added to the core list; and fomepizole, hydromorphone, oxycodone and protonamide which were added to the complementary list.

The Expert Committee deleted dithranol, which is used topically for the treatment of psoriasis. The adverse effects could be severe and, when compared with other treatments, the relative efficacy was poor.

The Expert Committee did not approve the following proposals for addition of medicines: colchicine, naproxen, bedaquiline, a fixed-dose combination of isoniazid + pyridoxine + sulfamethoxazole + trimethoprim (because there is currently no marketed product), a new formulation of ferrous salt + folic acid, a fixed-dose combination for secondary prevention of cardiovascular disease, ketorolac eye drops, ketotifen eye drops, and montelukast.

The Expert Committee also noted that, given the increasing number of applications, the limited time available at Expert Committee meetings and the need to coordinate with the development of WHO guidelines, more frequent meetings and alternative methods such as virtual meetings are required to respond in a timely manner to new clinical developments.

All applications and documents considered by the Expert Committee remain available on the WHO website for the meeting.<sup>2</sup>

Further information on the current EML (the 18th edition) and the EMLc (the 4th edition) can be found on the WHO website.<sup>3</sup>

<sup>2</sup> See: [http://www.who.int/selection\\_medicines/committees/expert/19](http://www.who.int/selection_medicines/committees/expert/19).

<sup>3</sup> See: <http://www.who.int/medicines/publications/essentialmedicines>.

# List of participants

## Members of the committee

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## Agencies

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Dr Clive Ondari, Coordinator, Medicine Access and Rational Use

Dr Krisantha Weerasuriya, Medicine Access and Rational Use, Secretary of the Expert Committee on the Selection and Use of Essential Medicines

Dr Elizabeth Mathai, Technical Officer, Medicine Access and Rational Use

Dr Simon Larkin, Volunteer, Medicine Access and Rational Use

Ms Monique Renevier, Web support, Medicine Access and Rational Use

Mrs Joanna McMahon, Administration, Medicine Access and Rational Use

## Declarations of interests

### Members reported the following interests

Dr Abdol Majid Cheraghali declared that he was currently a board member of the Iranian Blood Research and Fractionation company (IBRF) and received remuneration for this work. The IBRF is a state-owned company controlled by the Ministry of Health of the Islamic Republic of Iran. The company is responsible for logistic and operational aspects of plasma toll manufacturing for converting plasma produced in the Iranian national blood transfusion centre to plasma-derived medicines. It was decided that Dr Cheraghali would be allowed to take part in the discussion of applications relating to blood and blood products, but would not contribute to any decisions on these applications.

Dr Liliana de Lima declared being the Executive Director of the International Association for Hospice and Palliative Care. As this organization was an applicant in relation to the palliative care listings, Dr de Lima was recused from involvement in the consideration of these applications. Dr de Lima also disclosed her involvement in various WHO committees, including those dealing with ensuring balance in controlled substances policies and paediatric pain.

Mr Andrew Gray disclosed remunerated consultancies for UNAIDS and WHO relating to the preparation of a strategic report on development and cooperation in the pharmaceutical sectors in Brazil, the Russian Federation, India, China and South Africa (the BRICS countries), in relation to medicines for HIV/AIDS, tuberculosis and malaria and priority medicines for noncommunicable diseases, and the preparation of a systematic review and position paper on the interchangeability of lamivudine and emtricitabine. Mr Gray declared having received support from Fresenius Kabi and Pfizer for continuing education presentations unrelated to any specific products. He also disclosed that he was involved as a consultant pharmacist to the Centre for the AIDS Programme of Research in South Africa (CAPRISA), which was a site for National Institute of Health trials (AIDS Clinical Trials Group and International Maternal Pediatric Adolescent AIDS Clinical Trials Group networks). The networks received donated trial medication from various manufacturers, including Abbott, Boehringer Ingelheim, Bristol Myers Squibb, Gilead, GlaxoSmithKline, Merck Sharpe & Dohme, and Roche. In addition, he had been a co-investigator in a USAID and LifeLab-funded phase IIb clinical trial of a microbicide containing tenofovir (active ingredient supplied by Gilead, and packed by Conrad). Mr Gray further disclosed that he was a member of an expert committee of the South African Medicines Control Council.

Dr Suzanne Hill disclosed being a former staff member of WHO, and in that context having been the principal investigator of the Bill & Melinda Gates Foundation-funded Better Medicines for Children project, which had been completed. Dr Hill disclosed that she was chairperson of the Australian Pharmaceutical Benefit Advisory Committee, in which capacity she had made public statements on general issues related to medicines.



Dr Alar Irs disclosed being employed by the Estonian State Agency of Medicines and being a member of various scientific committees of the European Medicines Agency.

Apart from where specifically mentioned, none of these disclosures was considered material to the work of the Expert Committee and no actions were necessary in relation to the involvement of any of these members.

Professor Hany Abdel-Aleem, Professor Lisa Bero, Dr Youping Li, Professor Johannes Löwer, Dr Nicola Magrini and Dr Shalini Sri Ranganathan reported no conflicts of interest.

### **The temporary advisers present declared the following interests**

Dr Kuruvilla Prasad Mathews disclosed having previously been a member of a committee constituted by the Office of the Drug Controller General – New Drugs Division, New Delhi (part of the Indian Ministry of Health).

Dr Eva W. Njenga disclosed having received travel support from Eli Lilly and Novo Nordisk to attend conferences in 2011 and 2012.

Dr Le Van Truyen disclosed being the chairman of the Scientific Board of the Vietnam Institute of Dietary Supplements (VIDS).

Professor Gitanjali Batmanabane disclosed having previously worked for the Better Medicines for Children project in the WHO Regional Office for South-East Asia.

None of these disclosures was considered material to the work of the Expert Committee and no actions were necessary in relation to the involvement of any of these temporary advisers.

Dr Gilles Sama Kwende disclosed no potential conflicts of interest.

In addition, the Secretary of the Expert Committee, Dr Krisantha Weerasuriya, disclosed that he had been a member of the Scientific Advisory Committee of the Drugs for Neglected Diseases initiative (DNDi) since 2007. On the advice of the WHO Legal department, Dr Weerasuriya was recused from all discussion of any applications submitted by DNDi.



# 1. Introduction

The 19th meeting of the World Health Organization (WHO) Expert Committee on the Selection and Use of Essential Medicines was held from 8 to 12 March 2013, in Geneva, Switzerland.

The meeting was opened on behalf of the Director-General of WHO by Dr Marie-Paule Kieny, Assistant Director-General for Health Systems and Innovation. Dr Kieny welcomed the participants to the meeting and summarized the history of the WHO Model List of Essential Medicines (EML), beginning with the request of Member States in the 1970s for a list of “important medicines”. The Essential Medicines concept was elaborated in 1975 and the first WHO EML was developed by the first meeting of the Expert Committee on the Selection of Essential Medicines in 1977. At its second meeting the Expert Committee decided that its focus should be “the Selection and Use of Essential Medicines”, thus emphasizing that selection of medicines is by itself insufficient and that it should always be accompanied by consideration of the use of those medicines. The 19th meeting of the Expert Committee revised the 17th Model List of Essential Medicines, which would then become the 18th EML.

Dr Kieny highlighted three changes that had taken place since 1977. The first change was the evolution from an expert opinion-based process to an evidence-based one. Second, the EML had gone from a list that was selected from existing medicines to a list that also recommended specific indications and, where necessary, proposed what new formulations should be available on the basis of health-care needs. Third, the Expert Committee had progressed from a consultation of experts to a wider consultative process involving the global health community.

The wide spectrum of applications was highlighted, ranging from dexamethasone used since the 1970s for pregnant women at risk of preterm labour to improve the lung maturity in the unborn child to monoclonal antibodies for the treatment of cancer. The EML provided support for the Millennium Development Goals, especially in relation to the fourth goal (reducing child mortality rates), the fifth goal (improving maternal health) and the sixth goal (combating HIV, malaria and other diseases).

Dr Kieny noted that Expert Committee members are selected from panels of experts that are nominated from many organizations and governments. Expert Panel and Expert Committee members are required to provide advice as individuals, however, and may not take directions from any external organization or government. She thanked the members for their participation and expressed appreciation for their deliberations.

## 2. Open session

The open session of the meeting was chaired by Dr Marie-Paule Kiény, WHO Assistant Director-General for Health Systems and Innovation, on behalf of the Director-General, and was attended by several interested parties. Participants were welcomed by Mr Kees de Joncheere, Director of the Department of Essential Medicines and Health Products.

The Secretary of the Expert Committee, Dr Krisantha Weerasuriya, provided a brief update on activities since the last meeting of the Expert Committee. Dr Weerasuriya described the dissemination of the report of the 18th meeting of the Expert Committee, efforts to ensure access to priority life-saving medicines for women and children, the Better Medicines for Children Project and the WHO Model Formulary. Ms Hanne Bak Pedersen of the WHO Regional Office for Europe drew attention to the need for a similar process for the evidence-based selection of essential medical devices, including diagnostic tests. Dr Hill, a member of the Expert Committee, noted that all countries, including high-income countries, are facing significant challenges with new and expensive medicines. International efforts to ensure affordable prices for such products are urgently needed. Work in the area of public health, innovation and intellectual property has been ongoing for several years, but progress has been slow.

The following presentations, of relevance to the agenda of the Expert Committee, were made by interested parties:

- Dr Willem Scholten (Consultant, Medicines and Controlled Substances, Geneva, Switzerland) – “Messages on WHO essential medicines: pivotal for access to pain management”
- Professor Lukas Radbruch (Incoming Chair of the International Association for Hospice and Palliative Care, Houston, TX, USA; Director, Department of Palliative Medicine, University Hospital Bonn, Germany) – “Relieving suffering: essential medicines in palliative care”
- Dr Leslie Lehmann (Clinical Director, Pediatric Hematopoietic Stem Cell Transplant Program, Dana/Farber/Children’s Hospital Cancer Center, Boston; Assistant Professor of Pediatrics, Harvard Medical School, Boston, MA, USA) in collaboration with Ms Julie Torode (Deputy CEO, Union for International Cancer Control, Geneva, Switzerland) and Ms Mélanie Samsom (Global Advocacy Specialist, Union for International Cancer Control, Geneva, Switzerland) – “The case for support: addressing the needs of cancer patients worldwide in the WHO Model Essential Medicines List”

- Professor Tom Harrison and Professor Juan Luis Rodriguez Tudela (Global Action Fund for Fungal Infections, Geneva, Switzerland) - “Essential antifungals”
- Dr Harvey G. Klein (Department of Transfusion Medicine, Clinical Center, National Institutes of Health, Bethesda, MD, USA) – “Blood is an essential medicine”
- Dr Gilles Folléa (Executive Director, European Blood Alliance, Brussels, Belgium) – “Addition of whole blood and red blood cells on the WHO essential medicine lists: an assessment of pros and cons from the European Blood Alliance”
- Dr Che Kit Lin (Chief Executive and Medical Director, Hong Kong Red Cross Blood Transfusion Service, Hong Kong, China) – “Statement from international transfusion medicine experts”.

### 3. General items

#### 3.1 Defining public health relevance

WHO currently defines essential medicines as follows:

“Essential medicines are those that satisfy the priority health care needs of the population”.

Essential medicines are selected with due regard to their public health relevance, evidence of efficacy and safety, and comparative cost-effectiveness.

The public health relevance of a medicine has been variously described by previous Expert Committees meetings as including:

- the incidence and prevalence of the disease;
- the burden of disease, based on formal Global Burden of Disease estimates, disability-adjusted life-years or other evaluations;
- region-specific needs (e.g. medicines for visceral leishmaniasis are on the EML but this disease is prevalent in only two WHO regions);
- evidence of potential impact or high effectiveness (e.g. if a medicine is highly effective in relation to relevant outcomes – in terms of magnitude of effects or capacity to cure or control – for a particular condition, it has been more likely to be accepted as essential even if the target disease is relatively uncommon (e.g. recombinant surfactant in acute respiratory distress syndrome in infants);
- the potential political impact of identifying a medicine as essential for advocacy purposes.

The Expert Committee previously considered the question of drugs for orphan diseases in 2007. Although a proposal to add a separate list of drugs for rare diseases was debated at that time, the Expert Committee did not accept the proposal. Cost-effectiveness criteria were suggested as an alternative approach, but experience in high-income countries with “orphan drugs” suggested that total expenditure on very expensive medicines for very rare disorders can become unaffordable very rapidly.

To date the Expert Committee has not set rigid rules for defining when a proposal for a particular medicine satisfies the criterion of public health relevance. However, several applications before the 19th meeting were for conditions that challenged the Expert Committee’s interpretation of public health relevance. These included, but were not limited to, imatinib for chronic myeloid leukaemia and colchicine for familial Mediterranean fever.

A potentially useful consideration is described in the report by Kanavos et al. on value-based pricing (1). The authors note, with respect to antiretrovirals:

“HIV treatment is a special case, where, in the face of a new global pandemic affecting both rich and poor populations, new products were priced at levels affordable in the context of rich world health care delivery (i.e. to include R&D costs and/or investment returns sufficient to justify continuing highly risked research expenditures). As was obvious from a very early stage in the pandemic, these were unaffordable in the areas of greatest need. Hence special intervention before the normal processes of patent expiry and mass commodity level production had occurred was required, leading to considerable controversy.”

Arguably, adding a medicine to the WHO EML might precipitate a “special intervention” before the normal processes of patent expiry and could be used as an advocacy tool to reduce the price of the medicine. This would be an additional consideration regarding the public health relevance of the medicine.

As in its previous meetings, the Expert Committee relied on a case-by-case consideration of public health relevance and potential health impact in evaluating applications for inclusion in the EML. The Expert Committee confirmed that it would need to be convinced in each case primarily on the basis of the incidence and prevalence of the disease being addressed (even if limited to a single geographical region) and evidence of the burden of disease, and that it would also take into account the value represented in terms of effectiveness, as well as the potential for advocacy purposes. The Expert Committee decided that any simple, mechanical cut-off point based on any one of these considerations would not be consistent with its established principles.

### 3.2 Medicines information as a global public good

Since the start of effective regulation of medicines in the early 1960s, the usual system for licensing a new medicine has been for a sponsor of a product to nominate an indication for use, and for this indication or claim to become the basis for a review by regulatory authorities. Over time, additional indications may develop and be proposed for licensing – or not – on the basis of commercial and clinical considerations. Once a product is off-patent, however, the original sponsor’s responsibility for keeping the indications consistent with clinical evidence and medical practice seems to end. Safety-related changes to product documentation may occur in some systems but generally the product-specific information document is no longer adequately maintained. Ensuring correct and updated information on a medicine is not only a regulatory issue but is also relevant to the medicine’s rational and appropriate use.

Some commercial or not-for-profit drug information sources – such as the British National Formulary or Micromedex (a commercial drug information source) – may provide information on the newer, unapproved indications, contraindications and adverse effects. However, the information that is published

by these organizations does not have the same legal and regulatory basis as a product information sheet supported by a manufacturer or product sponsor.

Examples of medicines for which the original information is now obsolete include cytotoxics such as dacarbazine (in some countries contraindicated in the Summary of Product Characteristics (SPC) for Hodgkin lymphoma, for which it is a standard of care), methotrexate (used for multiple autoimmune and inflammatory disorders), and changed indications for anti-inflammatory drugs such as colchicine. In relation to medicines for children, indications and dosing regimens are often off-label, although increasingly there is evidence to support some uses (e.g. first-line drugs for tuberculosis) or doses.

The difficulty at national level is to determine who should take responsibility for maintaining “old” product SPCs. Depending on the national legislation relating to the supply of medicines, the production of new labelling may also require assuming legal liability. Given that the majority of medicine regulatory authorities now depend on application fees from industry to support their activities, the resources available to noncommercial entities to update such documents are nearly always scarce. While the capacity to prepare such a dossier may exist in many pharmaceutical companies, such resources may not be available to an academic group acting in the public interest.

The Expert Committee considered the potential role of WHO in supporting countries in maintaining up-to-date product information documents. One option could be to use the WHO Essential Medicines process to identify essential medicines for which the product information documents do not reflect the most recent clinical evidence and clinical practice. By working globally it might be possible to organize collaboration with groups such as the Cochrane Collaboration to summarize the clinical evidence and make it generally available. Although there would still need to be national processes in place to manage the legal requirements, a global approach to maintaining information about a medicine could be seen as a global public health good. Such documents could be particularly useful for drug regulatory authorities in low- and middle-income countries.

The Expert Committee noted that it had previously considered evidence of efficacy and safety and demonstrable public health importance as the main criteria for inclusion in the EML, rather than the indications having been approved by regulatory authorities in national settings (e.g. ribavirin for haemorrhagic fever). The Expert Committee noted that the inclusion of indications in regulatory documents (such as the label or SPC) was nearly always based on the request of the sponsor/applicant. The Expert Committee was therefore in favour of an expanded role for WHO in ensuring that indications for which evidence exists are recognized in product information documents. The Expert Committee recommended that this issue be raised with the International Conference of Drug Regulatory Authorities (ICDRA).

### 3.3 Other

The Expert Committee encouraged the Secretariat to evaluate different options for convening the Committee and for modifying the Committee processes for updating the EML. The Expert Committee noted the necessity for more frequent meetings, making use of facilities such as video-conferencing and teleconferencing. The Expert Committee also noted the large number of applications to be considered at its 19th meeting and suggested that the Secretariat should consider whether there is a maximum number of applications that it is feasible to consider in a single meeting.

The Expert Committee recalled the decision made at the 17th meeting with respect to applications for medicines for children, namely: “In its report, the Subcommittee concluded that it had satisfied its terms of reference and recommended, in principle, that the Subcommittee be dissolved. The Expert Committee agreed and made the recommendation to the Executive Board and the Director-General that the Subcommittee had fulfilled its terms of reference regarding the development and revision of the WHO Model List of Essential Medicines for Children and should now be dissolved. Future Expert Committees should, however, include adequate expertise to consider medicines for children and maintain the EMLc.”

The Expert Committee noted that the numbers of applications for adult and paediatric medicines considered at the 19th meeting were almost equal, but that the composition of the Committee did not reflect this distribution. It was felt that there is a need to ensure adequate expertise when convening future Expert Committees. A possible alternative would be to re-establish the Subcommittee as part of an overall reform of the working methods of the Expert Committee.

The Expert Committee also drew attention to another comment from the report of the 17th meeting: “The Committee recognized the importance of coordinating the maintenance and further development of the two lists, for example, by requiring that use in children and adults be considered in every application for inclusion in the Model List. If the applicant leaves either aspect out, the Secretariat should request this omission to be addressed by the applicant or other party as appropriate.” It was felt that the applications submitted to the 19th meeting did not uniformly consider adult and child indications when relevant.

## 4. Applications only for paediatric medicines

### Section 1: Anaesthetics

#### *Anaesthetics (review) – Children*

The 18th meeting of the Expert Committee posed the question: “What anaesthetics can be safely used in neonates?” A review on this topic, limited to general anaesthetics, was prepared by Dr Elizabeth Zisovska, Skopje, the former Yugoslav Republic of Macedonia.

Expert reviews were provided by Dr Gitanjali Batmanabane and Dr Gilles Sama Kwende.

Several studies in immature animal models were reviewed and there was some evidence of degenerative effects of several anaesthetics on neuronal structure. However, the relevance of these effects to neonates was not clear (2, 3). It was noted that many general anaesthetics are not licensed for children, and especially neonates. The reasons for this are complex but may be related to the lack of data on safety or toxicity in children, again especially in neonates.

There are physiological and pharmacological differences between neonates and children as well as between children and adults, which have been partially reflected in modifications of dose (4). In neonates there is good evidence that inadequate pain relief is associated with negative short-term and long-term effects. Neonatal boys who were circumcised without analgesia had a more pronounced pain reaction to later immunization injections compared with those who had received active analgesia with a mixture of lidocaine and prilocaine (5, 6). Hence adequate pain relief and anaesthesia appear to be important for the neonate.

The goals of anaesthesia in neonates are largely the same as in adults and children (7), namely:

- minimization of physiological, humoral and behavioural signs of distress;
- reduction of pain;
- ablation of consciousness;
- maximization of perioperative outcomes.

The major issue is lack of appropriate studies – and therefore lack of evidence – in neonates. This is a common problem with medicines for children. Hence any extrapolation from adult data needs to be reviewed when data from neonates become available.

The review proposed:

- Halothane should not be the preferred inhalational anaesthetic in neonates, and an age restriction of above 1 month should be included in the listing.



- Isoflurane is safe in neonates for induction and maintenance and should therefore be retained in the WHO Model List of Essential Medicines for Children (EMLc).
- Nitrous oxide and oxygen should both be retained in the EMLc.
- Ketamine should be retained in the EMLc, although a paediatric formulation would be useful to improve safety during administration.
- The use of propofol should be restricted to patients aged over 1 month.
- Thiopental should be added to the EMLc as it is licensed for use in neonates.

Having considered the review, the Expert Committee recommended no additions to the list but agreed to add clarifications on age restrictions where these have been specified by regulatory authorities. Propofol was approved for induction but not for maintenance in neonates. Since thiopental is licensed for use in neonates, this fact should be mentioned in the list. The Expert Committee noted the declining use of halothane but felt that, in the absence of alternatives, it remains an accessible option in some settings.

## **Section 2: Non-steroidal anti-inflammatory medicines (NSAIDs) and medicines used to treat gout and disease-modifying agents in rheumatoid disorders (DMARDs)**

### **2.2: Opioid analgesics**

*Hydromorphone (addition) – Children*

*Oxycodone (addition) – Children*

Two applications were submitted by Dr Willem Scholten, former team leader (until 31 October 2012), Access to Controlled Medicines, WHO. The first application was for the addition of hydromorphone and oxycodone, as examples of the opioid class, to the EMLc.

Expert reviews were provided by Dr Gitanjali Batmanabane and Dr Le Van Truyen.

These two applications were based on recommendations in the WHO *Guidelines on the pharmacological treatment of persisting pain in children with medical illnesses*, published in 2012, and the WHO policy guidelines *Ensuring balance in national policies on controlled substances: guidance for availability and accessibility of controlled medicines* (8, 9). The listing was requested as a footnote to the square box appended to the morphine listing, which would read as “Examples for alternative opioids for morphine. Two or more alternatives should be available in addition to morphine.”

The WHO documents advise that two or more opioids should be made available to allow switching of opioids and/or route of administration in children in the presence of inadequate analgesic effect and/or intolerable side-effects. However, the application itself stated that there is a need for comparative trials of opioids in terms of effectiveness, adverse effects and feasibility of use in children with persistent pain due to medical illnesses. No evidence was provided on specific subsets of patients responding to a second opioid when there has been no response to the first. There was also no estimate of the proportion of children who might have a poor response to morphine. The bulk of the evidence presented in relation to both the hydromorphone and oxycodone applications dealt with acute pain in children.

There is high availability of oxycodone (though less of hydromorphone) in high-income countries, with multiple formulations being marketed. However, no listing was provided of the formulations that are available in low- and middle-income countries.

The Expert Committee recommended that a square box symbol be added to the listing for morphine, with a note that alternatives would be limited to hydromorphone and oxycodone.

### *Morphine (new formulation) – Children*

The second application submitted by Dr Willem Scholten, team leader (until 31 October 2012), Access to Controlled Medicines, WHO, was for the addition of morphine granules and tablets (both slow-release) to the EMLc. The application also requested that the terminology be standardized as slow-release and requested that dosage and formulae for morphine oral solution should be published as an annex to the published meeting report in the WHO Technical Report Series.

Expert reviews were provided by Dr Abdol Majid Cheraghali and Dr Le Van Truyen.

The WHO *Guidelines on the pharmacological treatment of persisting pain in children with medical illnesses* recommend morphine as the first-line strong opioid treatment for persisting moderate to severe pain (8). The application stated that insufficient formulations and strengths of morphine were available to treat pain in paediatric groups ranging from infants to children of 12 years of age. Therefore, it was proposed that slow-release granules, which would allow morphine to be administered as liquid in very small doses for infants, should be added to the EMLc. The advantage of slow-release morphine is longer dose intervals, which could improve patient compliance by decreasing dose frequency. Additional points relate to the inter-individual variation in the response to morphine and the need for titration for pain relief. As there is no upper dosage limit for opioid analgesics, the application also noted the need for high-end strengths of morphine to be added to the EMLc.

The Expert Committee noted that the available studies that support the use of oral morphine in cancer have been conducted in adults. Thus there is a need for comparative trials of opioids in terms of effectiveness, side-effects and feasibility of use in children with persisting pain due to medical illness.

The Expert Committee noted requests that the standard term “slow-release” should be used rather than “controlled-release”, “modified-release” and “prolonged-release” and recommended that this term be implemented in the EMLc section on morphine. However, it was felt that use of the same approach in other sections would require a review of the applicability of this terminology for the full range of preparations in all therapeutic areas.

The Expert Committee recommended the addition of morphine granules and slow-release tablets to the EMLc and noted the dosage recommendations in the WHO guidelines (8) and in the formulas for morphine oral solution included in the highlights for pharmacists in *Persisting pain in children*, published in 2012 (8).

## Section 6: Anti-infective medicines

### 6.2: Antibacterials

#### 6.2.4: Antituberculosis medicines

##### *Second-line antituberculosis medicines (review) – Children*

An application to review second-line antituberculosis medicines was prepared by staff of the Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, South Africa.

Expert reviews were prepared by Dr Lisa Bero and Dr Gitanjali Batmanabane. Comments were received from Médecins Sans Frontières (MSF).

Assuming that 10–15% of the disease burden is in children, a conservative estimate of 63 000 prevalent cases of multidrug-resistant tuberculosis (MDR-TB) per year in children can be made. Possibly due to challenges in confirming the diagnosis in younger ages, lack of awareness of the disease, limited experience in its management, and lack of access to child-friendly or otherwise adequate drugs, few children are being diagnosed and treated for MDR-TB and there is a paucity of published experience on paediatric MDR-TB.

WHO categorizes the antituberculosis drugs in five groups (10, 11). Group 1 is “First-line oral agents” (e.g. isoniazid, rifampicin), Group 2 is “Injectable agents” (e.g. kanamycin, amikacin), Group 3 is “Fluoroquinolones”, Group 4 is “Oral bacteriostatic second-line agents” (e.g. ethionamide, cycloserine) and Group 5 is “Agents with unclear efficacy or concerns regarding usage” (e.g. clofazimine, linezolid). WHO guidelines recommend including a second-line injectable agent from Group 2 and a fluoroquinolone from Group 3, with additional drugs from Groups 4 and 5 to create a treatment regimen with at

least 4–5 active drugs (10). These guidelines are generally consistent with those recommended by other organizations (12).

The Expert Committee noted that the evaluation of the efficacy of antituberculosis drugs has generally relied on microbiological, and not clinical, end-points. Due to differences in the pathophysiology of tuberculosis in children – especially the paucibacillary nature of the majority of paediatric disease – and difficulties with obtaining sputum specimens, the evaluation of microbiological end-points in children is challenging. Evidence to inform the selection of agents for treating MDR-TB (defined as disease caused by *Mycobacterium tuberculosis* resistant to at least rifampicin and isoniazid) in children is essentially limited to outcome data from treatment cohorts and these confirm the efficacy of the medicines in Groups 2–4.

The efficacy of ofloxacin, levofloxacin, and moxifloxacin against MDR-TB has been extensively evaluated in vitro, in both animals and humans. Although multiple systematic reviews did not identify any randomized trials in MDR-TB, they synthesized the data from many observational studies. A recent individual patient data (IPD) meta-analysis used reports identified in these systematic reviews to provide a more detailed analysis (13). This review included data from 9153 patients drawn from 32 observational cohorts, and reported improved treatment success with the use of a later-generation fluoroquinolone (FLQ) versus no FLQ (adjusted odds ratio, aOR: 2.8; 95% confidence interval, CI: 1.3–6.1) and versus ofloxacin (aOR: 2.1, 95% CI: 1.2–3.9), and with the use of ofloxacin versus no FLQ (aOR: 2.0, 95% CI: 1.2–3.3). In a retrospective observational study comparing ofloxacin and levofloxacin for MDR-TB treatment in adults, levofloxacin was more efficacious, with increased treatment success in ofloxacin-susceptible isolates (96.2% for levofloxacin versus 87.5% for ofloxacin) and in ofloxacin-resistant isolates (78.6% for levofloxacin versus 45.5% for ofloxacin) (14). A systematic review of adults with extensively drug-resistant tuberculosis (XDR-TB) reported that use of later-generation FLQs was associated with improved outcomes (15).

In a systematic review of children treated for MDR-TB, FLQs were an important component of the treatment regimen in all included studies, which had a pooled treatment success of 81.7% (16). More recently, in a cohort of children with MDR-TB in which an FLQ was a key component of the treatment regimen, 137 of 149 (92%) achieved a cure or probable cure (17).

The FLQs are generally well tolerated by adults receiving the prolonged treatment required for MDR-TB. Data on extended administration of FLQs to children have not demonstrated serious adverse effects. Despite a lack of randomized trials of the FLQs in the treatment of MDR-TB in adults or children, their strong bactericidal and sterilizing activity, favourable pharmacokinetics and toxicity profile have made them an important component of existing MDR-TB treatment regimens. WHO's *Rapid advice: treatment of tuberculosis in children*,

published in 2010, makes a strong recommendation for the use of FLQs in the treatment of drug-resistant TB but did not specify which of the FLQs are preferred in children (18). Additional data are needed with regard to paediatric dosing of the FLQs in MDR-TB, particularly in the case of levofloxacin and moxifloxacin. Pharmacokinetic data to inform the most appropriate dosing in children are urgently needed and are likely to be forthcoming from ongoing studies. Existing formulations of these drugs are difficult to dose appropriately and to administer to children.

All three injectable medicines – kanamycin, amikacin and capreomycin – are currently included in the EMLc. There are few data on use in children although, in a subgroup analysis in a systematic review of paediatric MDR-TB, treatment success was higher in studies in which patients received injectables compared with studies where they were not commonly used (87.2% versus 62.6%,  $P = 0.02$ ) (16).

Ethionamide (ETH) is already included in the EMLc. ETH and prothionamide (PTH) have shown bactericidal activity in vitro against *M. tuberculosis*, with PTH minimum inhibitory concentrations usually reported as either equal to or half that of ETH. In a trial in adults that compared ETH 500 mg in two divided doses with PTH 500 mg in two divided doses, in combination with isoniazid and streptomycin, there was no difference in treatment efficacy, with 98% and 96% of patients respectively having negative cultures at six months (19). In an IPD meta-analysis of 9153 patients with MDR-TB, the use of ETH or PTH was associated with increased odds of treatment success versus failure or relapse (aOR: 1.7, 95% CI: 1.3–2.3) and versus failure, relapse or death (aOR: 1.7, 95% CI: 1.4–2.1) (13). ETH was a component of the usual treatment regimens in all the cohorts included in a recent systematic review of children with MDR-TB, which reported a pooled treatment success of 81.7% (16). There is expected to be complete cross-resistance between ETH and PTH.

Cycloserine is already included in the EMLc. There are questions about the efficacy of cycloserine, and neurotoxicity is an important adverse event in the treatment of MDR-TB in adults (20). Published paediatric experience consists of two small series in the 1960s which described the use of cycloserine in combination with isoniazid in the treatment of 29 children and which reported generally good outcomes and few adverse effects (21, 22). Because of the limited choices available for treatment, cycloserine remains an important option in the treatment of MDR-TB.

There is very little English-language literature on the use of terizidone (TZD) for tuberculosis. In combination with other drugs, TZD at a dose of 250 mg three times daily was shown to be well tolerated and effective for the treatment of urogenital tuberculosis in 51 adults (23).

Para-aminosalicylic acid (PAS) is already included in the EMLc. Although not a potent drug, its efficacy against *M. tuberculosis* has been well established

in adults, particularly in protecting companion drugs against resistance. On the basis of existing data, experience and recommendations, many children with MDR-TB will be successfully treated without PAS, although for children with additional drug resistance, including pre-XDR or XDR-TB, drug options are much more limited and PAS will be an important component of treatment regimens in that context.

The *in vitro* activity of linezolid against *M. tuberculosis* has been consistently demonstrated. Emerging data in adults and children have also shown it to be effective in difficult cases of drug-resistant tuberculosis, with good long-term outcomes. Two systematic reviews in 2012 reported on the safety and efficacy of linezolid for the treatment of drug-resistant tuberculosis in adults. The first included 11 studies representing 148 patients (24). The pooled percentage of patients with treatment success was 67.9% (95% CI: 58–79%). The second review included 207 patients in 12 studies, of which many but not all were the same studies as those of the first review (25). Of 121 patients with definite treatment outcomes, 82% (95% CI: 74–88%) had successful treatment outcomes, with 93% (95% CI: 86–97%) having sputum smear conversion and 93% (95% CI: 87–97%) having culture conversion. Two more recent cohorts have reported similar findings (26, 27). All 16 children on linezolid had culture conversion, most within 1–3 months, and 14 of 16 (87.5%) had a successful long-term outcome, with one lost to follow-up and one death (respiratory failure, culture-negative at the time of death). There are no formal recommendations for paediatric dosing of linezolid for MDR-TB. Because of the high cost, toxicity and good clinical outcomes with existing treatment regimens for children with MDR-TB, routine use of linezolid is not supported.

Clofazimine – with its pharmacological characteristics, ability to concentrate in macrophages, potential sterilizing activity, lack of cross-resistance with other agents and apparent inability to foster resistance – is a potentially attractive option for treatment of drug-resistant tuberculosis. In one study in adults, a four-month intensive phase containing kanamycin, gatifloxacin, clofazimine, ethambutol, high-dose isoniazid, pyrazinamide and protionamide, followed by a five-month continuation phase containing gatifloxacin, ethambutol, pyrazinamide and clofazimine, resulted in 87.8% cure with only 0.5% relapsing (28). Additional support for clofazimine includes the report of a cohort of adults with XDR-TB in which more than 60% of patients had a successful treatment outcome with a clofazimine-containing regimen (29). The WHO 2008 guidelines (11) recommend the use of Group 5 drugs, of which clofazimine is one, only when a regimen containing four drugs with likely activity cannot be created from Groups 1–4. No other specific recommendation regarding clofazimine is made.

On the basis of WHO guideline recommendations, public health needs and available evidence on efficacy and safety, the Expert Committee recommended the following changes to update the complementary list in the EMLc:

- Ofloxacin should be replaced by levofloxacin, with an asterisk note to indicate that ofloxacin and moxifloxacin may be used as alternatives.
- Ethionamide should be retained, but with an asterisk note to indicate that prothionamide may be used as an alternative.

The Expert Committee noted that child-friendly formulations are urgently needed for some of the second-line antituberculosis medicines to improve dosing and adherence.

No other changes were made as there were insufficient data to justify the inclusion of clofazimine or linezolid. Cycloserine would also be retained, without mention of terizidone. No changes were made to the existing listings on amikacin, capreomycin, kanamycin and para-aminosalicylic acid.

### *Streptomycin injections (to be moved to the complementary list) – Children*

An application to move streptomycin to the complementary list for children was prepared by the Stop TB Department, WHO.

Expert reviews were prepared by Dr Lisa Bero and Dr Gitanjali Batmanabane. Comments were received from Médecins Sans Frontières.

Overall, evidence for the efficacy of streptomycin for the treatment of tuberculosis in children is lacking. There is toxicity (ototoxicity and nephrotoxicity) associated with all aminoglycosides. In addition, streptomycin can be administered only by injection.

According to WHO's *Rapid advice: treatment of tuberculosis in children (18)*, streptomycin should not be used as part of first-line treatment regimens for children with pulmonary tuberculosis or tuberculous peripheral lymphadenitis. Streptomycin use is reserved for those with MDR-TB with known susceptibility to this medicine.

The Expert Committee accordingly decided to place streptomycin in the complementary list of the EMLc. Its use for MDR-TB will require specialist care and facilities.

## **6.4: Antiviral medicines**

### **6.4.2: Antiretrovirals**

*Abacavir (new formulation); Abacavir + lamivudine (addition); Efavirenz (new formulation); Lamivudine + nevirapine + zidovudine (new formulation); Lamivudine + stavudine (new formulation); Lamivudine + zidovudine (new formulation); Nevirapine (new formulation)*

Applications for additions and changes in formulations to update both the EML and EMLc were submitted by the Clinton Health Access Initiative, with the support of the HIV Department of WHO. At the time of the meeting, the current WHO guidelines for the treatment of both adults and children living with HIV/AIDS were those issued in 2010 (30).



Expert reviews were prepared by Dr Eva Njenga and Dr Liliana de Lima.

The Expert Committee received a progress report on the updating of the guidelines, which were expected to be completed by mid-2013. The Committee noted that proposals originally submitted in the application were subsequently amended by the HIV Department, reflecting ongoing work on the 2013 guidelines. However, as these guidelines (for both adults and children) were as yet incomplete, and had yet to be approved by WHO's Guidelines Review Committee, the Expert Committee was reluctant to make any changes to the EML at this point.

Instead, the Expert Committee recommended that there should be an extraordinary meeting (possibly electronically) to consider a limited list of applications, specifically to align the EML with the expected 2013 WHO guidelines, before the planned Committee meeting in 2015. Nonetheless, the Expert Committee underscored the established principle that the mention of a medicine in an approved WHO guideline did not automatically guarantee its inclusion in the EML. Each such application would still be considered on its own merits and in accordance with the principles that inform the selection of essential medicines.

## 6.5: Antiprotozoal medicines

### 6.5.5: Antitrypanosomal medicines

#### 6.5.5.1: *African trypanosomiasis*

##### *Nifurtimox tablets (addition) – Children*

An application for the addition of nifurtimox tablets to the EMLc was submitted by the Drugs for Neglected Diseases initiative (DNDi), Geneva, Switzerland.

Expert reviews were prepared by Dr Eva Njenga and Dr Gilles Sama Kwende.

Human African trypanosomiasis is transmitted by tsetse flies which are present in 36 sub-Saharan African countries. Of those, 13 countries have reported cases of sleeping sickness since 2000, with a declining trend. Treatment strategies have played a major role in this decline. Children account for approximately 25% of the total cases reported.

Nifurtimox–eflornithine combination therapy (NECT) is as effective as eflornithine alone for treating second-stage African trypanosomiasis but also has safety advantages and is easier to administer (infusion every 12 hours for 7 days versus every 6 hours for 14 days). Both are listed in the EML. Data from the seven most affected countries show that 59% of adult patients were treated with the combination in 2010 (31) and 86% in 2011. Listing of both medicines in the EML has helped to scale up access to NECT.

Eflornithine is already listed in the EMLc for second-stage African trypanosomiasis. Nifurtimox is listed in the EMLc only for American



trypanosomiasis, but is listed for both American and African trypanosomiasis in the EML.

Additional data are now available on children and hence this application was submitted to include nifurtimox in the EMLc to facilitate the combination therapy for sleeping sickness. There are no randomized controlled trials to assess the combination of nifurtimox and eflornithine specifically in children. A clinical trial (multicentre, open-label, phase IIIb) to assess NECT in field conditions was conducted in six sites in the Democratic Republic of the Congo. Of a total of 629 patients included in the trial, 100 were children below 12 years of age, 14 were pregnant women and 33 were breastfeeding mothers. Ninety-eight percent of the 629 patients were alive and well on discharge (32). With 24-month follow-up, similar cure rates were shown in children and adults, with close to 89% alive and well.

A cohort study of patients from Médecins sans Frontières (MSF) treatment centres, including 120 children, also showed good results (33). Adverse reactions were common (60–90%) but severe events were relatively rare. A pharmacovigilance study of NECT reported adverse effects, the commonest being vomiting/nausea and abdominal pain followed by headache, musculoskeletal pains and vertigo. Adverse events in children were similar to those in adults but the major adverse events were less frequent (34).

Both NECT and eflornithine monotherapy have similar health-system requirements, such as the need for intravenous infusion in a hospital setting. Nifurtimox is supplied free of charge according to an agreement with WHO and, in practice, it is less costly to procure the combination than the individual components.

Considering the public health need for this combination in the affected countries and the data on effectiveness and safety particularly in children, the Expert Committee recommended that nifurtimox be added to the EMLc. It was noted that this would also help countries to scale up treatment programmes for *Trypanosoma brucei gambiense* second-stage infection.

#### 6.5.5.2: American trypanosomiasis

##### *Benznidazole tablets (new formulation) – Children*

An application for adding the 12.5-mg benznidazole tablet presentation was received from the Drugs for Neglected Diseases initiative (DNDi), Rio de Janeiro, Brazil. Another application to add the 50-mg scored tablet was received from the Department for Control of Neglected Tropical Diseases, WHO, based on the same considerations as those for the 12.5-mg tablet.

Expert reviews were prepared by Dr Gilles Sama Kwende and Dr Eva Njenga.

A recent WHO report estimated that 10 million people worldwide are infected by *Trypanosoma cruzi*, mostly in the endemic areas of 21 Latin

American countries, but also in non-endemic countries as a consequence of population mobility (35). Most infections occur during childhood, and there are also congenital infections. However, until recently the only registered dosage form of benznidazole, the first-line treatment for Chagas disease, was a 100-mg tablet suitable for adults.

Despite the heterogeneity of studies presented in terms of objectives, geographical location, age ranges, numbers of children included, therapeutic schemes used, duration of post-treatment monitoring and the cure control tests deployed, there is clear evidence of the efficacy of benznidazole for the treatment of children infected by *Trypanosoma cruzi*, including those less than a year old, and this evidence suggests that greater efficacy is associated with early treatment. Seroconversion rates vary from 87% at 36 months (36) (100% in the 0–3 months age group) to 100% (37) at 24 months in children up to 2 years of age.

Adverse events during treatment are more frequent and more severe in adults than in children, and are particularly infrequent in children below 1 year. Fewer neurological events were noted among children, who present mainly with dermatological and gastrointestinal adverse events.

Treatment with benznidazole is of long duration and usually is given outside the hospital setting. Benznidazole is listed in the EMLc and WHO recommends it for the treatment of neonates, infants and children. The recommended dose is 5–10 mg/kg per day. The Expert Committee noted that the proposed formulations of benznidazole that are essential for the treatment of *T. cruzi* infections achieve paediatric doses more easily even in ambulatory care settings. The 12.5-mg tablet is registered in Brazil and the 50-mg tablet is registered in Argentina.

Taking into consideration the need for child-friendly formulations of benznidazole, the Expert Committee decided to add both the 12.5-mg and 50-mg scored tablets to the EMLc.

## Section 8: Antineoplastics

### 8.4: Medicines used in palliative care

#### *Palliative care (new section) – Children*

An application was submitted by Dr Willem Scholten, team leader (until 31 October 2012), Access to Controlled Medicines, WHO, for palliative care to be moved to a separate highest-level section of the EMLc. The Committee was also asked to consider a recommendation for a similar section in the EML.

Expert reviews were provided by Dr Lisa Bero, Mr Andrew Gray, Dr Gitanjali Batmanabane and Dr Abdol Majid Cheraghali.

This request was based on WHO's *Guidelines on pharmacological treatment of persisting pain in children with medical illnesses* and the WHO policy

guidelines *Ensuring balance in national policies on controlled substances: guidance for availability and accessibility of controlled medicines* (8, 9). The World Health Assembly in its resolution WHA58.22 on “Cancer prevention and control” (2005) called on WHO to address access to opioid analgesics. Other international bodies, such as the International Narcotics Control Board and the United Nations Commission on Narcotic Drugs, have called for greater access for patients to these medicines.

It was noted that the opioids were listed under Section 8 since palliative care was initially addressed by the WHO Cancer Control Programme more than 20 years ago. The Expert Committee recognized that medicines in palliative care are needed for conditions other than cancer – such as HIV/AIDS (38), MDR-TB (39) and severe congenital diseases (40). The present listing under Section 8.4 (antineoplastic, immunosuppressive and medicines used in palliative care) may be interpreted by some countries as indicating that palliative care medicines are needed for use in cancer only. Listing palliative care medicines as a separate category would signify the importance of this group of medicines and promote their use in all conditions that require such care.

The Expert Committee consequently recommended changing the title of Section 2 of the EMLc to “Medicines for pain and palliative care”. The corresponding change would also be made in the EML. In addition, the Expert Committee recommended that the medicines for rheumatic conditions be moved from Section 2 to a new Section 30 (Medicines for diseases of joints).

## Section 11: Blood products and plasma substitutes

### 11.1: Plasma substitutes

#### *Colloids (review) – Children*

At its 18th meeting the Expert Committee requested a review to determine whether adults and children with dengue fever should be treated with intravenous colloids rather than with crystalloids. The Committee also requested a review to determine whether plasma substitutes are essential medicines for children. It was not possible to address such a broad topic and therefore two reviews were commissioned by the Secretariat on two common causes of the need for volume replacement in children. The reviews considered by the Expert Committee were:

1. *Colloids versus crystalloids for fluid resuscitation in dengue fever patients – a review*, prepared by Dr Pablo Perel, London School of Hygiene & Tropical Medicine, London, United Kingdom.
2. *Are colloid solutions essential for the treatment of paediatric trauma or burn patients?* prepared by Christina Huwer, Department of Violence and Injury, Prevention and Disability, WHO, Geneva, Switzerland.

Expert reviews were prepared by Dr Liliana de Lima and Dr Le Van Truyen. Comments were received from the Director of the Special Programme for Research and Training in Tropical Diseases (TDR).

Currently, the EMLc does not list plasma substitutes. The EML lists 6% dextran 70, with 3.5% polygeline noted as equivalent.

### ***Colloids versus crystalloids in dengue fever***

The purpose of the systematic review prepared for this meeting was to identify and synthesize the available evidence to assess the effect on mortality of using colloids compared with crystalloids for fluid resuscitation in patients with dengue fever. Current recommendations for the management of dengue patients with hypotensive shock include the administration of either crystalloids or colloids (41).

A recently published Cochrane systematic review found no evidence that colloids, in comparison to crystalloids, reduced the risk of death in critically ill patients (42). This review included 74 trials, 66 of which reported mortality data. Although trials involving patients with dengue fever were included, the review did not report the results in these patients separately.

The present review identified five trials evaluating colloids versus crystalloids in children with shock associated with dengue fever. Overall, the quality of the evidence for the effect of colloids versus crystalloids for fluid resuscitation was low. All of the included studies were underpowered, making any reliable assessment of the effect of colloids compared with crystalloids on mortality in dengue patients impossible. The review found no evidence that resuscitation with colloids reduced the risk of death compared with resuscitation with crystalloids (42–45).

However, the Expert Committee noted the comment from the Director of TDR that it is not possible to conclude from the studies (and probably from any study) whether colloids could be beneficial for the small subset of very severe dengue shock patients who do not respond to crystalloids or who present with no measurable blood pressure. Clinical experience suggested that such patients may benefit from treatment with colloids. Without colloids being available, clinicians may resort to using albumin, freeze-dried plasma or blood, which may pose different safety or cost challenges. The Expert Committee therefore decided that, for the same reason that colloids had been retained on the EML for the same indication, colloids would be added to the EMLc.

### ***Colloids in paediatric trauma and burns***

Fluid therapy plays an important role in the treatment of trauma patients with substantial blood loss, as well as in patients with burn injuries. The review

prepared for the 19th meeting of the Expert Committee focused on these indications for the use of colloids in children. No evidence from randomized controlled trials could be identified (41, 46, 47). All articles reviewed indicated that there was very little evidence available either for or against the use of colloids in children.

Volume replacement with colloids is considerably more expensive than with crystalloids. *The International drug price indicator guide* (48) shows that the supplier median price for dextran 70 is almost 12 times higher than that for normal saline.

In view of the low quality of evidence available on the clinical questions reviewed, the lack of evidence for the superiority of colloids compared with crystalloids in critically ill patients in general, and the higher cost of colloids, the Expert Committee decided that there is no justification for the inclusion of specific colloids for volume replacement in the EMLc. However, colloids would be added to EMLc for consistency with the EML and for use when safer alternatives are not available.

## Section 12: Cardiovascular medicines

### 12.2: Antiarrhythmic medicines

#### *Antiarrhythmics (review) – Children*

In 2011 the Expert Committee requested a review to determine which antiarrhythmic medicines are essential for children. The topic was reviewed by Dr Pablo Perel, London School of Hygiene & Tropical Medicine, London, United Kingdom.

Expert reviews were prepared by Dr Shalini Sri Ranganathan and Dr Le Van Truyen.

Available data show that arrhythmias, and especially serious arrhythmias, are rare in children. Among the more common causes are congenital heart disease and rheumatic heart disease. For congenital heart disease, the appropriate treatment strategy is surgical correction. However, children sometimes do not receive the necessary surgical management, especially in developing countries. Arrhythmias associated with rheumatic heart disease usually present after childhood.

There is limited published evidence about the effectiveness of antiarrhythmic medicines in children (49).

Recognizing that arrhythmias in children are rare and that they are typically managed in specialized settings, it was noted that there does not appear to be a need to list antiarrhythmic medicines in the EMLc. Given that this section has limited public health relevance to children, the Expert Committee decided to delete it from the EMLc.

## 12.6: Lipid-lowering agents

### *Statins (review) – Children*

The 18th meeting of the Expert Committee had questioned the relevance of lipid-lowering agents in children and requested a review of this section in the EMLc. Currently simvastatin is listed on the EML for use in high-risk patients.

The review on the need for statins in children was submitted by Dr Marcus M. Reidenberg, Weill Cornell Medical College, New York, NY, USA.

Expert reviews were prepared by Dr Shalini Sri Ranganathan and Dr Le Van Truyen.

Statins lower cholesterol in children just as they do in adults. The duration of reported randomized controlled trials in children showing change in blood lipids as the benefit ranged from 8 weeks to 3 years, with the median being 6 months (50). No clinical trials showed that lowering cholesterol with statins was effective in preventing or delaying cardiovascular events in children with high plasma cholesterol and no initial clinical evidence of atherosclerosis. Statins are considered to be effective in secondary prevention of cardiovascular events in adults, but there is controversy about the effectiveness of statins for primary prevention in healthy adults (51–54).

Heterozygous familial hypercholesterolaemia (FH) occurs in about one in every 500 children. The estimated 10-year risk of a cardiovascular event in such patients is around 1%. However, available risk calculation tools do not include children and hence their predictive accuracy in children is unknown.

In general the safety profile of statins in children (including in relation to the hepatic and musculoskeletal systems) is similar to that observed in adults. However, long-term data in children are lacking.

The United States Food and Drug Administration (US FDA) has approved the use of pravastatin in children of 8 years or older with FH, and other statins in children of 10 years or older, where dietary measures have failed. The United States National Cholesterol Education Program (NCEP) recommends that drugs be used only in patients older than 10 years of age following failure of aggressive dieting. The American Heart Association (AHA) and the American Academy of Pediatrics (AAP) have recommended statin therapy for children with high-risk lipid abnormalities.

Considering that the indications for statin use in children were rare and that the long-term risks and benefits had not been well established (50), the Expert Committee decided not to add statins to the EMLc. However, given the global prevalence of obesity, including in children, the Committee recommended that a “watching brief” be maintained on this topic. Not only will the public health relevance need to be considered, but emerging evidence on the choice of an appropriate approach to lowering very high lipids levels in children would need to be informed by sufficiently good evidence. As a result, it was agreed that the section heading would be retained although no medicines would be listed.

## Section 15: Disinfectants and antiseptics

### 15.1: Antiseptics

#### *Chlorhexidine (new formulation) – Children*

The application to include chlorhexidine digluconate 7.1% solution or gel delivering 4% chlorhexidine for cord care was submitted by the Program for Appropriate Technology in Health (PATH), Chlorhexidine Working Group.

Expert reviews were provided by Dr Lisa Bero and Dr Suzanne Hill.

In 2009, the Expert Committee reviewed an application to include this formulation of chlorhexidine. Although there was general consensus that, in unclean deliveries, topical antiseptics may help in reducing infections, there was no clear evidence regarding the superiority of any one product. In addition, no product was commercially available at that time. A 20% solution was added for dilution. In 2011 an updated application was submitted to replace the 20% listing with a ready-made 7.1% digluconate solution or gel. At that time, trials were continuing and the product was still not commercially available. The Committee then decided to list 4% chlorhexidine as one of the missing priority products in the “Priority medicines for mothers and children – 2011”.

An updated application was submitted to the 19th meeting of the Expert Committee for inclusion of the 7.1% concentration providing 4% free chlorhexidine formulation. It was felt that there is a need to specify concentrations correctly: 20.0% chlorhexidine digluconate provides 11.3% free chlorhexidine, while 7.1% provides 4.0%, and 5.0% provides 2.8%.

The evidence in the application consisted of three trials conducted in community settings in Bangladesh, Nepal and Pakistan where there were high rates of home deliveries and high neonatal mortality (55–57). Over 50 000 newborns were enrolled, and the trial compared single or multiple applications of chlorhexidine with standard dry cord care practices. The results showed significant reductions in neonatal mortality (24%) and omphalitis (75%).

Systematically collected data on long- and short-term adverse events are scant. However, chlorhexidine was used widely in randomized trials and has been used elsewhere for neonates (58, 59). Transient contact dermatitis has been reported in preterm very-low-birth-weight infants after long-term (> 7 days) placement of chlorhexidine-impregnated dressings for central venous catheters (58).

Although a significant effect was seen for neonatal mortality and omphalitis, the studies were predominantly in high-mortality home birth settings in South Asia. The findings are therefore difficult to generalize to settings where the majority of births take place in health facilities and where neonatal mortality rates are lower.

Questions remain about the optimal treatment regimen with respect to timing of the application of chlorhexidine, as well as the number of applications.



Compared with dry and clean care (mean 4.78 days), separation time of the umbilical cord was longer in the single (mean 6.90 days, difference = 2.10, 95% CI: 1.85–2.35) and multiple (mean 7.49 days, difference = 2.69, 95% CI: 2.44–2.95) cleansing groups in a cluster randomized trial (60). This outcome may affect carer satisfaction, but the clinical importance is unclear.

The scalability and integration of the use of chlorhexidine into existing health systems have yet to be established. Two of the three studies that showed beneficial effects of chlorhexidine application to the cord included several visits by health-care workers, which may not be possible in all settings.

There is now a commercially available product in at least Bangladesh and India but there is as yet no global supply. Local production of the product may be an appropriate strategy to ensure adequate supply, although the precise concentration required in the formulation means that standards for the manufacturing process need to be ensured.

The Expert Committee recommended the listing of the new 4% gel formulation, the deletion of the 20% solution, and the retention of the 5% solution. The Committee hoped that inclusion in the list would increase the chances of making a commercial product available and noted that three manufacturers (two in India and one in Belgium) are already providing the gel product.

## Section 24: Medicines for mental and behavioural disorders

### 24.1: Medicines used in psychotic disorders

#### *Chlorpromazine and haloperidol (deletion) – Children only*

The 18th meeting of the Expert Committee had noted the potential importance of chlorpromazine and haloperidol for a variety of disorders in children, but requested a review of the entire section. The Department of Mental Health and Substance Abuse, WHO, reviewed the section and submitted applications for (1) the deletion of chlorpromazine and haloperidol from the EMLc, (2) an increase in the minimum age for the use of fluoxetine, and (3) the inclusion of clozapine on the complementary list for the treatment of resistant schizophrenia in adults.

Expert reviews were prepared by Dr Kuruvilla Prasad Mathews and Mr Andrew Gray.

Psychosis is rare in childhood, with the prevalence estimated to be as low as 1.6 per 100 000 (61, 62). However, subclinical psychotic experiences (including delusions or hallucinations) are much more common. These more common conditions (which affect 6% of 11-year-olds) are usually benign and, in 75–90% of cases, spontaneously remit over time (63). Psychosocial interventions are the treatment of preference in the first instance.

Children on chlorpromazine and haloperidol are prone to sedation, extrapyramidal syndrome, withdrawal dyskinesia and tardive dyskinesia (64, 65).



Various guidance documents suggest that pharmacotherapy has a very limited role in the management of childhood mental disorders, and especially behavioural disorders, before puberty. Even for unresponsive cases, medication may be considered only after specialist consultation (66). WHO does not recommend using pharmacotherapy for behavioural problems except for attention deficit hyperactivity disorder (ADHD) after a first trial with psychological interventions (67).

The Expert Committee recognized that the indications for using chlorpromazine and haloperidol are very rare in children. Adverse events from these medicines may be more frequent in children than in adults. However, the Committee recognized the importance of ensuring that treatment is available for these severe psychiatric disorders in children and also noted that the application did not fully review all treatment options. The Expert Committee therefore requested a specific review of the evidence for the benefits and risks of each medicine in the paediatric population and decided to make no changes to the list until such reviews had been considered.

## 24.2: Medicines used in mood disorders

### 24.2.1: Medicines used in depressive disorders

*Fluoxetine (change to age restriction/deletion from EMLC) – Adults and Children*

See under Section 24: Medicines for mental and behavioural disorders.

## Section 28: Ear, nose and throat medicines

*Montelukast (addition) – Children*

During the 18th meeting of the Expert Committee, a request was made to review the role of leukotriene receptor antagonists (LTRAs) in the management of childhood allergic rhinitis. The review was prepared by Dr Achal Gulati, Director/Professor, Department of ENT and Head & Neck Surgery, Maulana Azad Medical College, New Delhi, India.

Expert reviews were prepared by Dr Shalini Sri Ranganathan and Dr Abdol Majid Cheraghali.

Therapeutic options for relief of allergic rhinitis include avoidance measures, oral antihistamines, intranasal corticosteroids (INCS), LTRAs, or allergen immunotherapy. The available LTRAs are montelukast, pranlukast and zafirlukast.

Randomized controlled trials and observational studies suggest that LTRAs as a class are effective in controlling symptoms related to allergic rhinitis. In a meta-analysis, the clinical efficacy of LTRAs, including montelukast, in the treatment of patients with allergic rhinosinusitis and nasal polyposis was compared with that of placebo, antihistamines, and nasal corticosteroids. The composite daily rhinitis symptom scores in each trial were standardized and pooled. Among

the trials included in the meta-analysis, eight compared LTRAs with a placebo (five montelukast trials, two zafirlukast trials, one L-649923 trial), two compared an LTRA and an antihistamine (both montelukast versus loratadine), and four compared an LTRA with a nasal corticosteroid (montelukast versus mometasone; montelukast versus budesonide; montelukast versus fluticasone and zafirlukast versus beclomethasone). In the composite daily rhinitis symptom score, LTRAs decreased the score by 5% when compared with placebo, antihistamine decreased the score by 2% compared with LTRAs, and intranasal corticosteroids were the most effective, decreasing the score by 12% compared with antihistamines (68). Two separate studies comparing montelukast, loratadine or cetirizine to placebo groups in children showed some benefits in various symptom assessments relative to placebo, but no consistent benefit of one treatment type over the other (69, 70).

Guidelines on allergic rhinitis and its impact on asthma (ARIA) propose antihistamines and intranasal corticosteroids as preferred first-line management. LTRAs are suggested either alone or in combination therapies after the antihistamines and intranasal steroids. However, individual management options can vary.

A post-marketing report suggests an association between neuropsychiatric events (mood and behavioural adverse effects) and montelukast, the most commonly prescribed of the agents in the group. The US FDA confirmed the association with neuropsychiatric adverse reactions and in June 2009 requested that manufacturers add a precaution to the prescribing information (71). Such reactions may also occur in children (71–73).

In view of the lack of evidence for the superiority of montelukast over other readily-available treatments for allergic rhinitis, the potential adverse events and the uncertainties regarding its cost and availability in most low- and middle-income countries, the Expert Committee decided not to include montelukast in the EMLc.

## Section 29: Specific medicines for neonatal care

### *Dexamethasone (new indication) – Children*

An application was submitted by Dr Joy Lawn, Director of Global Evidence and Policy Saving Newborn Lives/Save the Children, London, United Kingdom and Fernando Althaea Instituto de Efectividad Clínica y Sanitaria, Buenos Aires, Argentina, for the addition of dexamethasone for the indication of accelerating lung maturation in preterm babies.

Expert reviews were provided by Dr Shalini Sri Ranganathan and Dr Liliana de Lima.

Preterm birth is the leading cause of neonatal deaths and the second most common cause of under-5 mortality, as well as a leading contributor to the global burden of disease because of a significant risk of disability. Each year an

estimated 15 million babies are born preterm, three-quarters of them in South Asia and sub-Saharan Africa. Over 85% are moderate or late preterm, who are likely to survive without intensive care. However, if access to basic care is limited, antenatal corticosteroids could make a considerable difference to mortality and morbidity, primarily by reducing the risk of respiratory distress syndrome (RDS).

There is high-quality evidence showing that antenatal corticosteroids reduce all-cause neonatal mortality. A Cochrane review and meta-analysis of 18 trials (3956 infants) of antenatal corticosteroids found that the risk of neonatal mortality was reduced by approximately 30% (relative risk, RR: 0.69, 95% CI: 0.58–0.81) (74). The same meta-analysis found that there was reduced incidence of RDS (RR: 0.66, 95% CI: 0.59–0.73, 21 studies, 4038 infants) and cerebroventricular haemorrhage (RR: 0.54, 95% CI: 0.43–0.69, 13 studies, 2872 infants). A meta-analysis of four randomized controlled trials (672 infants) from middle-income countries found a decrease in neonatal mortality following preterm birth (RR: 0.47, 95% CI: 0.35–0.64). No studies were found from low-income settings (75).

Two products – dexamethasone and betamethasone – were used in the majority of trials. No differences in effects were found between the two products. A large trial that is powered to detect a difference was continuing at the time of the 19th meeting of the Expert Committee but results were not expected until 2015 (76).

The adverse effects of dexamethasone are well defined. A retrospective cohort study compared preterm babies exposed prenatally to dexamethasone to those not exposed and found no differences in verbal intelligence quotient, performance intelligence, body length, head circumference and body weight at one, three and six years (77).

Dexamethasone is recommended in WHO global clinical guidelines such as *Managing complications in pregnancy and childbirth: a guide for midwives and doctors* (78). The National Institutes of Health (79), the American College of Obstetricians and Gynecologists (80), and the Royal College of Obstetricians and Gynaecologists (81) have recommended antenatal corticosteroid treatment for women at risk for preterm delivery before 34 weeks of gestation to reduce the morbidity and mortality associated with preterm birth.

The most extensively studied regimens of corticosteroid treatment for the prevention of RDS are two doses of betamethasone 12 mg given intramuscularly 24 hours apart, or four doses of dexamethasone 6 mg given intramuscularly 12 hours apart. Evidence for other dosing regimens, such as the commonly used two doses of betamethasone 12 mg given 12 hours apart, is sparse, but it would seem reasonable to use a regimen that delivers 24 mg of either drug within a 24–48-hour period (81).

Dexamethasone is generally inexpensive (<US\$ 1 per four-injection course) and is widely available, making it the cheapest and most accessible means

of preventing RDS and deaths due to preterm birth. Dexamethasone treatment is likely to be cost-effective in most settings, at an estimated cost per case (including the cost of syringes, needles, swabs, personnel and clinic visits) of US\$ 16.25, which is around one-third the cost of betamethasone treatment.

Dexamethasone was already listed on the EML in the same formulation (4 mg/ml) that is commonly used for this indication.

Given the compelling evidence of effectiveness, safety and cost-effectiveness, the Expert Committee recommended the inclusion of dexamethasone in Section 29, under a new subheading of “Medicines for administered to the mother”.

## 5. Applications for the 18th Model List and the 4th EMLc

### Section 2: NSAIDs and DMARDs

#### 2.1: Non-opioids and non-steroidal anti-inflammatory medicines (NSAIDs)

##### *Naproxen (addition) – Adults*

An application was submitted by Dr Patricia McGettigan, William Harvey Research Institute at Barts and The London School of Medicine and Dentistry, London, United Kingdom and Dr David Henry, Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada, for the inclusion of naproxen as an individual medicine by virtue of its having the safest cardiovascular risk profile among non-steroidal anti-inflammatory medicines (82).

Expert reviews were provided by Mr Andrew Gray and Dr Alar Irs.

Ibuprofen is specifically listed in the WHO Model List of Essential Medicines and not as a representative of the non-steroidal anti-inflammatory medicines (NSAIDs). This application requested the addition of naproxen because of its low cardiovascular risk. The application also highlighted the extensive listing of diclofenac in national essential medicines lists despite its high cardiovascular risk (83).

The data presented are from an update of the cardiovascular safety of various NSAIDs based on a meta-analysis of results from observational studies (case-control and controlled cohort studies). The pooled relative risk of a cardiovascular event in users of ibuprofen was 1.18 (95% CI: 1.11–1.25) and 1.09 (95% CI: 1.02–1.16) with naproxen. In a pair-wise comparison of ibuprofen and naproxen, the ratio of relative risks (RRR) for naproxen was just significantly lower than for ibuprofen: RRR = 0.92 (99% CI: 0.87–0.99). However, when dose was taken into account, only high-dose ibuprofen (> 1200 mg/day) was associated with higher risk. Naproxen was risk-neutral at all doses.

No comparison of the analgesic effects of naproxen and ibuprofen was provided in the application. The pricing data showed ibuprofen and naproxen to be similarly priced. There was also no comparison of naproxen with other NSAIDs in terms of adverse effects and toxicities in other systems (e.g. gastrointestinal). A review in 1999 stated that ibuprofen was associated with the lowest risk of side-effects (84).

The increase in cardiovascular risk with ibuprofen applies to the higher doses only and the Expert Committee did not consider that there was adequate justification for including both ibuprofen and naproxen in the EML. However, the Committee noted that, in populations with high cardiovascular risk, it would be important to indicate that naproxen has the lowest cardiovascular risk. Since the application focused only on the cardiovascular outcomes for NSAIDs and not

the comparative gastrointestinal outcomes or comparative analgesia, the Expert Committee decided to keep only ibuprofen on the list.

However, the Expert Committee also drew attention to the evidence for not choosing diclofenac as a preferred NSAID. Selection of an NSAID needs to take gastrointestinal, renal and cardiovascular safety into account.

## 2.3: Medicines used to treat gout

### *Colchicine (reinstatement) – Adults*

#### **Gout**

An application was submitted by Laboratoires Mayoly-Spindler, Chatou Cedex, France, for reinstatement of colchicine for gout, with an addition for familial Mediterranean fever.

Expert reviews were provided by Dr Youping Li and Dr Eva W. Njenga.

Colchicine was deleted from the EML in 2005 on the basis that “its usefulness for treating acute attacks is limited by its dose-dependent toxicity and the therapeutic margin is narrow”. That year the meeting of the Expert Committee also noted that colchicine was not cheaper than ibuprofen and that it had not been procured to any great extent by international suppliers over the previous five years. The Committee recommended that colchicine be deleted from the EML because of its unfavourable benefit–risk ratio when compared with NSAIDs for most people with gout (85).

The application to reinstate colchicine was based on a multicentre, randomized, double-blind, placebo-controlled, parallel-group study of a total of 185 patients, published in 2010, which compared self-administered low-dose colchicine (total 1.8 mg over 1 hour) and high-dose colchicine (total 4.8 mg over 6 hours) with placebo. The end-point of > 50% reduction of pain was observed in 37.8% in the low-dose colchicine group, 32.7% in the high-dose group, and 15.5% in the placebo group ( $P = 0.005$  and  $P = 0.0034$ , respectively, versus placebo). Rescue therapy with NSAIDs was administered in the first 24 hours to 31.1% of patients in the low-dose group ( $P = 0.027$  versus placebo), 34.6% in the high-dose group ( $P = 0.103$  versus placebo), and 50.0% in the placebo group. With high-dose colchicine, 40 patients (76.9%) had diarrhoea (OR: 21.3, 95% CI: 7.9–56.9), 10 (19.2%) had severe diarrhoea, and nine (17.3%) had vomiting. With low-dose colchicine, 23.0% of the patients had diarrhoea (OR: 1.9, 95% CI: 0.8–4.8), none had severe diarrhoea, and none had vomiting (86).

No clinical trials comparing NSAIDs with colchicine were provided in the application. Colchicine appears as a first-line treatment in both the European and British Society of Rheumatology recommendations and is seen as an effective alternative to NSAIDs (87, 88).

The Expert Committee decided that, if commonly-available NSAIDs are as effective as colchicine in the treatment of gout, the necessity for a medicine

useful only for gout is not clear. Additionally, the application was based on a single trial that showed the low dose to be as effective as the high dose. Reinstating colchicine would require a comprehensive assessment of the comparative benefits and harms of the proposed lower-dose regimen as well as information about the comparative costs.

The Expert Committee therefore did not recommend reinstatement of colchicine on the EML for the management of gout.

### ***Familial Mediterranean fever***

Familial Mediterranean fever is a common auto-inflammatory disease in the Eastern Mediterranean region. It has traditionally been regarded as inherited in an autosomal recessive manner, although some recent articles had reported a significant number of patients with only one mutation. Familial Mediterranean fever is divided into two main phenotypes. Type 1 is characterized by recurrent short episodes of inflammation and serositis including fever, peritonitis, synovitis, pleuritis and – rarely – pericarditis and meningitis. There is considerable variation in symptoms. Type 2 is characterized by amyloidosis as the first clinical manifestation of the disease in otherwise asymptomatic individuals (89). The mean age at the onset of clinical disease is 4 years (90% before 20 years). Renal failure as a result of amyloidosis is the most severe complication of Type 2 familial Mediterranean fever (90).

Familial Mediterranean fever generally affects people in the Eastern Mediterranean – mainly non-Ashkenazi Jews, Arabs, Armenians and Turks – with a prevalence between 1 in 200 and 1 in 1000 population (91). However, possibly due to extensive population movements, familial Mediterranean fever has been reported throughout the world, including in Japan (92).

The clinical trials of colchicine in familial Mediterranean fever were carried out in the early 1970s (93–95). Subsequent work focused on defining the appropriate dose, although there is no clear recommendation as yet. Paediatricians treating children with familial Mediterranean fever appear to be aware of the necessity to treat with colchicine, as the national registry in Turkey showed that over 95% of the eligible patients were being prescribed colchicine, with 80% reporting regular use (91).

The Expert Committee decided that, while colchicine may be effective for this condition, the relatively limited population at risk does not justify inclusion in a global list. Additionally, physicians dealing with this condition appear to be aware of the necessity to use colchicine and including it in the EML therefore is unlikely to improve access.

The Expert Committee therefore recommended that colchicine for familial Mediterranean fever should not be included in the EML.

## Section 3: Antiallergics and medicines used in anaphylaxis

### *Histamine-1 receptor antagonists (review) – Adults and Children*

The 18th meeting of the Expert Committee requested a comparative review of the safety and efficacy of chlorphenamine (which is listed in both the EML and the EMLc) and diphenhydramine, to provide information regarding the possible inclusion of diphenhydramine. Given the possible favourable clinical effects and side-effect profile of second-generation systemic antihistamines (SGAHs), three over-the-counter SGAHs (cetirizine, loratadine and fexofenadine) were also reviewed and compared with chlorphenamine and diphenhydramine (which are first-generation antihistamines, or FGAHs). The use in children and elderly people was specifically considered in the review, and the national essential medicines lists of 15 countries were checked for the availability of SGAHs. The review was prepared by Mr Harinder Chahal, Doctor of Pharmacy Candidate at the University of California, San Francisco, CA, USA.

Expert reviews were prepared by Dr Liliana de Lima and Dr Kuruvilla Prasad Mathews.

Evidence of the efficacy and safety of these five antihistamines in allergic rhinitis and urticaria was provided. Overall, there was a lack of high-quality data to compare the two FGAHs. The review found no randomized controlled trials that satisfactorily compared efficacy and safety of chlorphenamine and diphenhydramine for use in allergic rhinitis or urticarial conditions. The evidence from five randomized controlled trials comparing them with placebo or other medicines show similar effectiveness and side-effect profiles of the two medications for both allergic rhinitis and urticaria (96).

Fifteen randomized controlled trials showed similar efficacy of FGAHs and SGAHs in treating allergic rhinitis, with significantly fewer side-effects (in frequency and severity) with SGAHs. For treatment of urticaria, nine randomized controlled trials showed similar efficacy between FGAHs and SGAHs, with lower incidence of side-effects with SGAHs. Six randomized controlled trials, three retrospective studies and one systematic review provided evidence establishing the safety profile of SGAHs as superior to that of FGAHs (97). Significant sedation and psychomotor impairment were observed with FGAHs compared with SGAHs.

Due to the anticholinergic side-effects and the reduced drug clearance in elderly people, the use of FGAHs in this population is strongly discouraged. Evidence from five randomized controlled trials, two pharmacokinetic studies, a systematic review and from guidelines, recommends against the use of FGAHs in infants and children, due to risk of sedation and death (96, 98).

The review provided a detailed discussion on the use of antihistamines in anaphylaxis and concluded that there was no strong evidence to recommend the use of antihistamines for this indication.



The review also found that the monthly treatment cost of loratadine was lower than that of chlorphenamine and that 53% of the 15 low- and middle-income countries surveyed already had an SGAH on their respective national essential medicines lists.

The Expert Committee further considered the evidence on safety. The FGAHs are referred to as “sedating” and the SGAHs as “non-sedating”. This broad distinction is based on two primary differences between these medicine classes: (1) SGAHs are more specific to H-1 receptors than are FGAHs and (2) FGAHs are able to cross the blood–brain barrier while the SGAHs are not. These differences in receptor specificity and lipophilicity cause FGAHs to display significant central nervous system, cardiovascular system and gastrointestinal system side-effects. These effects were seen during clinical trials.

Based on considerations of inferior safety, especially in children and elderly people, and the equal efficacy of SGAHs and FGAHs, the Expert Committee decided to delete chlorphenamine from the EML and EMLc, and to recommend the addition of loratadine tablets (10 mg) and oral liquid (1 mg/ml) to the EML and EMLc with a square box. A lower age limit of 2 years for loratadine may be applied, although use below this age has occurred in some settings (99–104).

## Section 4: Antidotes and other substances used in poisonings

### *Fomepizole (addition) – Adults and Children*

An application to include fomepizole on both the EML and the EMLc was submitted by Guangduo Zhang, Kasumi Crews, Heather Wiseman and Nicola Bates of Medical Toxicology Information Services Ltd, London, United Kingdom; Dr Knut Erik Hovda of The National NBC Center, Department of Acute Medicine, Oslo University Hospital Ullevaal, Oslo, Norway; and Dr John Archer and Dr Paul Dargan of Clinical Toxicology, Guy’s and St Thomas’ NHS Foundation Trust and King’s Health Partners, London, United Kingdom.

Expert reviews were prepared by Dr Le Van Truyen and Dr Gilles Sama Kwende. Comments were received from the Department of Evidence and Policy on Environmental Health Issues, WHO; the Department of Pharmacology, Toxicology and Neuroscience, Louisiana State University Health Sciences Center, Shreveport, LA, USA; and Dr Hans Perrson, former Director of the Swedish Poisons Information Centre.

Fomepizole is used for the treatment of toxic alcohol and glycol poisoning – principally methanol and ethylene glycol – in adults and children. Ethylene glycol poisoning occurs worldwide and in the majority of cases is due to the ingestion of substances such as antifreeze, vehicle screen wash and fuel additives. Methanol poisoning is usually associated with illicit alcohol. Epidemics

of methanol poisoning (caused by ingestion of contaminated beverages) and of diethylene glycol poisoning (caused by adulterated medications) continue to occur worldwide, predominantly in developing countries and among economically disadvantaged communities. Poisoning with these agents is associated with severe morbidity and mortality.

The toxicity associated with the toxic alcohols and glycols is due to their metabolism by the enzyme alcohol dehydrogenase to toxic intermediates. Fomepizole prevents formation of the toxic metabolites by competitively inhibiting alcohol dehydrogenase. Ethanol can also be used as an antidote and acts through the same mechanism. Experimental studies have demonstrated the ability of fomepizole to inhibit alcohol dehydrogenase, and animal studies have shown that fomepizole reverses the toxic effects of methanol and ethylene glycol poisoning.

Prospective observational studies, clinical trials and retrospective case reviews have demonstrated that fomepizole improves outcomes by improving renal function, preventing visual impairment associated with methanol poisoning, and preventing metabolic acidosis (105, 106). In a retrospective case series, ethanol and fomepizole were equally effective but fomepizole provided practical advantages, such as ease of administration and monitoring, and a better adverse events profile (106–111). However, no high-quality studies have directly compared fomepizole with ethanol.

Fomepizole is approved by the US FDA for these indications and is recommended by American and European associations of clinical toxicologists. Ethanol is not US FDA-approved for this indication.

The relative ease of use of fomepizole may confer some benefits through the potential avoidance of intensive therapy, although this would not apply to severely ill patients who would require intensive support. The limited data made it difficult to determine whether the greater cost of fomepizole was offset by any potential savings. The laboratory tests that are needed to initiate treatment and monitor therapy may not be available in all situations where poisonings occur. There are insufficient data from children and elderly people. However, most available information suggests that fomepizole is a safe medicine. It is classified as US FDA pregnancy category C.

It was also noted that access to parenteral ethanol was problematic as this product was difficult to manufacture and pack in ampoule form.

Though rare in some settings, toxic alcohol and glycol poisoning can lead to serious harm. Considering this need, the Expert Committee recommended the addition of fomepizole to the complementary list of the EML. The need for specialist care was a consideration for inclusion on the complementary list rather than on the core list.

## Section 6: Anti-infective medicines

### 6.2: Antibacterials

#### 6.2.2: Other antibacterials

##### *Isoniazid + pyridoxine + sulfamethoxazole + trimethoprim (addition) – Adults and Children*

An updated application to include the fixed-dose combination of isoniazid + pyridoxine + sulfamethoxazole + trimethoprim was submitted by the Department of HIV/AIDS, WHO.

An application for addition of this product had been submitted to the 18th meeting of the Expert Committee but the addition was not made at that time since the product was not then commercially available.

An expert review was prepared by Mr Andrew Gray.

On the basis of known activities of the component medicines, the fixed-dose combination was expected to be of use in preventing tuberculosis, bacterial pneumonia, malaria, isosporiasis and other infections and to reduce mortality and hospitalizations among adults and children living with HIV/AIDS (PLHIV).

WHO had listed this fixed-dose combination in the 10th Invitation for Expression of Interest for HIV medicinal products. A product – once available and prequalified by WHO – would provide a reliable and safe source for this fixed-dose combination.

Current WHO guidelines recommend both co-trimoxazole preventive therapy (CPT) and isoniazid preventive therapy (IPT) as part of the standard package of care for PLHIV (112). In most settings CPT is recommended indefinitely while IPT is recommended for at least 6 months. CPT prevents *Pneumocystis jiroveci* pneumonia, cerebral toxoplasmosis, bacterial pneumonia, diarrhoea, *Isospora belli* infections, malaria and other infections, and its use has led to significant reduction in mortality in clinical trials in low- and high-income countries. IPT prevents active tuberculosis in HIV-infected persons. Pyridoxine is recommended in all HIV-infected persons receiving isoniazid, though it may be difficult for countries to procure and distribute pyridoxine with isoniazid. Including pyridoxine in the fixed-dose combination ensures that all patients on IPT are on concomitant pyridoxine, thereby preventing isoniazid-induced neuropathy.

The efficacy of CPT and IPT are compromised by lapses in adherence. Fixed-dose combinations have the potential to improve adherence and reduce the pill burden. Access to the fixed-dose combination was also proposed as a means to address the lower uptake of IPT compared with CPT.

The data on efficacy and safety presented to the meeting were mainly from studies of the individual components or prophylactic IPT and CPT regimens. These regimens are clearly effective for improving outcomes in PLHIV.

The safety profiles of the components are also well characterized. Though rare, the risk of Stevens–Johnson syndrome with CPT must be taken into account. All the constituent elements of this proposed fixed-dose combination were already included in the EML.

The application presented to the 19th meeting of the Expert Committee contained no new evidence compared with the application presented to the previous meeting.

The Expert Committee noted that, although the public health arguments for increased use of fixed-dose combinations to enhance compliance with recommended standard regimens and to avoid prescriber error are compelling, much depends on the availability of a quality-assured and affordable commercial product for procurement by country programmes and donors. In this case, no such product was yet commercially available. The Expert Committee noted that Cipla, India, manufactures the fixed-dose combination for clinical trials and was reported to be scaling up production. It appeared from the application that bioequivalence studies of the proposed fixed-dose combination formulation had not yet been conducted.

This application provided no additional information that could justify a different conclusion from that reached by the previous meeting, and therefore the Expert Committee recommended that the proposed fixed-dose combination should not be included in the EML.

#### 6.2.4: Antituberculosis medicines

An application to include bedaquiline in the EML was submitted by Janssen Research & Development LLC, Beerse, Belgium.

Expert reviews were provided by Dr Lisa Bero and Dr Gitanjali Batmanabane.

There are an estimated 630 000 prevalent cases of MDR-TB globally (113), but appropriate treatment remains a problem. Bedaquiline is the first new drug with a novel mechanism of action (adenosine triphosphate, or ATP, synthase inhibition) for tuberculosis in more than 40 years. The proposed use of this medicine is as part of combination therapy, preferably as directly-observed therapy (DOT), for persons over 18 years of age newly diagnosed with MDR pulmonary tuberculosis. The total duration of treatment is 24 weeks.

On the basis of the available phase IIb data, the US FDA approved bedaquiline in late 2012 under its accelerated approval programme, as part of combination therapy to treat adults with MDR-TB when other alternatives are not available.

WHO's Stop TB Department noted the accelerated approval by the US FDA, and in December 2012 a rapid interim guidance on the potential use

of bedaquiline for the treatment of MDR-TB was being developed. However, this was not available to the Expert Committee.

The Expert Committee noted that available trial data (consisting of two phase IIb trials) suggested that bedaquiline is effective in MDR pulmonary tuberculosis in adults. Primary efficacy analysis was based on a modified intention to treat (mITT) the population, which excluded subjects who had drug-susceptible tuberculosis, XDR-TB or unconfirmed MDR-TB (based on susceptibility tests taken before randomization), or had missing or negative baseline cultures, or were positive at baseline but had no post-baseline culture results. The mITT population comprised 132 subjects (66 in each of the bedaquiline and placebo groups). The median time to culture conversion was 83 days (95% CI: 56–97) in the bedaquiline group compared with 125 days (95% CI: 98–168) in the placebo group.

Twelve deaths were reported in total; of these, 10 (12.7% of 79) came from the bedaquiline group and two (2.5% of 81) from the placebo group ( $P = 0.017$ ). In the bedaquiline group, eight of the 10 deaths occurred in culture converters. Tuberculosis was the cause of death in the two placebo-arm deaths and in five of the 10 bedaquiline-arm deaths (all occurred when off bedaquiline treatment). Counting deaths strictly at the 120 weeks cut-off point revealed nine deaths in the bedaquiline group and one death in the placebo group. There was no discernible relationship between death and culture conversion, relapse, microbiological response, susceptibility to drugs used in the MDR-TB background medication regimen, HIV status, or severity of disease. The reasons for the imbalance were not clear.

The Expert Committee considered that further efficacy and safety data from clinical trials conducted in different backgrounds were needed and noted that bedaquiline was registered only in the USA (114). Bedaquiline was also not currently available commercially outside the USA and was expected to be available in some countries only by the end of 2013. The cost in high-burden countries was unknown.

On the basis of these considerations, the Expert Committee recommended that bedaquiline should not be included in the EML. However, the Committee also recommended that there should be efficient and timely alignment of the EML with WHO guidelines on the use of new medicines for MDR-TB.

### 6.3: Antifungal medicines

*Amphotericin B (to be moved to the core list);*

*Flucytosine (to be moved to the core list) – Adults and Children*

The Department of HIV/AIDS, WHO, submitted applications to move amphotericin B and flucytosine to the core list of the EML and the EMLc.

Dr Suzanne Hill reviewed both amphotericin B and flucytosine, and Dr Gilles Sama Kwende and Dr Hany Abdel-Aleem reviewed flucytosine.

Comments were received from Dr Myriam Henkens, International Medical Coordinator, MSF.

Cryptococcal meningitis accounts for 20–25% of AIDS-related mortality and is the most common cause of adult meningitis in sub-Saharan Africa, constituting a major public health burden. The mortality from this infection remains high at 35–65%. Poor or delayed access to effective drug treatments is an important contributing factor to mortality.

WHO rapid advice guidelines on *Diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children* were published in December 2011 (115). Amphotericin-based regimens were recommended as preferred in three of the five regimens. A two-week regimen of amphotericin B plus flucytosine was recommended as the preferred option. Where amphotericin is unavailable, or cannot be monitored safely, the treatment guidelines recommend flucytosine in conjunction with high-dose fluconazole. However, the guidelines with flucytosine could not be followed in many parts of Africa because flucytosine was not available.

A cost-effectiveness analysis that also analysed mortality from pooled clinical trial data showed that regimens containing amphotericin were consistently superior (116). The addition of flucytosine to amphotericin B during induction therapy, compared with amphotericin B alone, was found to be associated with increased rates of cerebrospinal fluid (CSF) sterilization, a reduced risk of relapse, and a nonsignificant reduction in mortality at 2 weeks and a significant reduction at 10 weeks (116).

The 2011 WHO rapid advice guidelines also recommended appropriate strategies to ensure the safe administration of amphotericin, including intravenous hydration coupled with electrolyte monitoring. In a review of seven trials, using the recommended dose of 100 mg/kg per day of flucytosine for 14 days with either amphotericin B or fluconazole, the incidence of grade IV neutropenia was 8 out of 183 (4.4%). A dose adjustment for renal function is needed for flucytosine.

Amphotericin B is produced by multiple generic manufacturers; generic flucytosine is not available in many countries although it has been off-patent for many years. The combination of flucytosine + fluconazole can be managed in resource-limited settings and an effective oral option is important.

The evidence provided to the Expert Committee included a published cost-utility analysis cited in the WHO guidelines (116). The Expert Committee noted that there were several problems with the analysis that led to difficulty in interpreting the results. The estimates of survival from different treatment regimens were extrapolated from 10 weeks to 1–3 years on the basis of several different cohorts that may or may not provide valid data for deriving incremental survival benefit. Quality-adjusted life years (QALYs) were calculated on the basis of Karnofsky performance scores from patients treated with antiretroviral

treatment (a completely different intervention), and these scores were then used to calculate incremental changes in estimated life years. This is not a valid approach to calculating QALYs, which should be calculated on the basis of an implied trade-off between survival and quality of life. As it was difficult to rely on the results of the analysis as presented, the Expert Committee decided that its decision should be weighted by other factors.

Given the obvious public health need, the potential to promote the availability of effective combinations in countries with heavy disease burdens, and the evidence of safety in the context where the products will be used, the Expert Committee decided to move these products to the core list. The Committee considered that transferring these medicines to the core list could improve availability. The Committee also strongly recommended that WHO should monitor the change in availability over the next five years.

## 6.4: Antiviral medicines

### 6.4.2: Antiretrovirals

*Abacavir + Lamivudine (addition); Atazanavir + Ritonavir (addition); Tenofovir disoproxil fumarate + Lamivudine (addition); Tenofovir disoproxil fumarate + Lamivudine + Efavirenz (addition) – Adults*

As described above, decisions on these applications were deferred.

*Antiretrovirals (formulations to be considered for possible deletion) – Adults and Children*

As described above, decisions on these applications were deferred.

### 6.4.3: Other antivirals

*Oseltamivir (deletion) – Adults and Children*

An application to delete oseltamivir from the EML was submitted by the Acute Respiratory Infections Cochrane Review group.

Expert reviews were provided by Dr Nicola Magrini and Dr Alar Irs. Comments were received from the WHO Department of Pandemic and Epidemic Diseases.

Oseltamivir was added to the EML and EMLc in 2010, with notes to indicate the conditions of use in compliance with WHO treatment guidelines. These notes specified that oseltamivir should be used only in patients with severe or progressive clinical illness with confirmed or suspected influenza A(H1N1)pdm09 and in patients with confirmed or suspected but uncomplicated illness due to pandemic influenza virus infections who were in higher-risk groups – most notably pregnant women and children under 2 years of age.

The effect of oseltamivir in reducing the complications of influenza was originally reported in a pooled analysis of 10 manufacturer-sponsored randomized trials of oseltamivir for the treatment of seasonal influenza (117).



This analysis and an independent re-analysis of 11 randomized controlled trials (118) found that oseltamivir treatment reduced the risk of lower respiratory tract complications requiring antibiotic treatment by 28% overall (95% CI: 11–42%) and by 37% among patients with confirmed influenza infections (95% CI: 18–52%).

The application proposed deletion of oseltamivir from the EML, citing a systematic review done by the applicants (119) which re-examined the evidence base for neuraminidase inhibitors and found that the only benefit was reduction in time to first alleviation of symptoms. The application also argued that – because of limitations in the design, conduct and reporting of the trials – there was insufficient detail to assess the credibility of the possible effect of oseltamivir on complications and viral transmission. The applicants also noted the significant publication and reporting bias in trials of oseltamivir.

The Expert Committee recalled that the addition of oseltamivir to the EML in 2011 was based on consideration of not only the randomized trials but also systematic reviews of observational studies (120). The Expert Committee had also been provided with some unpublished data in relation to the use and dose of oseltamivir in children. The observational studies reported outcomes that were relevant to the assessment of effectiveness and safety in the context of pandemic influenza, and also in populations that were not included in the trials (e.g. pregnant women).

The meta-analysis of observational data examined by the supplementary meeting of the Expert Committee in 2010 was published as an independent systematic review and meta-analyses of 74 studies (120). The few studies providing effects with adjustment for confounders suggest that, in high-risk populations, oral oseltamivir may reduce mortality (OR: 0.23, 95% CI: 0.13–0.43; low-quality evidence), hospitalization (OR: 0.75, 95% CI: 0.66–0.89; low-quality evidence), and duration of symptoms (33 hours, 95% CI: 21–45; very low-quality evidence) compared with no treatment. This very large effect on mortality was taken into account when deciding whether to include oseltamivir for treatment.

The 19th Expert Committee also acknowledged an additional recent systematic review and meta-analysis (121) of observational data from 90 studies (80 reported exclusively laboratory-confirmed diagnoses) that assessed the impact of neuraminidase inhibitor treatment on severe outcomes in hospitalized patients during the 2009–2010 influenza A(H1N1) pandemic. There was a nonsignificant reduction in mortality associated with neuraminidase inhibitor treatment (at any time) versus none (OR: 0.72, 95% CI: 0.51–1.01), a significant reduction for early treatment ( $\leq 48$  hours after symptom onset) versus late (OR: 0.38, 95% CI: 0.27–0.53) and for early treatment versus none (OR: 0.35, 95% CI: 0.18–0.71). This study and the previously reviewed studies did not provide sufficiently compelling evidence to alter the current assessment of safety and benefit.



The Expert Committee acknowledged that, although observational studies have inherent biases and estimates of effect from such studies may be subject to confounding, when there is a large effect on the most relevant outcomes (such as mortality) these studies should be part of the evidence base and can be taken into account in policy decision-making and in formulating a recommendation.

The Expert Committee noted that the WHO guidelines assessed the quality of the clinical evidence in relation to oseltamivir as low. While noting the limitations of the evidence, the previous decision to include oseltamivir in the EML took account of the magnitude of the effect on mortality and hospitalization, principles of equity, lack of alternative and the severity of infection, and strongly recommended it for restricted use (122).

In August 2010 WHO declared the H1N1 pandemic over. However, the responsible influenza strain continues to circulate and neuraminidase inhibitors are the only antiviral medicines that are effective against currently circulating strains. The recently identified H7N9 virus seen in China also appeared to be sensitive to oseltamivir.

Oseltamivir is widely available and is the only neuraminidase inhibitor suitable for children (noting that zanamivir cannot be used in children under 5 years of age).

The Expert Committee decided, on the balance of the updated evidence and the strain susceptibility, to retain oseltamivir in the EML for the restricted indication of potentially severe or complicated illness due to confirmed or suspected influenza virus infection, in accordance with WHO treatment guidelines.

The Expert Committee strongly supported the need for access to all randomized trial data but also expressed reservations about whether additional data from such trials would be applicable as the trials are generally conducted in healthy individuals with influenza-like illness. The Expert Committee also noted that influenza vaccines should remain the first-line intervention against such infections.

### *Pegylated interferon (addition) – Adults*

An application for addition of pegylated interferon was submitted by Médecins Sans Frontières – Access Campaign, Geneva, Switzerland.

Expert reviews were prepared by Dr Nicola Magrini and Dr Kuruvilla Prasad Mathews. Comments were received from the Global Hepatitis Programme of WHO, AIDS treatment organizations, multiple civil society organizations and patients' groups.

Peginterferon is a covalent conjugate of recombinant interferon alfa-2 with polyethylene glycol (PEG). The 2a and 2b formulations differ in the size and

nature of the covalently attached PEG, resulting in differences in pharmacokinetics and doses.

Globally, approximately 150 million people are infected with hepatitis C and it is estimated that 350 000 people die each year from hepatitis C-related liver disease (123). The goal of therapy is to produce a sustainable virological response (SVR) which can potentially result in the reversal of liver injury and can prevent serious consequences such as cirrhosis, end-stage liver disease, hepatocellular carcinoma and death.

When compared with standard interferon-alfa alone, interferon-alfa in combination with ribavirin increased the SVR from 10–20% to 40–60% (124, 125). The long-acting pegylated formulation in combination with ribavirin has further increased SVR rates to 50–60% for genotype 1 and to 80% for genotypes 2 and 3 (126, 127). A recent meta-analysis showed that treatment success rates in low- and middle-income countries were similar to those obtained in high-income countries (128). Head-to-head randomized controlled trials – including the large randomized IDEAL trial ( $n = 3070$ ) – demonstrated similar SVR rates for peginterferon alfa-2a and alfa-2b (41% versus 39% in IDEAL) in combination with ribavirin (129). While peginterferon alfa-2a or alfa-2b in combination with ribavirin has been the standard of care for chronic hepatitis C, the new direct-acting oral antiviral agents (bocepravir and telapravir) are more effective but more expensive (130, 131). The Expert Committee noted that there are several more direct-acting antivirals in development.

Pegylated interferons + ribavirine are associated with a range of adverse events that often require dose reduction and discontinuation. Adverse events that resulted in treatment termination were reported in 39 studies and were present in 4% (95% CI: 3–5) (128). Peginterferon alfa-2a and alfa-2b appear to be similarly tolerated (125).

Before treatment patients must be screened, RNA measurements and genotyping (which require high-level laboratory support) must take place, and facilities are required for liver biopsy and for detecting and managing complications.

WHO is developing guidelines for the screening, care and treatment of hepatitis C. Other expert bodies such as NICE (132), the European Association for the Study of the Liver (133) and the American Association for the Study of Liver Diseases (134) recommend peginterferon alfa-2a or alfa-2b with ribavirin for treatment of hepatitis C. Ribavirin was already listed in the EML and EMLC for viral haemorrhagic fevers.

The Expert Committee agreed on the public health need for this medicine and, because of the high level of expertise and facilities needed and the high cost, decided to list pegylated interferon alfa-2a and alfa-2b in the complementary list, to be used with ribavirin for treatment of hepatitis C when these products are available.

The Expert Committee stressed the need to follow the development of direct oral hepatitis C protease inhibitors and to consider applications for triple therapy or all-oral options for the treatment of hepatitis C.

## 6.5: Antiprotozoal medicines

### 6.5.3: Antimalarial medicines

#### 6.5.3.1: For curative treatment

#### *Artesunate + mefloquine (addition) – Adults and Children*

An application for the addition of the fixed-dose combination of artesunate + mefloquine was submitted by the Drugs for Neglected Diseases initiative (DNDi), Geneva, Switzerland.

Expert reviews were prepared by Dr Shalini Sri Ranganathan and Dr Eva Njenga.

Artesunate (AS) and mefloquine (MQ) are well established for the treatment of malaria and are listed in the EML and EMLc, with notes advocating their use in combination therapy. The combination artesunate + mefloquine (ASMQ) is recommended by WHO as one of five fixed-dose combinations for the treatment of uncomplicated falciparum malaria. The ASMQ combination is first-line therapy for *Plasmodium falciparum* malaria in the national policies of some Asian and South American countries.

Fixed-dose combinations of the drugs reduce the pill burden and, more importantly, eliminate the possibility of patients taking only one component of the combination or providers selling only one drug to reduce costs. The age-based unit dose packaging provided is appropriate for all age groups, which should make the dosing easier at all levels of the health care system, including in the community.

Evaluations of the fixed-dose combination in clinical studies have shown similar comparative efficacy to that demonstrated with separate tablets of artesunate and mefloquine (135, 136). Reported adverse events were also comparable between the fixed-dose combination and separate tablets. There is some evidence to suggest that transmission is decreased in places where the fixed-dose combination is used (137).

The current price per child and adult treatment with the ASMQ fixed-dose combination compares well with co-blister presentations or separate tablets of artesunate and mefloquine. DNDi and its partners are working towards lowering the price of the ASMQ combination in the future. ASMQ fixed-dose combination products are prequalified by WHO and the fixed-dose combination is currently registered in Brazil, India, Malaysia and Myanmar.

WHO does not recommend the use of separate tablets of artesunate and mefloquine in African children because of concerns about toxicity, including vomiting. To address these concerns DNDi is sponsoring a multicentre, open-

label, prospective, randomized and controlled phase IV study in Burkina Faso, Kenya and the United Republic of Tanzania to assess the efficacy, safety and pharmacokinetics of the ASMQ fixed-dose combination versus artemether-lumefantrine in approximately 1000 children with uncomplicated *P. falciparum* malaria (138).

The Expert Committee recommended the addition of both ASMQ 25+55 mg and ASMQ 100+220 mg to the EMLc and EML. The Committee further emphasized the need for access to the data from the planned clinical trial in children, as well as to evidence on the use in *P. vivax* malaria.

### 6.5.5: Antitrypanosomal medicines

#### 6.5.5.1: African trypanosomiasis

#### *Nifurtimox + eflornithine (review) – Adults and Children*

Please refer to Nifurtimox tablets (addition) – Children.

## Section 8: Antineoplastics, immunosuppressives and medicines used in palliative care

### 8.2: Cytotoxic and adjuvant medicines

During discussion on the addition of two new medicines to this section, the Expert Committee acknowledged the growing public health importance of cancer as a global health issue. The Expert Committee recognized the need for countries to consider the addition of highly effective but high-cost medicines for cancer treatment in the context of evidence-based treatment regimens, but also in the context of ensuring comprehensive systems and interventions for cancer care. The Committee also recognized the urgent need to review the section on cytotoxic medicines, using a process and structure similar to those used for the EMLc. The process would require the systematic identification of the most treatable tumours in adults and the medicines required to treat those tumours, within the context of a stepwise development of cancer care systems in the overall context of health system development.

It was proposed that the outcome of this review could be considered by an extraordinary meeting of the Expert Committee or through an ad hoc subgroup (possibly electronically). The review would also need to be accompanied by the development of a systematic approach to the consideration of expensive medicines and the pricing of such products.

The Expert Committee therefore decided to consider the applications in detail, and the results of its discussion are set out below. However, given the need to restructure the published EML, the decision was taken not to amend Section 8.2 of the list by adding or deleting medicines at this time. The Expert Committee noted that a comprehensive review of Section 8.2 would identify

other effective but high-cost medicines that should be considered in the overall allocation of resources for pharmaceuticals used for management of cancer.

*Imatinib (addition) – Adults*

*Imatinib (addition) – Adults and Children*

Two applications were submitted for the inclusion of imatinib for the treatment of chronic myeloid leukaemia.

The first application was from Dr Sandeep P. Kishore, Malini Aisola, Ruth Lopert and Nii Koney from the Weill Cornell Medical College, New York, NY, USA, for adult patients. The second application was from Dr Lawrence N. Shulman of the Center for Global Cancer Medicine, Dana-Farber Cancer Institute, Boston, MA, USA and Julie Torode, Deputy CEO, Union for International Cancer Control, Geneva, Switzerland; this application was for both adult and paediatric patients.

Expert reviews were provided by Dr Suzanne Hill and Dr Nicola Magrini.

The Expert Committee noted that chronic myelogenous leukaemia constitutes 15% of all adult leukaemia cases and 5% of all childhood leukaemias, with an estimated incidence of 1–1.5 per 100 000 people globally. In high-income countries, the estimated five-year survival rate of patients diagnosed between 2001 and 2007 (i.e. before wide use of imatinib) was 57%.

Imatinib has been in use since 2001 and has become the first-line treatment for Philadelphia chromosome positive-chronic myeloid leukaemia (139–141). It is now generally considered as the treatment of choice for disease control of chronic myeloid leukaemia in the chronic phase. The large randomized controlled trial that compared imatinib to interferon plus cytarabine (142) showed that, at 19 months, major cytogenetic remissions were seen in 87.1% of the imatinib-treated group compared with 34.7% of the comparator group. At six years, the overall survival in the imatinib-treated group was 88% (comparative data not available due to crossover of subjects) and the remission rate in the imatinib-treated group was also much higher (143). Data comparing survival before and after the introduction of imatinib show a large absolute improvement in survival rates at eight years from 45% (in the years 1991–2000) to 75% in the imatinib-treated cohorts (144).

The Expert Committee noted that the first application described the use of imatinib in low- and middle-income countries with results that were varied but were generally in line with the results from treatment in high-income countries (145–149). Access to imatinib in low- and middle-income settings has been highly variable and to some extent has depended on the original manufacturer supplying the product through compassionate access programmes.

The cost of imatinib has been very high. Generic preparations may become available: Europe has already granted approval for one generic imatinib

preparation and multiple applications for generic preparations in the USA are awaiting expiry of the patent period (150). The price of imatinib is therefore expected to decrease.

The Expert Committee considered that the evidence showed that imatinib is a highly effective treatment for Philadelphia chromosome-positive chronic myeloid leukaemia, which is a relatively uncommon form of leukaemia. While noting the limited population for which the drug might be useful, the Expert Committee agreed that imatinib meets the criteria for inclusion as an essential medicine. The Committee considered that the cost-effectiveness of imatinib would depend mainly on the price that countries could negotiate with suppliers, but also noted that long-term supply and use of the product are necessary to maintain the therapeutic effect. Thus it would be important for countries to consider total cost in making a decision on whether to include imatinib in national EMLs or reimbursement programmes.

Given the need for the list of medicines in Section 8.2 of the EML to be reviewed, the Expert Committee decided that the final specification of imatinib in the EML should be done by the Committee once the review is completed.

### *Trastuzumab (addition) – Adults*

There were two applications for the addition of trastuzumab for breast cancer. The first was from Dr Lawrence N. Shulman of the Center for Global Cancer Medicine, Dana-Farber Cancer Institute, Boston, MA, USA and Julie Torode, Deputy CEO, Union for International Cancer Control, Geneva, Switzerland. The second application was from Knowledge Ecology International, Washington, DC, USA, University of California, San Francisco, Department of Medicine, San Francisco, CA, USA, and Universities Allied for Essential Medicines and Young Professionals Chronic Disease Network, Weill Cornell Medical College, New York, NY, USA.

Expert reviews were provided by Dr Suzanne Hill, Dr Nicola Magrini and Dr Johannes Löwer.

The importance of breast cancer as a public health priority is recognized in the fact that many of the antineoplastics necessary for its treatment are available in Section 8 of the EML. Human epidermal growth factor receptor 2 (HER2) positive breast cancer is estimated to account for around 20% of patients with the disease.

The Expert Committee noted that, for adjuvant therapy, the systematic review (based on eight trials) cited in the applications showed that in early HER2-positive breast cancer the use of trastuzumab in combination with standard treatment (surgery, radiotherapy and chemotherapy) has been found to increase the likelihood of survival. The estimated relative effect (hazard ratio) from the review for overall survival and disease-free survival were 0.66 (95% CI: 0.57–0.77) and 0.60 (95% CI: 0.50–0.71) respectively (151–153). Viani et al.

(2007) found that the absolute effect on survival was a mortality of 6.0% (217 of 4555) in the group treated with trastuzumab compared with 8.5% (392 of 4562) in the group not treated with trastuzumab (154). The review noted that there was some risk of bias in the trials due to inadequate allocation concealment, and also noted that some of the trials were stopped early for benefit. The sensitivity analyses conducted in the review to examine these factors did not find changes in the size of relative effect. The review also noted that two trials, including approximately 2800 patients, had not been published. A Cochrane review in 2012 found a survival benefit of 3.3%, 9.0% and 13.3% in women with low, moderate and high risk of death at 36 months (151).

In metastatic breast cancer the addition of trastuzumab to standard chemotherapy may be associated with prolonged survival. The Expert Committee noted that the main evidence of benefit in this population is based on the trial published in 2001 (155) which found an increase of five months in overall survival. However, other studies have shown that the effect on advanced/metastatic breast cancer has been less.

The toxicity – including cardiac toxicity – of trastuzumab is well defined. The ongoing costs of managing congestive cardiac failure in patients on extended treatment could be significant and, if so, would have an effect on estimates of cost-effectiveness.

The Expert Committee noted that, to provide optimal use of trastuzumab for breast cancer, a health care system should ensure that there are appropriate screening programmes, surgery, radiotherapy and chemotherapy in place. In addition, specialized diagnostic facilities are needed for cytogenetic testing and the identification of different types of tumour receptors. The second application argued that simplified testing techniques were being developed but the Committee noted that these were not yet available or validated.

The cost of trastuzumab is very high. Biosimilar preparations are not yet available, and the costs differential between originator and biosimilar versions is not yet known.

The Expert Committee considered that the evidence showed that trastuzumab is an effective adjuvant treatment in early-stage breast cancer. The Committee agreed that trastuzumab meets the criteria for inclusion as an essential medicine in health systems that have the capacity for specialized diagnostic facilities and for delivering the other treatment modalities for the management of breast cancer. The Expert Committee considered that the cost-effectiveness is likely to be unfavourable and recommended that WHO should develop strategies to assist countries to determine how to manage purchasing decisions in relation to high-cost medicines in general, including those for cancer.

Given the need for the list of medicines in Section 8.2 of the EML to be reviewed, the Expert Committee decided that final specification of trastuzumab in the EML should be done by the Committee once the review is completed.



## 8.4: Medicines used in palliative care

An application for medicines for palliative care in adults was submitted by the International Association for Hospice and Palliative Care (IAHPC), Houston, TX, USA.

An expert review was provided by Dr Gitanjali Batmanabane. Comments were received from Dr Myriam Henkens, International Medical Coordinator, Médecins Sans Frontières.

In response to a request from the Expert Committee in 2005, the IAHPC developed a list of essential medicines for palliative care based on the consensus of palliative care workers from around the world (156). As this list was based on expert opinion, the Expert Committee requested that a list be developed on the basis of scientific evidence.

The 17th EML stated: “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” (157).

The second EMLc included 17 medicines for paediatric palliative care based on an application made by paediatric palliative care specialists.

The application submitted by the IAHPC describes the principles of palliative care which (158):

- provides relief from pain and other distressing symptoms;
- affirms life and regards dying as a normal process;
- intends neither to hasten nor postpone death;
- integrates the psychological and spiritual aspects of patient care;
- offers a support system to help patients live as actively as possible until death;
- offers a support system to help the family cope during the patient’s illness and in their own bereavement;
- uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated;
- will enhance quality of life, and may also positively influence the course of illness;
- is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications.



It was noted that there was a difficulty in implementing high-quality prospective studies of symptoms and associated distress in patients receiving palliative care. The data identified were mainly from retrospective case reviews, expert opinion and case reports (156, 159–162). However, there is an interest in systematically gathering evidence in the area of palliative care in adults (163, 164).

To develop the list of proposed medicines, a working group was constituted by IAHP. Using WHO global mortality data this group identified the most common causes of death, and the most common and distressing symptoms in palliative care by means of a literature search. The final step was identification of the medicines to be recommended for the treatment of symptoms. Table 1 lists the most common and distressing symptoms occurring in people receiving palliative care, and the medications included in the application:

Table 1  
**Symptoms in palliative care, and proposed medicines**

Symptom	Proposed medicine
<b>Anorexia (appetite loss)</b>	<b>Dexamethasone</b> Injection: 4 mg/ml in 1-ml ampoule (as disodium phosphate salt) Oral liquid: 2 mg/5 ml Tablet: 4 mg (not listed in the EML)
<b>Anxiety</b>	<b>Diazepam</b> Injection: 5 mg/ml Oral liquid: 2 mg/5 ml Rectal solution: 2.5 mg; 5 mg; 10 mg Tablet: 5 mg; 10 mg <b>Lorazepam</b> Injection: 2 mg/ml in 1-ml ampoule Tablet: 1 mg; 2.5 mg (not listed in the EML)
<b>Constipation</b>	<b>Docosate sodium</b> Capsule: 100 mg Oral liquid: 50 mg/5 ml <b>Senna</b> Oral liquid: 7.5 mg/5 ml <b>Sodium picosulfate</b> Oral liquid 7.5 mg/ml (not listed in the EML)
<b>Delirium (confusion)</b>	<b>Haloperidol</b> Injection: 5 mg in 1-ml ampoule Oral liquid: 2 mg/ml Solid oral dosage form: 0.5 mg; 2 mg; 5 mg

Table 1 *continued*

Symptom	Proposed medicine
Depression	<b>Amitriptyline</b> Tablet: 10 mg; 25 mg
	<b>Fluoxetine</b> Tablet or capsule: 20 mg (as hydrochloride)
Diarrhoea	<b>Loperamide</b> Tablet or capsule: 2 mg
Dyspnoea (breathlessness)	<b>Morphine</b>
	<b>Recommended formulations for inclusion:</b>
	Granules (modified release) (to mix with water): 20 mg; 30 mg; 60 mg; 100 mg; 200 mg
	Injection: 10 mg/ml
	Oral liquid: 10 mg/5 ml
Tablet (immediate release): 10 mg.	
Tablet (controlled release): 10 mg; 30 mg; 60 mg	
Fatigue	<b>Dexamethasone</b>
	Injection: 4 mg/ml in 1-ml ampoule (as disodium phosphate salt)
	Oral liquid: 2 mg/5 ml Tablet: 4 mg (not listed in the EML)
Nausea and vomiting	<b>Metoclopramide</b>
	Injection: 5 mg (hydrochloride)/ml in 2-ml ampoule
	Oral liquid: 5 mg/5 ml Tablet: 10 mg (hydrochloride)
Pain	<b>Ibuprofen</b>
	Oral liquid: 200 mg/5 ml
	Tablet: 200 mg; 400 mg; 600 mg
	<b>Morphine</b>
	Granules (modified release) (to mix with water): 20 mg; 30 mg; 60 mg; 100 mg; 200 mg
	Injection: 10 mg/ml
Oral liquid: 10 mg/5 ml	
Tablet (controlled release): 10 mg; 30 mg; 60 mg	
Tablet (immediate release): 10 mg	
Respiratory tract secretions	<b>Hyoscine butylbromide</b>
	Injection: 10 mg/ml (not listed in the EML)

The Expert Committee noted that good-quality evidence for rational pharmacotherapy for many of the symptoms was lacking. The systematic reviews in the literature of symptom management related to patients with cancer. These reviews concluded that there was insufficient evidence to draw any firm conclusions on medicines for the treatment of symptoms such as fatigue, anxiety or anorexia in cancer. However, there is extensive experience in the use of these medicines for the treatment of most of the common symptoms experienced in terminally ill patients. The medicines that have been recommended in the application are already listed in the EML, under either palliative care or another indication. The unique position of the terminally ill patient and the objectives of providing palliative care means that experience needs to be taken into account.

Given the above, much of the evidence for the efficacy of these drugs was based on studies that were not of patients receiving palliative care. The Expert Committee also noted the medicines that were included for palliative care in children.

Lorazepam was not considered necessary as diazepam and midazolam were already available. The evidence for sodium picosulfate was insufficient to justify inclusion and there were already two other laxatives (docusate and senna) on the list. Although the evidence for the benefit to the patient of the use of antimuscarinic agents in prevention of accumulation of respiratory tract secretions during the dying phase was acknowledged as weak, the inclusion of hyoscine butylbromide (which, in contrast to the hydrobromide included for children, does not cross the blood–brain barrier) was supported. The inclusion of loperamide, in accordance with the existing WHO guidelines for the treatment of HIV, was supported.

The Expert Committee therefore recommended the listing of medicines for adults for common symptoms in palliative care, other than for pain, as shown in Table 2.

Table 2  
Medicines for common symptoms other than pain in palliative care

Medicine	Dosages
amitriptyline	<b>Tablet:</b> 10 mg; 25 mg; 75 mg
dexamethasone	<b>Injection:</b> 4 mg/ml in 1-ml ampoule (as disodium phosphate salt) <b>Oral liquid:</b> 2 mg/5 ml <b>Tablet:</b> 4 mg

Table 2 *continued*

Medicine	Dosages
<b>diazepam</b>	<b>Injection:</b> 5 mg/ml <b>Oral liquid:</b> 2 mg/5 ml <b>Rectal solution:</b> 2.5 mg; 5 mg; 10 mg <b>Tablet:</b> 5 mg; 10 mg
<b>docusate sodium</b>	<b>Capsule:</b> 100 mg <b>Oral liquid:</b> 50 mg/5 ml
<b>fluoxetine</b>	<b>Solid oral dosage form:</b> 20 mg (as hydrochloride)
<b>haloperidol</b>	<b>Injection:</b> 5 mg in 1-ml ampoule <b>Oral liquid:</b> 2 mg/ml <b>Solid oral dosage form:</b> 0.5 mg; 2 mg; 5 mg
<b>hyoscine butylbromide</b>	<b>Injection:</b> 20 mg/ml
<b>loperamide</b>	<b>Solid oral dosage form:</b> 2 mg
<b>metoclopramide</b>	<b>Injection:</b> 5 mg (hydrochloride)/ml in 2-ml ampoule <b>Oral liquid:</b> 5 mg/5 ml <b>Solid oral dosage form:</b> 10 mg (hydrochloride)
<b>midazolam</b>	<b>Injection:</b> 1 mg/ml; 5 mg/ml <b>Solid oral dosage form:</b> 7.5 mg; 15 mg
<b>senna</b>	<b>Oral liquid:</b> 7.5 mg/5 ml

## Section 9: Antiparkinsonism medicines

### *Antiparkinsonism medicines (review) – Adults*

A review of this section was submitted by Professor Richard Walker (United Republic of Tanzania/United Kingdom) on behalf of the Africa Task Force of the Movement Disorders Society.

Expert reviews were prepared by Dr Alar Irs and Dr Youping Li. Comments were received from Dr Shekhar Saxena, Director, Mental Health and Substance Abuse, WHO.

Parkinson disease is prevalent the world over. Life expectancy for patients with Parkinson disease in Europe was shown to be severely limited before the introduction of levodopa. That is essentially the situation that still exists in resource-constrained settings such as sub-Saharan Africa.

The current EML lists levodopa + carbidopa as 100 mg + 10 mg and 250 mg + 25 mg. Also listed is biperiden, an anticholinergic. Evidence shows that

the risk of death was significantly reduced following the initiation of levodopa, regardless of pre-levodopa duration of Parkinson disease, and this reduction persisted over 17 years (165). Levodopa + carbidopa is the mainstay of therapy. The 10:1 ratio of levodopa:carbidopa that is listed is too high to prevent levodopa-induced nausea for many patients. The 100 mg + 25 mg tablet with its 4:1 ratio is preferable for use for titration to the effective dose. Many guidelines and use data from the United Kingdom, for instance, support this statement. Patients are usually started on a 50 mg + 12.5 mg dose twice daily and gradually increased to 100 mg + 25 mg three times daily. The application reported that the current WHO listing was affecting availability of the correct formulation, especially in some African countries.

The application reported that biperiden was not widely available. Anticholinergics as a class are now rarely used, except in younger patients with predominant tremor problems. Anticholinergic use in elderly patients and in patients with cognitive impairment is limited because of well-known side-effects, including confusion, dizziness, memory loss and psychosis (hallucinations and agitation). Hence, the application argued that retaining this medicine in the EML was not justified. Trihexphenidyl was reported to be more widely available and was therefore recommended for addition, with clear notes to indicate that it should be used only in younger patients.

The review mentioned other newer medicines for Parkinson disease, for use by clinicians with experience in treating this disease. Pramipexole and ropinirole are available in low- and middle-income countries but are expensive compared with levodopa/carbidopa. Selegiline, a monamine oxidase type B inhibitor, can be used both as initial and as add-on therapy. Amantadine has moderate antiparkinsonian effects but has been found to be potentially helpful for dyskinesia.

On the basis of the data presented, the Expert Committee decided to add the levodopa/carbidopa 100 mg + 25 mg dosage form, but decided to retain the 100 mg + 10 mg and 250 mg + 25 mg dosage forms as they were commonly used. The Committee agreed to add a square box symbol to biperiden to allow for the option of procuring trihexphenidyl. The Expert Committee called for a detailed application for the addition of a dopamine agonist.

## Section 10: Medicines affecting the blood

### 10.1: Antianaemia medicines

#### *Ferrous salt + folic acid (new formulation) – Adults*

An application was submitted by the Department of Nutrition for Health and Development, WHO, for inclusion of a new formulation of ferrous salt and folic acid (60 mg elemental iron in a ferrous form plus folic acid 2.8 mg tablet/capsule)

for the prevention of anaemia in menstruating women and adolescent girls through an intermittent treatment regimen.

Expert reviews were provided by Dr Eva Njenga and Dr Shalini Sri Ranganathan.

There is a high prevalence of anaemia in non-pregnant women, especially in low- and middle-income countries, leading to low resistance to infections and reduced work performance. Anaemic women who become pregnant have poor maternal and neonatal outcomes. The evidence in a Cochrane review shows that intermittent supplementation with iron (either alone or in combination with other nutrients) is significantly more effective in reducing anaemia among menstruating women compared with no supplementation or placebo (RR: 0.73, 95% CI: 0.56–0.95). The positive effect of the intermittent supplement was seen in patients receiving iron once or twice a week. Overall, the finding appears to remain constant whether the supplements were given once or twice weekly, for less or more than three months, contained less or more than 60 mg of elemental iron per week, or the populations had different degrees of anaemia at baseline. Intermittent iron and folic acid supplements could, therefore, reduce the risk of anaemia in menstruating women and adolescent girls.

The most common side-effects of iron supplementation include nausea, constipation, dark stools and metallic taste. There is no significant difference in adverse side-effects of once-weekly intermittent iron supplementation versus no intervention or placebo (RR: 1.98, 95% CI: 0.31–12.72) and of once-weekly intermittent iron supplementation versus daily iron supplementation (RR: 0.36, 95% CI: 0.10–1.31) (166).

The EML currently lists the fixed-dose combination “ferrous salt + folic acid tablet equivalent to 60 mg iron + 400 µg folic acid”. Ferrous salt and folic acid are also listed separately. There are no data on efficacy comparing the “ferrous 60 mg + folic acid 400 micrograms” to “ferrous 60 mg plus folic acid 2.8 mg” in preventing anaemia. The difference in folic acid dose (400 µg to be replaced with 2.8 mg) was based on minimal evidence. The Cochrane review (166) and WHO guidelines (167) state that the recommendation of 2.8 mg is based only on the rationale of providing seven times the recommended daily dose to prevent neural tube defects and experimental evidence that high weekly doses can improve red blood cell folate concentrations to levels that have been associated with a reduced risk of neural tube defects.

While recognizing the programmatic needs for appropriate supplementation in pregnancy, the Expert Committee decided after careful consideration not to include this combination in the EML. Data to show the intermittent regimen to be at least equivalent to existing options (and not placebo) for the prevention of anaemia and/or neural tube defects would be needed. It was also noted that no commercial preparation of this fixed-dose combination yet exists.

## Section 11: Blood products and plasma substitutes

### 11.2: Plasma fractions for specific use

#### *Human normal immunoglobulin (additional dosage) – Adults and Children*

An application was submitted by CSL Behring AG, Bern, Switzerland, for inclusion of subcutaneous immunoglobulin (SCIg) 20% in the complementary list of the EML.

Expert reviews were provided by Dr Abdol Majid Cheraghali, Dr Youping Li and Dr Johannes Löwer. Comments were received from International Patient Organisation for Primary Immunodeficiencies, the African Society for Immunodeficiencies, the Latin American Society for Immunodeficiencies and Dr Ana Padilla of the Department of Essential Medicines and Health Products, WHO.

Human normal immunoglobulin is included in the EML (Section 11.2 – Plasma fractions for specific use) in concentrations of 5–16%, for intramuscular, intravenous and subcutaneous administration. The application was for a 20% concentration to be used subcutaneously with no change in indications. The schedules and doses of SCIg 20% would be the same as with the 15–16% concentrations but the infusion volumes would be smaller (168).

The major advantage cited for this formulation was patient convenience, with a lesser volume being required for the repeated administration that is required for the chronic conditions. The applications stated that the new preparation would decrease the cost of home-based therapy but no formal cost analysis was provided.

The Expert Committee decided not to change the list at this stage, pending amendments to the pharmacopoeial monographs applicable to such products. Once the monographs are updated, a more general listing that is compliant with the pharmacopoeial standards will be possible.

#### *Whole blood and red blood cells (addition) – Adults and Children*

An application was submitted by AABB (formerly the American Association of Blood Banks), the American Red Cross and Canadian Blood Services for the inclusion of whole blood and red blood cells in the EML.

Extensive comments were received from ministries of health, medicines and blood regulatory authorities, multilateral agencies, experts in transfusion medicine and their professional associations, Red Cross national societies, patient organizations and associations of voluntary blood donors. All comments remain available on the WHO EML website at: [http://www.who.int/selection\\_medicines/committees/expert/19/applications/blood](http://www.who.int/selection_medicines/committees/expert/19/applications/blood).

Expert reviews were provided by Dr Suzanne Hill, Dr Liliana de Lima and Dr Johannes Löwer.

The application stated that the inclusion of whole blood and red blood cells in the EML would accomplish several critical objectives in furtherance of World Health Assembly resolution WHA63.12 on the availability, safety and quality of blood products. These would include:

- heightened awareness of the need for blood in every country and of the role of blood in protecting public health;
- government responsibility for ensuring sustainable funding and support for a safe and adequate supply of blood that is accessible to patients in need;
- creation of a favourable environment for governments for national regulation dealing with blood and blood products;
- investment in infrastructure, systems and governance for blood establishments;
- additional emphasis on the need for effective and efficient procurement systems to provide equipment, supplies and reagents to collect, process, test, store and transport blood;
- additional emphasis on the need to ensure that blood is cost-effective, affordable and available; and
- enabling, and putting additional emphasis on the importance of, appropriate regulatory oversight of blood collection, processing, testing, storage and distribution to ensure the safety and quality of blood and the safety of blood transfusion.

The Expert Committee noted the discussion in the Open Session which reflected the many comments received and made available on the WHO EML website, both supporting and opposing the inclusion of whole blood and red blood cells in the EML. The Committee considered the fact that the application raised many issues that span technical, clinical, ethical and regulatory issues.

The Expert Committee discussed whether blood could be considered as a “medicine”, since this was a key issue highlighted in many of the comments both for and against inclusion. While noting that blood may be different from conventional medicines in that it is a “human-derived biological material”, it was acknowledged that many countries already regulate blood as a “biological medicine”. The heading of Section 11 in the first EML of 1977 was “Blood and haematopoietic system drugs”. It was also noted that the WHO Expert Committee on Biological Standardization defines blood products as “any therapeutic substances derived from human blood, including whole blood, labile blood components and plasma-derived medicinal products”.

The Committee agreed that there was no need to debate whether blood and red blood cells were essential as they were necessary for the treatment and management of many clinical conditions – such as anaemia and diseases of the



blood (where the haemoglobin levels requiring transfusion are well defined), gastrointestinal bleeding and injuries – as well as during surgery, and for obstetric conditions such as postpartum haemorrhage and neonatal conditions requiring exchange transfusions (169–174).

The Expert Committee also considered the issue of safety of blood. On the basis of the application and the comments, the safety issues relating to the use of blood were well defined and the importance of appropriate quality standards for its production were clear. Global application of these standards would improve the safety of blood for use in transfusion. It was noted that the risk of transfusion-mediated viral infections remains a constant concern.

The Expert Committee discussed the cost of delivering appropriate quality blood products. The cost of production is recognized as significant but WHO has taken many steps over the years to support countries in developing affordable and high-quality transfusion services. The Committee recognized the need to promote the appropriate use of transfusion to ensure that its cost-effectiveness would be maintained.

The Expert Committee further considered the concerns raised by some Member States and organizations regarding payment for donors, commercialization and commodification, including arguments relating to factor VIII and factor IX complex that are currently in the EML. Factors VIII and IX are supplied as commercial products, are used for a very limited number of conditions affecting a small population, and require sophisticated manufacturing technology; therefore they cannot be seen as examples of commodification for whole blood or red blood cells which have a limited lifespan/shelf-life and are used in very different clinical situations that affect a much larger population. The Committee noted that neither the applicant nor any of the comments provided data to support the claims that listing blood and red blood cells in the EML would lead to their commodification.

It was noted that medicines regulatory authorities, through the ICDDA resolution,<sup>5</sup> had expressed a strong preference for listing blood and red blood cells as an essential medicine to advance access to safe blood products that are appropriately regulated and traceable. Listing as an essential medicine would not be a sufficient solution in itself but would enable the beginning of a systematic approach to improving access to safe blood products. The Expert Committee noted that World Health Assembly resolution WHA63.12 called on Member States “to enhance the quality of evaluation and regulatory actions in the area of blood products and associated medical devices, including in vitro diagnostic devices”.

<sup>5</sup> See: [http://www.who.int/medicines/areas/quality\\_safety/regulation\\_legislation/icddr/14-ICDDA\\_recommendations.pdf](http://www.who.int/medicines/areas/quality_safety/regulation_legislation/icddr/14-ICDDA_recommendations.pdf).

The Committee fully concurred that listing whole blood and red blood cells in the EML would not be contradictory to the principles of voluntary, non-remunerated blood donation, as noted in World Health Assembly resolution WHA63.12. Such a listing would strongly support these principles.

Having considered all the above arguments, the Expert Committee decided to change the heading of Section 11 to “Blood products of human origin and plasma substitutes” and to restructure the section to specify blood products clearly. The note under Subsection 11.2 would be moved to Subsection 11.1 and would be updated to reflect World Health Assembly resolution WHA63.12. Subsection 11.1 would be relabelled “Blood and blood components” and would list fresh–frozen plasma, red blood cells, platelets and whole blood. The balance of the section would be renumbered. Subsection 11.2 would be labelled “Plasma-derived medicinal products”, with a Subsection 11.2.1 labelled “Human immunoglobulins”. Subsection 11.2.2 would be labelled “Blood coagulation factors” and would list factor VIII and factor IX. Subsection 11.3 would be labelled “Plasma substitutes”. A note would also be inserted to indicate that a review of this last subsection would be needed at the next meeting of the Expert Committee as the subsection contains dextran, and that the Committee should also consider a possible move of the three immunoglobulins (anti-D, anti-tetanus and anti-rabies) from Section 19.2 to the new Subsection 11.2.1.

## Section 12: Cardiovascular medicines

### *Fixed-dose combination for secondary prevention of cardiovascular disease (addition) – Adults*

An application was submitted by Dr Mark D. Huffman, Northwestern University Feinberg School of Medicine, Chicago, IL, USA, Dr Shanthi Mendis, Director, Management of Noncommunicable Diseases, WHO, Dr Valentin Fuster, Mount Sinai School of Medicine, New York, NY, USA, Dr Anthony Rodgers, The George Institute, Sydney, Australia, Dr Sidney C. Smith Jr, University of North Carolina, Chapel Hill, NC, USA and Dr Salim Yusuf, Population Health Research Institute, McMaster University, Hamilton, Canada, for the inclusion of fixed-dose combination therapy for secondary prevention of cardiovascular disease (ischaemic heart disease and thrombotic stroke).

Expert reviews were provided by Mr Andrew Gray and Dr Lisa Bero. The three preparations mentioned in the application were:

- Indian Polycap in two strengths:
  - (low dose) aspirin 100 mg, simvastatin 20 mg, ramipril 5 mg, atenolol 50 mg, hydrochlorothiazide 12.5 mg;
  - (high dose) aspirin 200 mg, simvastatin 40 mg, ramipril 10 mg, atenolol 100 mg, hydrochlorothiazide 25 mg;

- Trinomia/Sincronium:
  - aspirin 100 mg, simvastatin 40 mg, ramipril (2.5 mg, 5 mg or 10 mg);
- Red Heart Pill in two strengths and combinations (not yet commercially available):
  - aspirin 75 mg, simvastatin (20 mg or 40 mg), lisinopril 10 mg, atenolol 50 mg;
  - aspirin 75 mg, simvastatin (20 mg or 40 mg), lisinopril 10 mg, hydrochlorothiazide 12.5 mg.

The Polycap brand is registered in India, while the Trinomia/Sincronium brand is available in Guatemala and Mexico. It was not clear to the Expert Committee which of these combinations was being proposed for inclusion in the EML and specifically in which strengths.

The Expert Committee noted that there is a need for access to effective and appropriate secondary prophylaxis for cardiovascular diseases. Although there is wide acceptance of the concept of using a fixed-dose combination for the prevention of cardiovascular disease, the proposal did not present a comprehensive review of the projected health gains from use of any of the fixed-dose combinations in either primary or secondary prophylaxis.

The clinical trials cited in the proposal were chiefly in primary prevention, were of short duration, and relied on surrogate end-points (175, 176). There is as yet no trial with any of the fixed-dose combinations that is powered to show a difference in morbidity and mortality. While the medicines in the proposed fixed-dose combinations have been individually tested, there have been no adequate trials of these combinations in secondary prophylaxis.

The Expert Committee considered that there might be improved adherence to treatment regimens using a fixed-dose combination as opposed to multiple separate agents. However, the Committee also noted that previous reviews of the effect of fixed-dose combinations on adherence in other therapeutic areas such as HIV and malaria may not be directly relevant to the potential adherence outcomes in patients with cardiovascular disease. In addition, there was no evidence to substantiate the claim that widespread use of the proposed fixed-dose combinations would translate into significant clinical benefits or whether such use would also be associated with increased adverse effects.

The Expert Committee noted that there are serious gaps in the data on the proposed fixed-dose combination formulations. Only one of the three dosage forms listed has undergone a bioavailability study comparing the individual components with the fixed-dose combination (177). The application stated that “other fixed-dose combination therapies demonstrate similar degrees of

bioequivalence with the individual components” but did not provide data to support this claim.

The Expert Committee therefore recommended that these products should not be included in the EML. However, it noted that the use of fixed-dose combinations for the prevention of cardiovascular disease is a promising concept and that a further submission should be made once adequate clinical trials are available and the choice of formulation is clear.

## 12.4: Medicines used in heart failure

### *Spironolactone (new indication) – Adults*

An application was submitted by Evan Blank, Claire Hutchinson, Alexander Peters and Rajesh Vedanthan, Mount Sinai School of Medicine, New York, NY, USA, Mark Huffman, Amisha Patel, Northwestern Feinberg School of Medicine, Chicago, IL, USA and Sandeep Kishore, Weill Cornell Medical College, New York, NY, USA, for aldosterone antagonists to be added as a therapeutic class (with spironolactone as the representative) to Section 12.4 of the EML.

Expert reviews were provided by Dr Kuruvilla Prasad Mathews and Dr Suzanne Hill. Comments were received from Dr Shanthi Mendis, Director, Management of Noncommunicable Diseases, WHO, Dr Valentin Fuster, Director, Sinai Heart, New York, Dr Prabhakaran, Public Health Foundation of India and Dr Myriam Henkens, International Medical Coordinator, Médecins Sans Frontières.

Spironolactone has been in the EML since 1983 as a potassium-sparing diuretic.

Three clinical trials were presented as evidence for efficacy in the application. The first was the Randomized Aldactone Evaluation Study (RALES, 1999), which demonstrated a significant benefit with the addition of spironolactone to the standard therapy of an angiotensin-converting-enzyme (ACE) inhibitor and a loop diuretic in patients with severe heart failure. This randomized, double-blinded, placebo-controlled trial assessed the efficacy of spironolactone (25 mg) in 1663 patients in 195 centres in 15 countries. Patients included in the trial had New York Heart Association (NYHA) class IV heart failure within the previous six months, NYHA class III or IV heart failure at the time of enrolment, and a left ventricular ejection fraction (LVEF) of no more than 35%.

The trial was stopped early after a mean follow-up period of 24 months due to an interim analysis showing that spironolactone was superior to placebo. The trial found a 30% reduction in overall mortality (hazard ratio, HR = 0.70, 95% CI: 0.60–0.82), a 35% reduction in hospitalization (HR = 0.65, 95% CI: 0.54–0.77), and significant improvement in heart failure symptoms based on the NYHA functional class ( $P < 0.001$ ) in the treatment group. The number needed to treat (NNT) to prevent one death over 24 months was 8.8 (178).

The second clinical trial was the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), which evaluated the effectiveness of eplerenone (25 mg initial dose, titrated to a maximum of 50 mg) in patients with post-myocardial infarction left ventricular systolic dysfunction (left ventricular ejection fraction (LVEF)  $\leq$  40%) in a randomized, double-blinded, placebo-controlled trial. Eplerenone reduced overall mortality by 15% (HR = 0.85, 95% CI: 0.75–0.96) and cardiovascular disease-specific mortality by 17% (HR = 0.83, 95% CI: 0.72–0.94) when compared with placebo over a mean follow-up of 16 months (179).

The third trial was the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF), a randomized, double-blinded, placebo-controlled study that also showed that eplerenone was effective in patients with left ventricular systolic dysfunction (EF < 35%) and mild symptoms (NYHA class II). The trial was also stopped early because of a significant decrease in deaths from cardiovascular causes (HR = 0.76, 95% CI: 0.61–0.94) and a decrease in hospitalization from heart failure (HR = 0.58, 95% CI: 0.47–0.70) in the eplerenone treatment group (180).

Spironolactone is associated with an increased risk of gynaecomastia, which may not be as frequent with eplerenone. However, both are associated with an increased risk of hyperkalaemia, which may be worse with eplerenone. Both products would require potassium concentrations to be monitored to ensure safe use.

The most recent systematic review concluded that eplerenone was similar to older, less expensive aldosterone antagonists, but hyperkalaemia may be more frequent with eplerenone whereas gynaecomastia was more frequent with the older aldosterone antagonists (181). Other systematic reviews have confirmed the decrease in mortality with aldosterone antagonists (182).

There are no direct comparative studies of spironolactone and eplerenone.

Spironolactone is widely available and inexpensive. Eplerenone is substantially more expensive. Several cost-effectiveness studies from high-income countries show that spironolactone, compared with placebo as an add-on therapy in heart failure patients already treated with ACE-inhibitors and beta-blockers, is cost effective under most assumptions.

The Heart Failure Society of America Guidelines Committee recommends: “Until such time as the effectiveness of these two drugs (spironolactone and eplerenone) in several different patient groups is compared in a well-designed clinical trial, it seems most reasonable for the clinical use of these agents to be consistent with their use in clinical trials. If cost or insurance reimbursement is an issue, as it will be for many, a reasonable choice is to substitute spironolactone” (183).

The Expert Committee recommended the expansion of the indication for spironolactone for heart failure (by listing in Section 12.4, as part of the

core list), without a square box because of the current price differential between spironolactone and eplerenone as the other main aldosterone antagonist and possible significant differences in safety profile with respect to hyperkalaemia. No change was made to the EMLc since additional data would be needed to justify inclusion for this patient group, in which the etiology of heart failure is very different.

## Section 13: Dermatological medicines (topical)

### 13.4: Medicines affecting skin differentiation and proliferation

#### *Benzoyl peroxide (review) – Adults and Children*

The 18th meeting of the Expert Committee requested a review of whether adults and children with mild-to-moderate acne should be treated with benzoyl peroxide compared with other topical preparations. The review was prepared by the International League of Dermatology Societies (ILDS).

Expert reviews were prepared by Dr Youping Li and Dr Alar Irs.

Acne is one of the common skin conditions mostly affecting the younger age group. Benzoyl peroxide has been in use in different formulations for over 50 years and is available worldwide. It remains the first-line choice of treatment for mild-to-moderate acne; it is effective and inexpensive and is mentioned in a large number of national treatment guidelines, such as those of the United Kingdom and the USA (184–186).

Systematic reviews have evaluated the efficacy and safety of benzoyl peroxide across a range of age groups and presentations and two reviews in 2001 (187) and 2004 (188) rated the treatment effect of benzoyl peroxide as favourable compared to placebo. Side-effects were erythema, peeling and occasionally burning. A recent systematic review using GRADE methodology on the management of acne compared benzoyl peroxide to other contemporary treatments and concluded that it should be considered as the first-line choice for mild acne (189). The adverse events mentioned, which were seldom severe, may be linked to the higher concentrations available, including the 10% formulation.

The Expert Committee recommended that benzoyl peroxide should be retained on the EML for both adults and children.

#### *Coal tar (review) – Adults*

At its 18th meeting, the Expert Committee requested a review of whether adults and children with psoriasis should be treated with coal tar solution rather than other topical preparations for psoriasis. The review was prepared by ILDS.

Expert reviews were prepared by Dr Youping Li and Dr Alar Irs.

Although coal tar preparations have been used for over 100 years in psoriasis, their mechanism of action is still unclear. Preparations are available

for the treatment of psoriasis in a variety of different formulations for lesions on the trunk and limbs, and as shampoos for scalp lesions.

A Cochrane systematic review of topical treatments for psoriasis included 131 randomized controlled trials some of which investigated coal tar versus placebo or alternative medicines, notably vitamin D analogues and topical corticosteroids (190). Both vitamin D analogues (e.g. calcipotriol) and corticosteroids performed better than placebo but no better than each other. Combined vitamin D and corticosteroids performed significantly better than either treatment alone.

Concerns have been expressed about the potential carcinogenicity of coal tar preparations. Reviews of the literature have, however, been unable to uncover evidence of increased risk of cancer in those treated with medical formulations of coal tar (191, 192).

One study has estimated the relative costs of coal tar and calcipotriol using contemporary measures of psoriasis area and severity. The coal tar treatment produced greater improvement in severity and at less cost (US\$ 0.92 per 1% improvement in scoring) than calcipotriol treatment (US\$ 35.42 per 1% improvement) after 12 weeks of treatment. After treatment and six weeks of follow-up (at week 18), the relative costs were US\$ 1.01 in the coal tar group and US\$ 58.11 in the calcipotriol group because the coal tar group maintained the improvement while the calcipotriol group significantly worsened (193). Although there are other medications available, coal tar is an effective and safe treatment for psoriasis, is affordable and is widely available.

The Expert Committee therefore recommended the retention of coal tar in the EML.

### *Dithranol (deletion) – Adults*

The 18th meeting of the Expert Committee requested a review of dithranol for possible deletion from the EML. The review was submitted by ILDS.

Expert reviews were prepared by Dr Youping Li and Dr Alar Irs.

Dithranol has been used topically for many years for the treatment of psoriasis. It is available in various formulations such as creams, ointments or pastes in strengths of 0.1–2%. However, clinical use of dithranol has decreased in most parts of the world and it is seldom available in resource-poor areas. The main reason for the decreased use has been the known risk of severe irritant reactions when the preparation is applied to psoriatic plaques and, in particular, on extra-lesional skin (190).

There is little evidence of the efficacy of dithranol as this is an old medication that has not been subject to substantive clinical trials. However, data collected in a Cochrane review of the treatment of plaque-type psoriasis with topical medications found that it was more effective than placebo (190). Burning and itching are very common adverse events that occur on skin lesions and



normal skin in contact with dithranol. In a systematic review of adverse events with topical treatments for psoriasis, dithranol performed worst with 72% of patients having adverse events (194).

The Expert Committee decided to delete dithranol from the EML due to concerns about the balance between benefits and risks and the low utilization of this medicine (190, 194). There are other suitable alternatives for this indication in the EML.

## Section 17: Gastrointestinal medicines

### 17.1: Antiulcer medicines

#### *Antiulcer medicines (review) – Adults*

At its 18th meeting, the Expert Committee requested a review for the possible deletion of histamine-2 receptor (H<sub>2</sub>) antagonists (currently exemplified by ranitidine) and another review to consider whether adults and children with gastro-oesophageal reflux or non-ulcer dyspepsia should be treated with H<sub>2</sub> antagonists compared with proton pump inhibitors. The need for parenteral preparation of omeprazole was also discussed in the review.

The review was prepared for the WHO Secretariat by Dr Grigorios I. Leontiadis, McMaster University, Hamilton, Ontario, Canada and Joint Coordinating Editor, Upper Gastrointestinal and Pancreatic Diseases Group, The Cochrane Collaboration, and Dr Yuhong Yuan, McMaster University, Hamilton, Ontario, Canada.

Expert reviews were prepared by Dr Nicola Magrini and Dr Gilles Sama Kwende. Comments were received from Dr Myriam Hekens, International Medical Coordinator, Médecins Sans Frontières.

#### ***H<sub>2</sub> receptor antagonists (H<sub>2</sub>RAs) versus proton pump inhibitors (PPIs) for gastro-oesophageal reflux disease (GERD)***

According to the most recent American Gastroenterological Association Medical Position Statement on the management of GERD, “for the treatment of patients with esophageal GERD syndromes (healing esophagitis and symptomatic relief) ... PPIs are more effective than H<sub>2</sub>RAs, which are more effective than placebo” (195). All other recent consensus guidelines agree with this recommendation (196, 197).

However, H<sub>2</sub>RAs have several advantages such as faster onset and longer duration of action, no need to time doses before meals, less harm in pregnancy and lower cost. Furthermore, H<sub>2</sub>RAs can be used in patients who cannot tolerate PPIs because of side-effects.

#### ***H<sub>2</sub>RAS versus PPIs for non-ulcer dyspepsia***

There is limited evidence on the efficacy of H<sub>2</sub>RAs and PPIs in patients with non-ulcer dyspepsia (NUD). A Cochrane systematic review and meta-analysis



of randomized controlled trials on pharmacological interventions for NUD concluded that both H<sub>2</sub>RAs and PPIs were more effective than placebo in symptoms of oesophagitis, and there was no evidence of a difference between H<sub>2</sub>RAs and PPIs (198, 199).

### ***PPI parenteral preparation***

Most patients who require PPI treatment can be treated with oral PPIs. However, there are some situations where intravenous PPI treatment is either preferable or is the only possible route of administration.

The most important and common indication for intravenous PPIs is peptic ulcer bleeding. Intravenous omeprazole has been approved for this indication in Europe, and the application is pending with the United States FDA. This is based mainly on the results of a large high-quality multicentre randomized controlled trial that was published in 2009 (200), but older Cochrane systematic reviews and meta-analyses of randomized controlled trials had found that there is strong evidence supporting the efficacy of high-dose intravenous PPI treatment in such patients (201).

### ***Comparative costs***

H<sub>2</sub>RAs cost less than PPIs and this is particularly important for low- and middle-income countries.

The Expert Committee recommended that no changes to the EML should be made at this time. A more extensive application would be needed to justify the addition of a parenteral PPI, including its place in the management of acute gastrointestinal bleeds where immediate access to endoscopy is not possible.

## **Section 18: Hormones, other endocrine medicines and contraceptives**

### **18.5: Insulins and other medicines used for diabetes**

#### ***Glibenclamide (review) – Adults***

At its 18th meeting, the Expert Committee requested a review on the safety of sulfonylureas in elderly patients to determine whether updates to the EML were needed.

The review was prepared by Mr Harinder Singh Chahal, Doctor of Pharmacy Candidate at the University of California – San Francisco, San Francisco, CA, USA.

Expert reviews were prepared by Mr Andrew Gray and Dr Kuruvilla Prasad Mathews. Comments were received from Dr Shanthi Mendis, Director, Management of Noncommunicable Diseases, WHO, and Dr Myriam Henkens, International Medical Coordinator, Médecins Sans Frontières.

The estimated worldwide prevalence of diabetes in the elderly population (60 years and above) is 18.6% or 134.6 million people (202). In 2013 the Expert Committee noted that the EML listed only glibenclamide from the sulfonylurea category. Elderly patients are a significant proportion of type II diabetics and the safety of sulfonylureas in this group is therefore important.

The review evaluated the comparative safety and efficacy of four second-generation sulfonylureas for the treatment of type 2 non-insulin dependent diabetes in elderly patients. The medications reviewed were glibenclamide (also called glyburide), gliclazide, glimepiride and glipizide. The review also analysed the cost of the four medications as well as their availability on the national essential medicines lists of 40 low- and middle-income countries.

A 2007 meta-analysis of 21 studies showed that, on the basis of HbA1c results, glibenclamide compared with other sulfonylureas – including gliclazide, glimepiride and glipizide – did not have an increased efficacy in the treatment of diabetes (203).

The same meta-analysis showed that there was an increased risk of hypoglycaemia of 52% with glibenclamide when compared with other insulin-secreting anti-diabetes medicines and an 83% higher risk compared with other sulfonylureas (203).

A retrospective cohort study of more than 13 000 patients concluded that glibenclamide had the highest rate of hypoglycaemia at 16.9 per 1000 person-years, compared with all other sulfonylureas (204). The authors also concluded that the physiological changes associated with increasing age, such as declining renal and hepatic function, as well as polypharmacy and concurrent illnesses, additionally predispose elderly patients to hypoglycaemia; this predisposition is further compounded by the use of glibenclamide. Another retrospective, cohort study of more than 33 000 patients in the United Kingdom showed that the risk of hypoglycaemia was higher with glibenclamide when compared with other sulfonylureas (205). The authors also concluded that patients older than 65 years were at higher risk of hypoglycaemia compared with adults less than 65 years of age with a relative risk of 1.27 (95% CI: 1.06–1.51).

In the analysis of the national essential medicines lists, the most widely available second-generation sulfonylurea was glibenclamide, with an overall listing on 39 of the 40 national essential medicines lists (97.5%), followed by gliclazide and glipizide which were available on 50% and 27.5% of the national lists, respectively.

The Expert Committee discussed the fact that all four sulfonylureas are available as generics, but there is considerable variation in price between countries and therefore it is not possible to make a clear decision on the basis of cost. However, glibenclamide appeared to be the cheapest in most countries.

The Expert Committee decided that glibenclamide should be replaced in the core list with gliclazide (30 mg, 60 mg, 80 mg), with a square box symbol

as the example of a second-generation sulfonylurea, and that a note should be added to the effect that glibenclamide should not be used in patients aged 60 years and older.

### *Oral hypoglycaemics (review) – Adults*

At its 18th meeting, the Expert Committee requested a review on oral hypoglycaemics. The Committee asked: “Should adults with type 2 diabetes be treated with (1) alpha-glucosidase inhibitors, such as acarbose; (2) amylin analogues, such as pramlintide; and (3) dipeptidyl peptidase-4 inhibitors such as sitagliptin and meglitinides such as repaglinide and mitiglinide compared with other classes of oral hypoglycaemic medicines (metformin; sulfonylureas such as glibenclamide, glimepiride, and gliclazide; thiazolidinediones such as pioglitazone and rosiglitazone)?”

The review was prepared by Mr Harinder Singh Chahal, Doctor of Pharmacy Candidate at the University of California – San Francisco, San Francisco, CA, USA. The review excluded pramlintide as it was a peptide for injection.

Expert reviews were provided by Mr Andrew Gray and Dr Kuruvilla Prasad Mathew. Comments were received from Dr Shanthi Mendis, Director, Management of Noncommunicable Diseases, WHO.

The review compared the four groups of oral hypoglycaemics: (1) dipeptidyl peptidase-4 (DPP-4) inhibitors, (2) thiazolidinediones, (3) alpha-glucosidase inhibitors, such as acarbose, and (4) meglitinides, against metformin (biguanide) and sulfonylureas. The base was a systematic review in 2010 (206), which was combined with other systematic reviews of oral hypoglycaemics (207–213).

A detailed comparison using the GRADE methodology was done of metformin with each of the four groups, and also of sulfonylureas and each of the four groups. The tables are available at: [http://www.who.int/selection\\_medicines/committees/expert/19/applications/Sulfonylurea\\_18\\_5\\_A\\_R.pdf](http://www.who.int/selection_medicines/committees/expert/19/applications/Sulfonylurea_18_5_A_R.pdf).

It was not possible to carry out an evaluation for each of the four groups versus metformin and sulfonylureas for all clinically relevant outcomes as there were insufficient studies. For instance, while there were studies reporting all-cause mortality (a critical outcome) for metformin versus DPP-4, thiazolidinediones and meglitinides, there was insufficient data to compare metformin versus acarbose.

For the effect on HbA1c, none of the medicines in the four groups were better than either metformin or sulfonylurea; the strength of the evidence ranged from low to high. For weight loss, metformin was better than the DPP-4 inhibitors and thiazolidinediones but there was no difference with alpha-glucosidase inhibitors and meglitinides. Sulfonylureas had a better effect on weight loss than the thiazolidinediones did but there was no difference between

sulfonylureas and the other three groups (DPP-4 inhibitors, alpha-glucosidase inhibitors and meglitinides).

As for the effect on high-density glycoprotein, triglycerides, hypoglycaemia and gastrointestinal adverse events, again none of the medicines in the four groups had a consistently favourable effect, or even a trend, compared with metformin and sulfonylureas.

For comparison of cost, all medicines in the four groups were more expensive than metformin and sulphonylureas.

None of the medicines in the four groups were shown to be better than metformin and sulphonylureas and at the most were equivalent only in some aspects. There were safety concerns with some medicines in the groups, and none of them offered any safety advantages over biguanides and sulphonylureas. Rosiglitazone had been withdrawn from European markets and pioglitazone was also withdrawn in France and Germany. The most recent concern about safety was on a potential increased risk of pancreatitis and pancreatic duct metaplasia in patients with type II diabetes treated with glucagon-like peptide (GLP)-1 receptor agonists and DPP-4 inhibitors (214).

The convenience sample of the national essential medicines lists of 15 low- and middle-income countries showed that only five countries had products from this group (rosiglitazone, pioglitazone, acarbose and repaglinide).

The Expert Committee decided that there was insufficient evidence to show that any of the medicines in the four groups (DPP-4 inhibitors, alpha-glucosidase inhibitors, meglitinides, or thiazolidinediones) offered any efficacy or safety advantages over the existing medicines included in the EML. WHO guidelines also do not recommend any medicines from these four groups.

The Expert Committee recommended that no medicines from the four groups should be added to the EML.

## Section 21: Ophthalmological preparations

### *Azithromycin (addition) – Adults and Children*

An application was submitted by the International Council of Ophthalmology for the addition of topical azithromycin 1.5% eye drops for the treatment of chronic keratoconjunctivitis caused by recurrent infection with *Chlamydia trachomatis*.

Expert reviews were provided by Dr Gitanjali Batmanabane and Dr Abdol Majid Cheraghali.

Trachoma, a chronic keratoconjunctivitis caused by recurrent infection from *C. trachomatis*, is the leading cause of infectious blindness worldwide (215). The current WHO guidelines recommend a single oral dose of azithromycin as the treatment. It was noted that oral azithromycin is not included in Section 21.1 of the EML.

Two studies were submitted in support of the application.

A randomized, controlled, double-masked, double-dummy, non-inferiority study including 670 children from Guinea and Pakistan was conducted. Three groups received one of three treatments: azithromycin 1.5% eye drops twice daily for two days, azithromycin 1.5% eye drops twice daily for three days, or azithromycin single 20 mg/kg oral dose.

The cure rate at day 60 in the per protocol analysis was 93.0%, 96.3% and 96.6% in the two-day group, three-day group, and oral treatment group, respectively. The azithromycin 1.5% eye drops groups were non-inferior to oral azithromycin. There were no significant differences between the groups with respect to re-emergence of trachoma ( $P > 0.545$ ).

All three treatments markedly reduced the trachomatous grading on days 30 and 60. It was noted that there were no significant differences between the treatment groups with respect to trachomatous grading ( $P > 0.170$ ) (216).

The second study was a mass treatment programme with no comparator. In February 2008, a programme was undertaken to treat the entire population of the Kolofata Health District in Cameroon (115 274 residents) with azithromycin 1.5% eye drops twice daily for three days. A total of 51 659 adults and 59 681 children over 15 years of age were treated. It was reported that: “One year after two rounds of topical treatment, prevalence dropped to 3.1% (95% CI 2.0–4.9) ( $P < 0.0001$ ), a decrease of 90%. The prevalence of trachomatous inflammation decreased significantly ( $P = 0.0001$ ) to 3.1% one year after the second round of treatment. The prevalence of intense trachomatous inflammation disappeared after two annual treatments (0% after second treatment ( $P = 0.0005$ ))” (217, 218).

The first trial showed similar efficacy of azithromycin eye drops compared with single-dose oral treatment. In the second study, the cure rates in the mass treatment were similar to what would have been achieved with single-dose oral treatment.

The WHO Prevention of Blindness and Deafness unit supported the application and mentioned future activities – including revision of WHO’s trachoma control manual – that would support azithromycin eye drops.

In summary, azithromycin eye drops produced similar results to the single-dose oral treatment but required three days of topical application. There appeared to be better safety with azithromycin eye drops. It was noted that donation programmes with suitable presentations of the ophthalmic solution were planned. The oral preparation is not recommended for pregnant women or children under 1 year of age; for these patient groups the ophthalmic solution offers an important option. The use of oral azithromycin and its limitations are given in the WHO guidelines (219). The only alternative for such patients is topical tetracycline, which requires a protracted course (six weeks or six months, depending on the dose regimen used).

The Expert Committee recognized the need for topical azithromycin in particular patient groups, and acknowledged the superiority of this option compared with topical tetracycline. The Committee therefore recommended the addition of azithromycin 1.5% ophthalmic solution to Section 21.1 of both the EML and EMLc.

### *Bevacizumab (addition) – Adults*

An application was submitted by the International Council of Ophthalmology for the inclusion of bevacizumab for the treatment of proliferative (neovascular) eye diseases.

Expert reviews were provided by Dr Gitanjali Batmanabane, Dr Abdol Majid Cheraghali and Dr Nicola Magrini. The application was supported by the Prevention of Blindness and Deafness unit, WHO.

Age-related macular degeneration (AMD) is the leading cause of blindness in persons over 50 years of age in developed countries. It is estimated that by 2020 as many as 7.5 million people worldwide over the age of 65 years may have vision loss attributable to this disease (220). Between 10% and 20% of patients with AMD are expected to have the neovascular form of AMD which is responsible for 90% of all cases of severe vision loss. The Expert Committee consequently accepted that there is a clear public health need for the treatment of neovascular AMD.

The application for bevacizumab was based on a large, randomized, controlled trial – the Comparison of AMD Treatments Trials (CATT) funded by the National Institutes of Health, USA – which compared bevacizumab with ranibizumab (221, 222). The trial randomized 1200 patients to one of four treatments: either bevacizumab or ranibizumab and either monthly or “as needed” treatment regimens. For the primary outcome of change in visual acuity at one and two years of follow-up, bevacizumab and ranibizumab were equivalent. Bevacizumab administered monthly was equivalent to ranibizumab administered monthly, with 8.0 and 8.5 letters gained on the visual acuity scores, respectively. Bevacizumab administered as needed was equivalent to ranibizumab as needed, with 5.9 and 6.8 letters gained, respectively.

The analysis of adverse outcomes showed that rates of death, myocardial infarction and stroke were similar for patients receiving either bevacizumab or ranibizumab. The Expert Committee also considered the hospitalization events with bevacizumab compared with ranibizumab (24.1% versus 19.0%; RR: 1.29, 95% CI: 1.01–1.66), and noted that the excess events were broadly distributed in disease categories that had not been identified in previous studies. The Committee accepted the explanation given in the study that the differences in hospitalization rates were probably due to baseline imbalances. The Committee also noted that in the trial the higher doses of bevacizumab (monthly regimen) were associated

with a lower hospitalization rate than the lower dose (“as needed” regimen), which might be explained by chance or by baseline imbalances in the groups for comorbidities or other patient characteristics.

The Expert Committee also considered the results from a second trial that was not mentioned in the application. This British study (IVAN)<sup>6</sup> with 300 patients per arm was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme (223). The results of the trial showed that the two treatments had similar efficacy and safety, including comparisons of monthly versus “as needed” treatment regimens. In the IVAN trial systemic arteriothrombotic events and heart failure were less frequent for bevacizumab than for ranibizumab (0.7% versus 2.9%, OR: 0.23, 95% CI: 0.05–1.07,  $P = 0.03$ ).

The Expert Committee considered the observational studies evaluating the safety of bevacizumab, or comparing bevacizumab and ranibizumab. These data were mostly from record-linkage studies or large pharmacoepidemiology databases. The European Medicines Agency report of July 2012 which reviewed all these safety studies of bevacizumab concluded that: “... the CHMP agreed that detailed safety information provided from the CATT and IVAN studies is reassuring and no evidence can be provided that bevacizumab is systemically more unsafe than ranibizumab and vice-versa. The CATT study was not powered to detect rare adverse events or to show differences in the number of events with a relatively high background incidence in elderly people with AMD” (224).

The Expert Committee noted that currently available formulations of bevacizumab are not specifically formulated for intravitreal injections. Bevacizumab comes in a sterile solution of 25 mg/ml (i.e. 1.25 mg per 0.05 ml) so it does not need to be diluted, reconstituted or altered in any way. The Committee considered that reports of adverse events (e.g. endophthalmitis) resulting from reformulation of the vial size currently available for use for multiple injections had been traced to inadequate sterility in the compounding process. The Committee noted, therefore, that safe use of bevacizumab as currently formulated requires that use may need to be restricted to a single patient per vial, notwithstanding the wastage. Any alternative approach to using a single vial for multiple patients would have to comply with appropriate safe and sterile injection practices, including any requirements for storage of the product, to ensure that there would be no possibility of contamination. However, even allowing for wastage, on the basis of anecdotal cost comparisons the cost of using currently available vials of bevacizumab for intravitreal injection may be less than one-twentieth of the cost of using alternative products such as ranibizumab.

<sup>6</sup> A randomized controlled trial of alternative treatments to inhibit vascular endothelial growth factor (VEGF) in age-related choroidal neovascularization.



The Expert Committee concluded that, on the basis of the head-to-head comparative trials and the observational safety data, intraocular bevacizumab is effective and safe for the treatment of neovascular AMD.

While noting the absence of stringent regulatory authority approval for the use of bevacizumab for the indication of AMD, the Expert Committee recommended that it be included in the EML on grounds of public health need, demonstrated safety and effectiveness, and favourable cost-effectiveness. The Committee again drew attention to the need for safe preparation and administration of intravitreal bevacizumab. The Committee recommended the listing of bevacizumab 25 mg/ml injection (100-mg vial) in the complementary list in a new Section 21.6 on anti-vascular endothelial growth factor (VEGF) preparations.

### *Ketorolac (addition) – Adults*

An application was submitted by the International Council of Ophthalmology for the addition of ketorolac eye drops to the EML.

Expert reviews were provided by Dr Gitanjali Batmanabane and Dr Abdol Majid Cheraghali. The WHO Prevention of Blindness and Deafness unit supported the application. The unit drew attention to the increased risk of post-surgical inflammatory reactions associated with modern surgical techniques, such as in high-throughput cataract procedures.

The claim of public health relevance for this proposed listing was based on multiple uses of ketorolac in seasonal allergic rhinoconjunctivitis, prevention of surgically-induced miosis, post operative inflammation after cataract surgery, postoperative inflammation after glaucoma surgery, postoperative inflammation after vitreoretinal surgery and for relieving discomfort and pain after ocular surgery and trauma.

There are no WHO guidelines for these conditions and it was unclear from the application whether NSAID eye drops are recommended as routine after surgery for the conditions mentioned above. Ketorolac was found to be effective in moderate-to-severe ocular inflammation after cataract surgery but the comparison was with the vehicle solution rather than with another medicine (225). A Cochrane review states that the role of NSAID in the treatment of cystoid macular oedema following cataract surgery is unclear (226).

In allergic conjunctivitis, a double-blind, placebo-controlled study of 148 patients evaluated treatment given four times daily over a seven-day period and showed that ketorolac was significantly better than placebo with regard to ocular itching, conjunctival inflammation, conjunctival injection, swollen eyes, foreign-body sensation and ocular discharge (227). A second study of 93 subjects with a similar design but lacking slit-lamp observations reported that ketorolac was significantly better than placebo in reducing conjunctival inflammation and photophobia after seven days of treatment (228). A significant placebo effect



(as seen in improvement from baseline in the control group) was noted in both trials. Ketorolac appears to be used widely but the application did not contain any systematic reviews of efficacy and safety or any comparative trials with other NSAID eye preparations. Seasonal allergic conjunctivitis was also not considered by the Expert Committee to be of sufficient public health relevance to require that ketorolac be added to the EML.

Given that the evidence for effectiveness was not consistent, and noting that allergic conjunctivitis was not a major public health problem, the Expert Committee recommended that ketorolac should not be added to the EML at this time. However, the Committee indicated that it would welcome resubmission of an application for an ophthalmic NSAID with data showing effectiveness and safety, particularly in use in ocular surgery.

#### *Ketotifen (addition) – Adults and Children*

An application was submitted by the International Council of Ophthalmology for the addition of ketotifen eyedrops for seasonal allergic rhinoconjunctivitis and as a topical anti-inflammatory for the eye.

Expert reviews were provided by Dr Gitanjali Batmanabane and Dr Abdol Majid Cheraghali. The WHO Prevention of Blindness and Deafness unit supported this application "... or any other suitable non-steroidal anti-inflammatory drug" and suggested that treatment with ketotifen may prevent the overuse of steroids and subsequent severe eye and systemic complications.

In the application, seasonal allergic conjunctivitis was quoted as being a common (20%), mild condition. However, this is based on estimates and there are no surveys to validate this figure (229). The application did not include estimates of the disability caused by this condition.

The current EML does not have a medicine for seasonal allergic conjunctivitis and there are no WHO guidelines for the treatment of this condition. There are no topical ocular antihistamines in the EML.

The application did not contain any systematic reviews of ketotifen efficacy in seasonal allergic conjunctivitis; the studies were mainly of conjunctival allergen challenge models, some of which compared ketotifen to placebo (230). A Cochrane review on "Topical antihistamines for treating perennial allergic conjunctivitis" is at the protocol stage (231).

The Expert Committee recommended that ketotifen should not be added to the EML in view of the lack of public health relevance and lack of evidence of efficacy of ketotifen in seasonal allergic conjunctivitis.

#### *Latanoprost (addition) – Adults*

An application was submitted by the International Council of Ophthalmology for the addition of latanoprost for the treatment of glaucoma.

Expert reviews were provided by Dr Gitanjali Batmanabane and Dr Abdol Majid Cheraghali. Comments were received from the WHO Prevention of Blindness and Deafness unit.

Glaucoma is the second leading cause of blindness worldwide (232), and acetazolamide tablets and timolol and pilocarpine eye drops are included in the EML for glaucoma.

The application summarized the older clinical trials for once-daily latanoprost in open-angle glaucoma. These showed a sustained decrease of intraocular pressure in 84% of patients, lasting up to 24 months.

Bron & Emmerich concluded: “Timolol, the leading topical beta-adrenergic antagonist, is often used as a first line therapy for the treatment of glaucoma. Dorzolamide, the first topical carbonic anhydrase inhibitor to become available on the market, is often prescribed as an add-on therapy. A review of studies comparing the efficacy of latanoprost to combined timolol and dorzolamide suggested that the intraocular pressure lowering effect of latanoprost is equivalent to that of concomitant timolol dorzolamide therapy. In addition, data suggests that adding latanoprost to timolol and dorzolamide leads to a further 16% reduction of intraocular pressure”(233).

A recent systematic review judged the prostaglandin agents to be superior to other monotherapies “We judged the strength of evidence from these 3 most recent trials to be low. However, with the addition of the consistent high-quality systematic reviews, the conclusion that topical glaucoma medications decrease intraocular pressure (IOP) is well supported, as is the conclusion that prostaglandin agents are superior to other monotherapies with regard to decreasing IOP”(234).

A meta-analysis that evaluated trials comparing latanoprost with timolol found latanoprost to be more effective than timolol. Additionally, latanoprost had the advantage of once-daily administration (235).

The main adverse effect is iris pigmentation which is seen in 12% of patients with light-coloured irises and which occurs with long-term use. It is seen in 18% of patients when used for two years. Other adverse effects are mild, are not very common and do not lead to stopping treatment.

The Expert Committee decided to recommend that latanoprost be added to the core list in the EML. Timolol is to be retained as there is evidence that timolol and latanoprost have additive effects.

### *Ofloxacin (addition) – Adults and Children*

An application was submitted by the International Council of Ophthalmology for the addition of ofloxacin 0.3% for infectious keratitis in Section 21.1 which included only gentamicin 0.3%.

Expert reviews were provided by Dr Gitanjali Batmanabane and Dr Abdol Majid Cheraghali.

It has been estimated that up to 5% of all blinding conditions in developing countries are directly related to ocular trauma and the subsequent infection (236). This estimate is supported by population-based studies in several countries. In a blindness survey in Nepal, corneal trauma and ulceration were found to be the second leading cause of unilateral visual loss after cataract, accounting for 7.9% of all blind eyes. A study in south India found that the incidence of ulcerative keratitis was 11.3 cases per 10 000 persons, resulting in an estimate of 840 000 new ulcers annually in India alone.

The application provided data on one clinical trial in which ofloxacin 0.3% was compared with fortified gentamicin (1.5%) plus cefuroxime (5%) in microbial keratitis, and which showed similar rates of cure. The authors stated that treatment with ofloxacin monotherapy was associated with less toxicity but did not provide data (237). Another trial was identified in the expert reviews in which ofloxacin was found to be more effective than gentamicin (238).

Ofloxacin eye drops have been approved for the treatment of bacterial keratitis by Australia, the United Kingdom and the US FDA.

In summary, ofloxacin eye drops have been shown to be as effective as other antibiotic eye drops and potentially to have less toxicity. The clinical trials cited in the application did not show ofloxacin to be clearly superior to any of the commonly used antibiotic eye drops. It has the advantage of being affordable and widely available. However, the other fluoroquinolones may be widely available and equally affordable in different settings.

The Expert Committee recommended that ofloxacin ophthalmic solution should be added to the EML and the EMLc with a square box symbol.

## Section 22: Oxytocics and antioxytocics

### 22.1: Oxytocics

#### *Misoprostol (deletion) for prevention of postpartum haemorrhage – Adults*

An application was submitted by Professor Allyson Pollock, Dr Petra Sevcikova-Brhlikova, Barts and The London School of Medicine and Dentistry, London, United Kingdom, for the deletion of the indication of misoprostol for the prevention of postpartum haemorrhage.

Expert reviews were provided by Dr Lisa Bero, Dr Alar Irs and Dr Hany Abdel-Aleem. Comments were received from the Concept Foundation, Bangkok and Geneva, Gynuity Health Projects, New York, NY, USA, and Professor Anthony Mbonye, Ministry of Health, Kampala, Uganda.

Misoprostol was considered by the Expert Committee at its 18th meeting and was added to the 17th EML for prevention of postpartum haemorrhage.

However, a note was added, stating: “For prevention of postpartum haemorrhage where oxytocin is not available or cannot be safely used”.

The application for deletion presented no new data and was based on a reinterpretation of the data previously presented to the Expert Committee. The Expert Committee considered that, in the absence of new evidence to support a change to its previous recommendation, the existing listing and note should stand, i.e. the retention of misoprostol in Section 22.1 with the note stating that it is for the prevention of postpartum haemorrhage where oxytocin is not available or cannot be safely used.

### *Misoprostol (new indication) – Adults*

An application was submitted by Gynuity Health Projects, New York, NY, USA, for the inclusion of misoprostol for the treatment of postpartum haemorrhage attributable to uterine atony.

Expert reviews were provided by Dr Lisa Bero, Dr Alar Irs and Dr Hany Abdel-Aleem.

Comments were received from the International Federation of Gynecology and Obstetrics, the Bill & Melinda Gates Foundation and Dr Myriam Henkens, International Medical Coordinator, Médecins Sans Frontières.

The application requested that misoprostol be listed with an indication for the treatment of postpartum haemorrhage when oxytocin is unavailable. Specifically “Intravenous oxytocin should be used when available, but misoprostol could be an effective alternative in settings in which IV oxytocin is not feasible”.

Misoprostol for treatment of postpartum haemorrhage was considered at the 18th meeting of the Expert Committee (157). The data presented in the application to the 19th meeting of the Committee had already been considered at the 18th meeting and there were no new clinical trials. Since the 18th meeting, however, there had been a change in WHO treatment guidelines, with the use of misoprostol in the treatment of postpartum haemorrhage now recommended as follows (239):

- Intravenous oxytocin alone is the recommended uterotonic drug for the treatment of PPH.
- If intravenous oxytocin is unavailable, or if the bleeding does not respond to oxytocin, the use of intravenous ergometrine, oxytocin-ergometrine fixed dose, or a prostaglandin drug (including sublingual misoprostol, 800 µg) is recommended.

The Expert Committee has previously recommended misoprostol for prevention of postpartum haemorrhage where oxytocin is not available or cannot

be safely used. It had, however, not recommended the use of misoprostol for the treatment of postpartum haemorrhage.

The Expert Committee noted that the evidence showed that, for important clinical outcomes such as overall blood loss, misoprostol was inferior to oxytocin. The Committee also noted the concern that including misoprostol for treatment of postpartum haemorrhage might detract from efforts to ensure that the more effective and safer medicine – oxytocin – is available.

While recognizing the importance of effective management strategies for postpartum haemorrhage in resource-constrained settings, the Expert Committee decided not to add misoprostol to the EML for the treatment of postpartum haemorrhage, as the evidence relied on at the 18th meeting remained valid. The Committee also emphasized the need for active management of the third stage of labour, beyond pharmacological interventions. The Committee noted that the use of sublingual misoprostol, as described in the WHO guideline, was for last-resort use or “rescue” where all other alternatives were unavailable. This was by no means a preferred option, nor should it be a reason not to pursue improved availability of parenteral uterotonics. However, in settings where oxytocin was not available or could not be safely used, the existing listing of misoprostol for prevention of postpartum haemorrhage should ensure its availability for rescue purposes.

## **Section 24: Medicines for mental and behavioural disorders**

### **24.1: Medicines used in psychotic disorders**

Referring to Section 24 of the EML and EMLc, the Expert Committee at its 18th meeting in 2011 noted “... the potential importance of these medicines in children for a variety of disorders” and requested a review of the entire section.

The following applications were received:

- a proposal for the deletion of haloperidol and chlorpromazine from the EMLc;
- a request for inclusion of clozapine as a complementary medicine for treatment-resistant schizophrenia in adults;
- two applications for inclusion of the second-generation antipsychotic risperidone (one proposing inclusion in the core EML only and the other proposing inclusion of tablets in the core list and other formulations in the complementary list in both the EML and the EMLc);
- a proposal to modify the minimum age for the use of fluoxetine as a complementary medication in childhood depression.

### *Clozapine (addition as complementary medicine) – Adults*

An application to include clozapine as a complementary medicine for treatment-resistant schizophrenia in adults was submitted by the Department of Mental Health and Substance Abuse, WHO.

Expert reviews were prepared by Dr Kuruvilla Prasad Mathews and Mr Andrew Gray.

The 17th EML includes haloperidol and chlorpromazine in Section 24.1 (Medicines used in psychotic disorders). In 2009 the evidence review and the consequent recommendations of the guideline development group for WHO's Mental Health Gap Action Programme Intervention Guide identified some medicines, in addition to psychosocial interventions, for the treatment of psychotic disorders. The recommendations identified first-generation antipsychotics (broadly equivalent to typical antipsychotics) haloperidol or chlorpromazine as a first choice, and second-generation antipsychotics (broadly equivalent to the group of atypical antipsychotics) as their alternatives if availability and cost are not constraints (66).

The same recommendations reserved clozapine for individuals with psychosis who do not respond to other antipsychotics provided that laboratory facilities are available for regular monitoring of white blood cells.

In the pivotal trial comparing clozapine to chlorpromazine published in 1988, 30% of treatment-resistant patients responded to clozapine as compared with 4% to chlorpromazine (240). Later clinical trials have shown a response rate of 30–50% (241).

A 2010 guideline from the United Kingdom's National Institute for Health and Care Excellence suggests that clozapine be offered "to people with schizophrenia whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least two different antipsychotic drugs ..." (242).

Randomized clinical trials involving a large number of patients have been done with second-generation antipsychotics and two major long-term studies have been conducted by the United States National Institute of Mental Health (243, 244). These studies have shown a broadly similar response rate but differences in adverse effects (243, 244). Clozapine has been shown to be better than other second-generation antipsychotics in patients with an inadequate response to other antipsychotics (245).

However, although uncommon, agranulocytosis associated with clozapine treatment is a potentially fatal adverse event. Thus the use of clozapine is restricted to refractory patients principally because of the risk of agranulocytosis and the associated need for white cell monitoring.

The application requested the addition of clozapine for the management of cases refractory to other antipsychotics. The Expert Committee therefore decided to recommend addition of clozapine to the complementary list of the EML.

## 24.2: Medicines used in mood disorders

### 24.2.1: Medicines used in depressive disorders

#### *Fluoxetine (change to age restriction/deletion from EMLc) – Adults and Children*

An application was submitted by the Mental Health: Evidence and Research team, WHO, to update the fluoxetine age restriction from > 8 years to > 12 years.

Expert reviews were provided by Dr Nicola Magrini and Dr Gitanjali Batmanabane. Comments were received from Dr Myriam Henkens, International Medical Coordinator, Médecins Sans Frontières.

Depression appears to be rare in children younger than 6 years; the prevalence from 6 years to adolescence is less than that in adolescents. In a meta-analysis of 26 studies including 60 000 observations on children, the overall prevalence estimate for children under 13 years of age was 2.8% (standard error, SE = 0.5%), and for those aged 13–18 years it was 5.6% (SE = 0.3%) which is close to adult figures (246).

WHO's Mental Health Gap Action Programme Intervention Guide was published in 2010 based on WHO guidelines, which in turn were based on a series of evidence reviews conducted in 2009. The guideline development group for the intervention guide made the following strong recommendation:

“Antidepressants [tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI)] should not be used for the treatment of children 6–12 years of age with depressive episode/disorder in non-specialist settings.”

For the above reasons, the guideline development group made a strong recommendation to set the age limit of 12 years, as mentioned above (66, 67).

In 2007 the Subcommittee of the Expert Committee had noted the discrepancies in the minimum age for fluoxetine approved by several regulatory authorities and endorsed the inclusion of fluoxetine in EMLc with an age restriction of 8 years (247).

At its 19th meeting in 2013 the Expert Committee decided to retain the minimum age for fluoxetine at 8 years as the evidence submitted to raise the age to 12 years was not considered sufficient. However, the need for a thorough review of the section was noted as a priority.

#### *Risperidone (addition) – Adults*

The Expert Committee received two applications to include risperidone in the WHO Essential Medicines List, as follows:

The Mount Sinai School of Medicine, Program in Global Mental Health, New York, NY, USA, proposed the inclusion of the second-generation antipsychotic risperidone formulations in the core and complementary EML and EMLc.



Massachusetts General Hospital, The Chester M. Pierce MD Division of Global Psychiatry, Boston, MA, USA, (Young Professionals Chronic Disease Network) proposed the inclusion of the second-generation antipsychotic risperidone in the core EML.

Expert reviews were prepared by Mr Andrew Gray and Dr Kuruvilla Prasad Mathews. Comments were received from Dr Shekar Saxena, Director, Mental Health and Substance Abuse, WHO and Dr Myriam Henkens, International Medical Coordinator, Médecins Sans Frontières.

An application to add risperidone to the EML was first made in 1998. At that time risperidone had been available for only four years and it was still under patent and was expensive. A second application was made in 2009 several years after generic products of risperidone had become available but was rejected because of the incompleteness of the literature review and pricing data.

It is estimated that some 41.7 million people need treatment for schizophrenia and related disorders in low- and middle-income countries. The majority of these cases are in Asia (70%) and Africa (16%) (248). Schizophrenia is a significant contributor to the global disease burden, accounting for 1.1% of disability-adjusted life-years lost (249).

The Mental Health Gap Action Programme Intervention Guide published by WHO in 2010 (67) has three antipsychotics (haloperidol, chlorpromazine and fluphenazine), all of which are currently in the EML. The intervention guide states that, if the responses to these medications are inadequate, providers may choose to treat patients with a second-generation antipsychotic, if available and affordable. An excerpt from the guide states:

“If the response is inadequate to more than one antipsychotic medication using one medicine at a time at adequate dosage for adequate duration ... consider second-generation antipsychotics (with the exception of clozapine), if cost and availability is not a constraint, as an alternative to haloperidol or chlorpromazine.”

A 2010 Cochrane review of 23 randomized controlled trials including 4445 patients found risperidone to be more effective than typical antipsychotics in treating schizophrenia and schizoaffective disorder (250). On the basis of pooled data from nine randomized controlled trials, risperidone was more likely than haloperidol to produce clinical improvement in the short and longer term. Another more recent Cochrane review found that risperidone was more efficacious than both quetiapine and ziprasidone, though less efficacious than clozapine and olanzapine. Importantly, risperidone has a safer side-effect profile than both clozapine and olanzapine (250–253). Other reviews have also shown the overall efficacy of risperidone compared with first-generation antipsychotics (254, 255).



While risperidone and other second-generation antipsychotics are less likely to cause extrapyramidal side-effects when compared with typical antipsychotics, they are more likely to cause metabolic side-effects such as weight gain, hyperlipidaemia and hyperglycaemia.

The unit price of risperidone, including generics, has fallen substantially since 2008. A comparison of pre-generic and post-generic production data revealed the impact of generic production on the price. In 2002, the cost of a 2-mg tablet of risperidone ranged from US\$ 0.070 to US\$ 1.33, with the median price being roughly 70 US cents. In 2011, however, the cost of a 2-mg tablet of risperidone ranged from US\$ 0.0080 to US\$ 0.067, with the median price being just US\$ 0.034 (or roughly 3 US cents) (48). Data were also compared in the Indian market. Among 12 branded generic manufacturers the price of 10 units of 1-mg tablets ranged from 7.00 rupees to 19.70 rupees (256).

The Expert Committee considered the efficacy and safety of the atypical antipsychotics, apart from clozapine, to be broadly comparable but noted that availability of generics varies considerably.

The Expert Committee recommended that risperidone solid oral dosage forms should be added to the core list of the EML without the square box symbol. The Committee added that it would welcome further applications for additional second-generation (atypical) antipsychotics, based on careful consideration of suitable alternatives or additions to risperidone.

## Section 27: Vitamins and minerals

### *Calcium (addition) – Adults*

An application to include tablets of calcium (500 mg of elemental calcium as calcium carbonate) was prepared by the Department of Nutrition for Health and Development, Evidence and Programme Guidance unit, WHO.

Expert reviews were prepared by Dr Eva Njenga and Dr Shalini Sri Ranganathan.

The Expert Committee noted that the proposed inclusion of calcium supplementation in the EML followed two recent WHO guidelines assessing the use of calcium supplements in pregnant women: *WHO recommendations for the prevention and treatment of pre-eclampsia and eclampsia*, published in 2011, and *Calcium supplementation in pregnant women*, developed in 2012 (257, 258).

In both guidelines, WHO makes a strong recommendation for supplementation for pregnant women with 1.5–2 g of elemental calcium per day in areas where dietary calcium intake is low, and for women at high risk of developing hypertensive disorders during pregnancy.

Two recent Cochrane systematic reviews investigated whether calcium supplements consumed on a daily basis during pregnancy safely improved maternal and infant outcomes (259, 260). Calcium supplementation during

pregnancy significantly reduced the risk of pre-eclampsia and high blood pressure (with or without proteinuria).

Two types of calcium salts (lactate and carbonate) for oral supplementation are listed in the Management Sciences for Health *International Drug Price Indicator Guide* (48), with estimated monthly costs of approximately US\$ 11 and US\$ 4 respectively. However, given the scarcity of comparative price data for such products, the exact choice should be guided by local availability and cost.

The Executive Committee recommended the listing of solid oral dosage forms of calcium, providing 500 mg of elemental calcium per dose. The Committee also indicated that an application for calcium and other micronutrient supplementation in children would be required before this item could be considered for addition to the EMLC.

## Section 28: Ear, nose and throat medicines

### *Ear, nose and throat (review) – Adults and Children*

A review of the existing recommendations for essential medicines for ear, nose and throat conditions in adults and children and suggested modifications was submitted by Dr Shelly Chadha and Dr Andnet Kebede, Prevention of Blindness and Deafness unit, WHO, with a request for the inclusion of medicines and dosages for adults.

Expert reviews were prepared by Dr Shalini Sri Ranganathan and Dr Abdol Majid Cheraghali.

The Expert Committee supported the request in the review to change the title of Section 28 of the EMLC to “Ear, nose and throat medicines”. However, the proposal to review and update the EML to include adult formulations of topical or nasal spray medications analogous to those in the EMLC was not accepted. The medicines listed for children were based on the public health relevance of suppurative ear conditions, including otitis media and otitis externa. These conditions are not of equivalent public health relevance in adults. The Expert Committee therefore recommended no change to the existing listing. The Committee stated that any future application for medicines for the treatment of these conditions in adults must first demonstrate the public health relevance of the condition(s) to be treated or prevented, as well as presenting evidence of efficacy, safety and cost-effectiveness.

## 6. Summary of recommendations

### 18th WHO Model List of Essential Medicines

#### Additions to Model List

**Section 2.** Amitriptyline, diazepam, dexamethasone, docusate sodium, haloperidol, loperamide, hyoscine butylbromide, ibuprofen, metoclopramide and morphine were added to the core list for symptomatic treatment of palliative care.

**Section 3.** Loratadine solid oral dosage form and oral liquid were added to the core list because of their superior safety when compared with first-generation antihistamines.

**Section 4.** Fomepizole was added to the complementary list for the treatment of toxic alcohol and glycol poisoning.

**Section 6.4.3.** Pegylated interferon alfa-2a and alfa-2b were added to the complementary list to be used with ribavirin for treatment of hepatitis C.

**Section 6.5.3.1.** Artesunate + mefloquine 25 + 55 mg and 100 + 220 mg (as fixed-dose combinations) were added to the core list for treatment of uncomplicated falciparum malaria.

**Section 9.** Levodopa/carbidopa 100 mg + 25 mg was added to the core list for the treatment of Parkinson disease. A square box symbol was added to biperiden to allow for the option of procuring trihexphenidyl.

**Section 11.1.** Fresh–frozen plasma, platelets, red blood cells and whole blood were added to the core list. The Expert Committee strongly supported the principles of voluntary, nonremunerated blood donation contained in World Health Assembly resolution WHA63.12.

**Section 18.5.** Gliclazide (30 mg, 60 mg, 80 mg) replaced glibenclamide in the core list with a square box symbol to indicate it as the example of a second-generation sulfonylurea. A note that glibenclamide should not be used in patients aged 60 years and older was added.

**Section 21.** Azithromycin 1.5% eye drops were added to the core list for treatment of trachoma in pregnant women and children under one year of age. Bevacizumab was added to the complementary list for intravitreal injection for neovascular age-related macular degeneration. Latanoprost eye drops (50 µg/ml) were added to the core list, based on evidence of efficacy in multiple trials, for the treatment of open-angle glaucoma. Ofloxacin 0.3% eye drops were added to the core list for the treatment of bacterial keratitis based on efficacy in clinical trials.

**Section 24.1.** Risperidone solid oral dosage forms 0.25–6.0 mg were added to the core list for the treatment of schizophrenia.

**Section 24.1.** Clozapine solid oral dosage forms 25–200 mg were added to the complementary list for the treatment of patients with schizophrenia refractory to other treatments.

**Section 27.** Calcium tablets (500 mg of elemental calcium) were added to the core list for pregnant women in areas where dietary calcium intake is low and for women at high risk of developing hypertensive disorders during pregnancy.

### Deletions from Model List

**Section 3.** Chlorphenamine was deleted because of inferior safety when compared with second-generation antihistamines and loratadine, a second-generation antihistamine, was substituted.

**Section 13.4.** Dithranol (for topical treatment of psoriasis) was deleted because of concerns about the balance between benefits and risks and the low utilization.

### Changes to sections

**Section 2.** The section was renamed “Medicines for pain and palliative care” to include medicines for symptomatic treatment in palliative care.

**Section 6.3.** Amphotericin B and flucytosine for cryptococcal disease in HIV-infected adults and adolescents were moved from the complementary list to the core list.

**Section 8.** The heading was changed to “Antineoplastics and immunosuppressives” as medicines used in palliative care were moved to Section 2.

**Section 11.** The heading was changed to “Blood products of human origin and plasma substitutes”. Subsection 11.1 was retitled “Blood and blood components” and Subsection 11.2 was renamed “Plasma-derived medicinal products” with a Subsection 11.2.1 on “Human immunoglobulins” and a Subsection 11.2.2 on “Blood coagulation factors”. The title of Subsection 11.3 was changed to “Plasma substitutes”.

**Section 12.4.** Indications for spironolactone were expanded to include heart failure.

**Section 29.2.** A new section on “Medicines administered to the mother” was added to include dexamethasone under “Specific medicines for neonatal care”.

**Section 30.** A new section on “Medicines for diseases of joints” was created to list the treatments for gout, disease-modifying agents used in rheumatoid disorders and juvenile joint diseases that were moved from Section 2.

## Deferred applications

**Section 6.4.2.** Antiretroviral formulations to be added and deleted were not considered as the guidelines for treatment of both adults and children living with HIV/AIDS were as yet incomplete.

**Section 8.2.** The decisions on imatinib for chronic myeloid leukaemia and on trastuzumab for breast cancer were deferred until the medicines in the section are reviewed at the next meeting of the Expert Committee.

**Section 11.2.** The decision on human normal immunoglobulin 20% (a new concentration) for primary immune deficiencies was deferred pending amendments to the pharmacopoeial monographs applicable to such products.

## Rejected applications

**Section 2.1.** The application for the inclusion of naproxen was rejected as there was insufficient justification to include both ibuprofen and naproxen in the EML.

**Section 2.3.** The application for the reinstatement of colchicine for gout was rejected as commonly available NSAIDs are equally effective in the treatment of gout. Colchicine for familial Mediterranean fever was rejected since the relatively limited population affected did not justify its inclusion in a global list.

**Section 6.2.2.** The application regarding isoniazid + pyridoxine + sulfamethoxazole + trimethoprim (fixed-dose combination) was rejected because the product does not yet exist.

**Section 6.2.4.** The application for inclusion of bedaquiline was rejected as further efficacy and safety data from clinical trials conducted in different backgrounds were needed.

**Section 6.4.3.** The application to delete oseltamivir was rejected. Oseltamivir was retained for the restricted indication of potentially severe or complicated illness due to confirmed or suspected influenza virus infection, in accordance with WHO treatment guidelines.

**Section 10.2.** The application regarding a formulation of ferrous salt and folic acid (60 mg elemental iron in a ferrous form plus folic acid 2.8 mg tablet/capsule) for the prevention of anaemia in menstruating women and adolescent girls was rejected as data were lacking to show it to be at least equivalent to existing options (and not placebo) for the prevention of anaemia and/or neural tube defects and there was no commercial preparation of this fixed-dose combination.

**Section 12.** The application for fixed-dose combinations (various) of aspirin, simvastatin, ramipril, atenolol and hydrochlorothiazide for secondary prophylaxis

for cardiovascular diseases was rejected as there were gaps in the data presented for bioavailability, morbidity and mortality outcomes.

**Section 21.** The application for inclusion of ketorolac eye drops for allergic conjunctivitis was rejected as the evidence that the condition was a major public health problem and evidence for effectiveness of the medicine was insufficient. An application for ketotifen eye drops for seasonal allergic rhinoconjunctivitis, and as a topical anti-inflammatory for the eye, was rejected because of a lack of public health relevance and lack of evidence of efficacy in seasonal allergic conjunctivitis.

**Section 22.1.** The application for deletion of misoprostol for prevention of postpartum haemorrhage was rejected as no new data were submitted. Misoprostol was retained with the note stating that it is for the prevention of postpartum haemorrhage where oxytocin is not available or cannot be safely used.

## 4th Essential Medicines List for Children

### Additions to EMLc

**Section 2.** Morphine granules and slow-release tablets were added to the core list.

**Section 3.** Loratadine solid oral dosage form (10 mg) and oral liquid (1 mg/ml) were added to the core list because of superior safety when compared with first-generation antihistamines.

**Section 4.** Fomepizole was added to the complementary list for the treatment of toxic alcohol and glycol poisoning.

**Section 6.2.4.** Ofloxacin was replaced by levofloxacin in the complementary list with an asterisk to indicate that ofloxacin and moxifloxacin may be used as alternatives. Ethionamide had an asterisk to indicate that protionamide may be used as an alternative.

**Section 6.5.3.1.** Artesunate + mefloquine 25 + 55 mg and 100 + 220 mg (as a fixed-dose combination) were added to the core list for the treatment of uncomplicated falciparum malaria.

**Section 6.5.5.1.** Nifurtimox tablets 120 mg were added to the core list to be used in combination with eflornithine, for the treatment of *Trypanosoma brucei gambiense* infection.

**Section 6.5.5.2.** Benznidazole 12.5 mg and 50 mg scored solid oral dosage forms were added to the core list for the treatment of infections of *Trypanosoma cruzi*.

**Section 11.1.** Fresh-frozen plasma, platelets, red blood cells and whole blood were added to the core list. The Expert Committee strongly supported the

principles of voluntary, nonremunerated blood donation contained in World Health Assembly resolution WHA63.12.

**Section 11.3.** Dextran 70 was added to the core list for volume replacement when safer alternatives are not available.

**Section 29.1.** Chlorhexidine 7.1% solution or gel delivering 4% was added to the core list for use in umbilical cord care in community settings.

### Deletions from EMLc

**Section 3.** Chlorphenamine was deleted because of its inferior safety when compared with second-generation antihistamines.

### Changes to sections

**Section 2.** The section was renamed “Medicines for pain and palliative care” to include medicines for symptomatic treatment in palliative care. The listing for morphine had a note added that it includes both hydromorphone and oxycodone as alternatives.

**Section 3.** A note was added that there may be a role for sedating antihistamines for limited indications.

**Section 6.3.** Amphotericin B and flucytosine for cryptococcal disease in HIV-infected adolescents were moved from the complementary list to the core list.

**Section 8.** The heading was changed to “Antineoplastics and immunosuppressives” as medicines used in palliative care were moved to Section 2.

**Section 11.** The heading was changed to “Blood products of human origin and plasma substitutes”. Subsection 11.1 was retitled “Blood and blood components” and Subsection 11.2 was renamed “Plasma-derived medicinal products” with a Subsection 11.2.1 on “Human immunoglobulins” and a Subsection 11.2.2 on “Blood coagulation factors”. The title of Subsection 11.3 was changed to “Plasma substitutes”.

**Section 30.** A new section on “Medicines for diseases of joints” was created to list the treatments for gout, disease-modifying agents used in rheumatoid disorders and juvenile joint diseases that were deleted from Section 2.

### Amended dosage strength and form

**Section 6.2.4.** Streptomycin injection was moved from the core list to the complementary list.

## Rejected applications

**Section 6.4.3.** The application to delete oseltamivir was rejected. Oseltamivir was retained for the restricted indication of potentially severe or complicated illness due to confirmed or suspected influenza virus infection, in accordance with WHO treatment guidelines.

**Section 28.** The application for montelukast was rejected because of a lack of evidence of superiority of montelukast over other modes of readily-available treatments for allergic rhinitis, the potential adverse events and the uncertainties regarding its cost and availability in low- and middle-income countries.

## Recommendations for reviews

- What is the place of a dopamine agonist in the treatment of Parkinson disease?
- What is the role of a parenteral PPI compared with oral PPIs in peptic ulcer bleeding, including its place where immediate access to endoscopy is not possible?
- What is the role of pharmacotherapy (especially chlorpromazine and haloperidol) in the treatment of severe psychiatric disorders in children?
- Review of Section 8.2 – Cytotoxic and adjuvant medicines.
- Review of the Section 6.4.2 – Antiretrovirals, after publication of *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach*, at an extraordinary meeting to consider a limited list of applications.
- Review of Subsection 11.3 as it contains dextran, and a possible move of the three immunoglobulins (anti-D, anti-tetanus and anti-rabies) from Section 19.2 to the new Subsection 11.2.1.



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# Annex 1

## 18th WHO Model List of Essential Medicines (April 2013)

### 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. Not all square boxes are applicable to medicine selection for children — see the 4th EMLC for details.

Therapeutic equivalence is indicated only on the basis of reviews of efficacy and safety and when consistent with WHO clinical guidelines. National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price.

The [a] symbol indicates that there is an age or weight restriction on use of the medicine; details for each medicine can be found in Table 1.1.

Where the [c] symbol is placed next to the complementary list it signifies that the medicine(s) require(s) specialist diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training for their use in children.

Where the [c] symbol is placed next to an individual medicine or strength of medicine it signifies that there is a specific indication for restricting its use to children.

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

national or regional drug regulatory authority to ensure that each product is of appropriate pharmaceutical quality (including stability) and that, when relevant, different products are interchangeable.

For recommendations and advice concerning all aspects of the quality assurance of medicines see the WHO Medicines website [http://www.who.int/medicines/areas/quality\\_assurance](http://www.who.int/medicines/areas/quality_assurance).

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

The main terms used for dosage forms in the Essential Medicines List can be found in Table 1.2.

Definitions of many of these terms and pharmaceutical quality requirements applicable to the different categories are published in the current edition of *The International Pharmacopoeia* <http://www.who.int/medicines/publications/pharmacopoeia>.

## 1. ANAESTHETICS

### 1.1 General anaesthetics and oxygen

#### 1.1.1 Inhalational medicines

halothane	<b>Inhalation.</b>
isoflurane	<b>Inhalation.</b>
nitrous oxide	<b>Inhalation.</b>
oxygen	<b>Inhalation</b> (medicinal gas).

#### 1.1.2 Injectable medicines

ketamine	<b>Injection:</b> 50 mg (as hydrochloride)/ml in 10-ml vial.
propofol*	<b>Injection:</b> 10 mg/ml; 20 mg/ml.

\* Thiopental may be used as an alternative depending on local availability and cost.

### 1.2 Local anaesthetics

<input type="checkbox"/> bupivacaine	<b>Injection:</b> 0.25%; 0.5% (hydrochloride) in vial. <b>Injection for spinal anaesthesia:</b> 0.5% (hydrochloride) in 4-ml ampoule to be mixed with 7.5% glucose solution.
<input type="checkbox"/> lidocaine	<b>Injection:</b> 1%; 2% (hydrochloride) in vial. <b>Injection for spinal anaesthesia:</b> 5% (hydrochloride) in 2-ml ampoule to be mixed with 7.5% glucose solution. <b>Topical forms:</b> 2% to 4% (hydrochloride).
lidocaine + epinephrine (adrenaline)	<b>Dental cartridge:</b> 2% (hydrochloride) + epinephrine 1:80 000. <b>Injection:</b> 1%; 2% (hydrochloride or sulfate) + epinephrine 1:200 000 in vial.

#### *Complementary List*

<i>ephedrine</i>	<b>Injection:</b> 30 mg (hydrochloride)/ml in 1-ml ampoule. (For use in spinal anaesthesia during delivery, to prevent hypotension).
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### 1.3 Preoperative medication and sedation for short-term procedures

atropine	<b>Injection:</b> 1 mg (sulfate) in 1-ml ampoule.
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## 1. ANAESTHETICS (continued)

<input type="checkbox"/> midazolam	<b>Injection:</b> 1 mg/ml. <b>Oral liquid:</b> 2 mg/ml [c]. <b>Tablet:</b> 7.5 mg; 15 mg.
morphine	<b>Injection:</b> 10 mg (sulfate or hydrochloride) in 1-ml ampoule.

## 2. MEDICINES FOR PAIN AND PALLIATIVE CARE

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

acetylsalicylic acid	<b>Suppository:</b> 50 mg to 150 mg. <b>Tablet:</b> 100 mg to 500 mg.
ibuprofen [a]	<b>Oral liquid:</b> 200 mg/5 ml. <b>Tablet:</b> 200 mg; 400 mg; 600 mg. [a] Not in children less than 3 months.
paracetamol*	<b>Oral liquid:</b> 125 mg/5 ml. <b>Suppository:</b> 100 mg. <b>Tablet:</b> 100 mg to 500 mg. * Not recommended for anti-inflammatory use due to lack of proven benefit to that effect.

### 2.2 Opioid analgesics

codeine	<b>Tablet:</b> 30 mg (phosphate).
<input type="checkbox"/> morphine*	<b>Granules (slow-release; to mix with water):</b> 20 mg – 200 mg (morphine sulfate). <b>Injection:</b> 10 mg (morphine hydrochloride or morphine sulfate) in 1-ml ampoule. <b>Oral liquid:</b> 10 mg (morphine hydrochloride or morphine sulfate)/5 ml. <b>Tablet (slow release):</b> 10 mg – 200mg (morphine hydrochloride or morphine sulfate). <b>Tablet (immediate release):</b> 10 mg (morphine sulfate). * Alternatives limited to hydromorphone and oxycodone.

### 2.3 Medicines for other common symptoms in palliative care

amitriptyline	<b>Tablet:</b> 10 mg; 25 mg; 75 mg.
cyclizine [c]	<b>Injection:</b> 50 mg/ml. <b>Tablet:</b> 50 mg.

**2. MEDICINES FOR PAIN AND PALLIATIVE CARE** *(continued)*

dexamethasone	<b>Injection:</b> 4 mg/ml in 1-ml ampoule (as disodium phosphate salt). <b>Oral liquid:</b> 2 mg/5 ml. <b>Tablet:</b> 2 mg [c]; 4 mg.
diazepam	<b>Injection:</b> 5 mg/ml. <b>Oral liquid:</b> 2 mg/5 ml. <b>Rectal solution:</b> 2.5 mg; 5 mg; 10 mg. <b>Tablet:</b> 5 mg; 10 mg.
docusate sodium	<b>Capsule:</b> 100 mg. <b>Oral liquid:</b> 50 mg/5 ml.
fluoxetine [a]	<b>Solid oral dosage form:</b> 20 mg (as hydrochloride). [a] >8 years.
haloperidol	<b>Injection:</b> 5 mg in 1-ml ampoule. <b>Oral liquid:</b> 2 mg/ml. <b>Solid oral dosage form:</b> 0.5 mg; 2mg; 5 mg.
hyoscine butylbromide	<b>Injection:</b> 20 mg/ml.
hyoscine hydrobromide [c]	<b>Injection:</b> 400 micrograms/ml; 600 micrograms/ml. <b>Transdermal patches:</b> 1 mg/72 hours.
lactulose [c]	<b>Oral liquid:</b> 3.1–3.7 g/5 ml.
loperamide	<b>Solid oral dosage form:</b> 2 mg.
metoclopramide	<b>Injection:</b> 5 mg (hydrochloride)/mL in 2-mL ampoule. <b>Oral liquid:</b> 5 mg/5 ml. <b>Solid oral form:</b> 10 mg (hydrochloride).
midazolam	<b>Injection:</b> 1 mg/ml; 5 mg/ml. <b>Solid oral dosage form:</b> 7.5 mg; 15 mg. <b>Oral liquid:</b> 2mg/ml [c].
ondansetron [c] [a]	<b>Injection:</b> 2 mg base/ml in 2-ml ampoule (as hydrochloride). <b>Oral liquid:</b> 4 mg base/5 ml. <b>Solid oral dosage form:</b> Eq 4 mg base; Eq 8 mg base. [a] >1 month.
senna	<b>Oral liquid:</b> 7.5 mg/5 ml.

### 3. ANTIALLERGICS AND MEDICINES USED IN ANAPHYLAXIS

dexamethasone	<b>Injection:</b> 4 mg/ml in 1-ml ampoule (as disodium phosphate salt).
epinephrine (adrenaline)	<b>Injection:</b> 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule.
hydrocortisone	<b>Powder for injection:</b> 100 mg (as sodium succinate) in vial.
<input type="checkbox"/> loratadine *	<b>Oral liquid:</b> 1 mg/ml. <b>Tablet:</b> 10 mg. <i>* There may be a role for sedating antihistamines for limited indications (EMLC).</i>
<input type="checkbox"/> prednisolone	<b>Oral liquid:</b> 5 mg/ml [c]. <b>Tablet:</b> 5 mg; 25 mg.

### 4. ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS

#### 4.1 Non-specific

charcoal, activated	<b>Powder.</b>
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#### 4.2 Specific

acetylcysteine	<b>Injection:</b> 200 mg/ml in 10-ml ampoule. <b>Oral liquid:</b> 10% [c]; 20% [c].
atropine	<b>Injection:</b> 1 mg (sulfate) in 1-ml ampoule.
calcium gluconate	<b>Injection:</b> 100 mg/ml in 10-ml ampoule.
methylthionium chloride (methylene blue)	<b>Injection:</b> 10 mg/ml in 10-ml ampoule.
naloxone	<b>Injection:</b> 400 micrograms (hydrochloride) in 1-ml ampoule.
penicillamine	<b>Solid oral dosage form:</b> 250 mg.
potassium ferric hexacyano-ferrate(II) ·2H <sub>2</sub> O (Prussian blue)	<b>Powder for oral administration.</b>
sodium nitrite	<b>Injection:</b> 30 mg/ml in 10-ml ampoule.
sodium thiosulfate	<b>Injection:</b> 250 mg/ml in 50-ml ampoule.

#### **Complementary List**

deferoxamine	<b>Powder for injection:</b> 500 mg (mesilate) in vial.
dimercaprol	<b>Injection in oil:</b> 50 mg/ml in 2-ml ampoule.



**4. ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS** *(continued)*

<i>fomepizole</i>	<b>Injection:</b> 5 mg/ml (sulfate) in 20-ml ampoule or 1 g/ml (base) in 1.5-ml ampoule.
<i>sodium calcium edetate</i>	<b>Injection:</b> 200 mg/ml in 5-ml ampoule.
<i>succimer</i>	<b>Solid oral dosage form:</b> 100 mg.

**5. ANTICONVULSANTS/ANTIEPILEPTICS**

carbamazepine	<b>Oral liquid:</b> 100 mg/5 ml. <b>Tablet (chewable):</b> 100 mg; 200 mg. <b>Tablet (scored):</b> 100 mg; 200 mg.
diazepam	<b>Gel or rectal solution:</b> 5 mg/ml in 0.5 ml; 2-ml; 4-ml tubes.
<input type="checkbox"/> lorazepam	<b>Parenteral formulation:</b> 2 mg/ml in 1-ml ampoule; 4 mg/ml in 1-ml ampoule.
magnesium sulfate*	<b>Injection:</b> 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.
phenobarbital	<b>Injection:</b> 200 mg/ml (sodium). <b>Oral liquid:</b> 15 mg/5 ml. <b>Tablet:</b> 15 mg to 100 mg.
phenytoin	<b>Injection:</b> 50 mg/ml in 5-ml vial (sodium salt). <b>Oral liquid:</b> 25 mg to 30 mg/5 ml.* <b>Solid oral dosage form:</b> 25 mg; 50 mg; 100 mg (sodium salt). <b>Tablet (chewable):</b> 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 (sodium valproate)	<b>Oral liquid:</b> 200 mg/5 ml. <b>Tablet (crushable):</b> 100 mg. <b>Tablet (enteric-coated):</b> 200 mg; 500 mg (sodium valproate).

**Complementary List**

<i>ethosuximide</i>	<b>Capsule:</b> 250 mg. <b>Oral liquid:</b> 250 mg/5 ml.
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## 6. ANTI-INFECTIVE MEDICINES

### 6.1 Anthelmintics

#### 6.1.1 *Intestinal anthelmintics*

albendazole	<b>Tablet (chewable):</b> 400 mg.
levamisole	<b>Tablet:</b> 50 mg; 150 mg (as hydrochloride).
mebendazole	<b>Tablet (chewable):</b> 100 mg; 500 mg.
niclosamide	<b>Tablet (chewable):</b> 500 mg.
praziquantel	<b>Tablet:</b> 150 mg; 600 mg.
pyrantel	<b>Oral liquid:</b> 50 mg (as embonate or pamoate)/ml. <b>Tablet (chewable):</b> 250 mg (as embonate or pamoate).

#### 6.1.2 *Antifilarials*

albendazole	<b>Tablet (chewable):</b> 400 mg.
diethylcarbamazine	<b>Tablet:</b> 50 mg; 100 mg (dihydrogen citrate).
ivermectin	<b>Tablet (scored):</b> 3 mg.

#### 6.1.3 *Antischistosomal and other antitrematode medicines*

praziquantel	<b>Tablet:</b> 600 mg.
triclabendazole	<b>Tablet:</b> 250 mg.

#### *Complementary List*

<i>oxamniquine*</i>	<b>Capsule:</b> 250 mg. <b>Oral liquid:</b> 250 mg/5 ml.
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\* Oxamniquine is listed for use when praziquantel treatment fails.

### 6.2 Antibacterials

#### 6.2.1 *Beta lactam medicines*

amoxicillin	<b>Powder for oral liquid:</b> 125 mg (as trihydrate)/5 ml; 250 mg (as trihydrate)/5 ml [C]. <b>Solid oral dosage form:</b> 250 mg; 500 mg (as trihydrate).
amoxicillin + clavulanic acid	<b>Oral liquid:</b> 125 mg amoxicillin + 31.25 mg clavulanic acid/5 ml AND 250 mg amoxicillin + 62.5 mg clavulanic acid/5 ml [C]. <b>Tablet:</b> 500 mg (as trihydrate) + 125 mg (as potassium salt).

**6. ANTI-INFECTIVE MEDICINES** (*continued*)

ampicillin	<b>Powder for injection:</b> 500 mg; 1 g (as sodium salt) in vial.
benzathine benzylpenicillin	<b>Powder for injection:</b> 900 mg benzylpenicillin (= 1.2 million IU) in 5-ml vial [c]; 1.44 g benzylpenicillin (= 2.4 million IU) in 5-ml vial.
benzylpenicillin	<b>Powder for injection:</b> 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial.
cefalexin [c]	<b>Powder for reconstitution with water:</b> 125 mg/5 ml; 250 mg/5 ml (anhydrous). <b>Solid oral dosage form:</b> 250 mg (as monohydrate).
<input type="checkbox"/> cefazolin* [a]	<b>Powder for injection:</b> 1 g (as sodium salt) in vial. * For surgical prophylaxis. [a] >1 month.
cefixime*	<b>Capsule:</b> 400 mg (as trihydrate). * Listed only for single-dose treatment of uncomplicated anogenital gonorrhoea.
ceftriaxone* [a]	<b>Powder for injection:</b> 250 mg; 1 g (as sodium salt) in vial. * Do not administer with calcium and avoid in infants with hyperbilirubinaemia. [a] >41 weeks corrected gestational age.
<input type="checkbox"/> cloxacillin	<b>Capsule:</b> 500 mg; 1 g (as sodium salt). <b>Powder for injection:</b> 500 mg (as sodium salt) in vial. <b>Powder for oral liquid:</b> 125 mg (as sodium salt)/5 ml.
phenoxymethylpenicillin	<b>Powder for oral liquid:</b> 250 mg (as potassium salt)/5 ml. <b>Tablet:</b> 250 mg (as potassium salt).
procaine benzylpenicillin*	<b>Powder for injection:</b> 1 g (=1 million IU); 3 g (=3 million IU) in vial. * Procaine benzylpenicillin is not recommended as first-line treatment for neonatal sepsis except in settings with high neonatal mortality, when given by trained health workers in cases where hospital care is not achievable.

**Complementary List**

cefotaxime* [c]	<b>Powder for injection:</b> 250 mg per vial (as sodium salt). * 3rd generation cephalosporin of choice for use in hospitalized neonates.
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## 6. ANTI-INFECTIVE MEDICINES (continued)

*ceftazidime* **Powder for injection:** 250 mg or 1 g (as pentahydrate) 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.

\* Listed only for the treatment of life-threatening hospital-based infection due to suspected or proven multidrug-resistant infection.

*Meropenem* is indicated for the treatment of meningitis and is licensed for use in children over the age of 3 months.

### 6.2.2 Other antibacterials

*azithromycin\** **Capsule:** 250 mg; 500 mg (anhydrous).

**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.

\* Only for the presumptive treatment of epidemic meningitis in children older than 2 years.

**Oral liquid:** 150 mg (as palmitate)/5 ml.

**Powder for injection:** 1 g (sodium succinate) in vial.

*ciprofloxacin\** **Oral liquid:** 250 mg/5 ml (anhydrous) [c].

**Solution for IV infusion:** 2 mg/ml (as hyclate) [c].

**Tablet:** 250 mg (as hydrochloride).

\* Square box applies to adults only.

*clarithromycin\** **Solid oral dosage form:** 500 mg.

\* For use in combination regimens for eradication of *H. Pylori* in adults.

*doxycycline* [a] **Oral liquid:** 25 mg/5 ml [c]; 50 mg/5 ml (anhydrous) [c].

**Solid oral dosage form:** 50 mg [c]; 100 mg (as hyclate).

[a] Use in children <8 years only for life-threatening infections when no alternative exists.

**6. ANTI-INFECTIVE MEDICINES** (*continued*)

<input type="checkbox"/> erythromycin	<b>Powder for injection:</b> 500 mg (as lactobionate) in vial. <b>Powder for oral liquid:</b> 125 mg/5 ml (as stearate or estolate or ethyl succinate). <b>Solid oral dosage form:</b> 250 mg (as stearate or estolate or ethyl succinate).
<input type="checkbox"/> gentamicin	<b>Injection:</b> 10 mg; 40 mg (as sulfate)/ml in 2-ml vial.
<input type="checkbox"/> metronidazole	<b>Injection:</b> 500 mg in 100-ml vial. <b>Oral liquid:</b> 200 mg (as benzoate)/5 ml. <b>Suppository:</b> 500 mg; 1 g. <b>Tablet:</b> 200 mg to 500 mg.
nitrofurantoin	<b>Oral liquid:</b> 25 mg/5 ml [C]. <b>Tablet:</b> 100 mg.
spectinomycin	<b>Powder for injection:</b> 2 g (as hydrochloride) in vial.
sulfamethoxazole + trimethoprim	<b>Injection:</b> 80 mg + 16 mg/ml in 5-ml ampoule; 80 mg + 16 mg/ml in 10-ml ampoule. <b>Oral liquid:</b> 200 mg + 40 mg/5 ml. <b>Tablet:</b> 100 mg + 20 mg; 400 mg + 80 mg; 800 mg + 160 mg.
trimethoprim [a]	<b>Oral liquid:</b> 50 mg/5 ml [C]. <b>Tablet:</b> 100 mg; 200 mg. [a] >6 months.

**Complementary List**

<i>clindamycin</i>	<b>Capsule:</b> 150 mg (as hydrochloride). <b>Injection:</b> 150 mg (as phosphate)/ml. <b>Oral liquid:</b> 75 mg/5 ml (as palmitate) [C].
<i>vancomycin</i>	<b>Powder for injection:</b> 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	<b>Capsule:</b> 50 mg; 100 mg.
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## 6. ANTI-INFECTIVE MEDICINES (continued)

dapsone	<b>Tablet:</b> 25 mg; 50 mg; 100 mg.
rifampicin	<b>Solid oral dosage form:</b> 150 mg; 300 mg.

### 6.2.4 Antituberculosis medicines

WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.

ethambutol	<b>Oral liquid:</b> 25 mg/ml [c]. <b>Tablet:</b> 100 mg to 400 mg (hydrochloride).
ethambutol + isoniazid	<b>Tablet:</b> 400 mg + 150 mg.
ethambutol + isoniazid + pyrazinamide + rifampicin	<b>Tablet:</b> 275 mg + 75 mg + 400 mg + 150 mg.
ethambutol + isoniazid + rifampicin	<b>Tablet:</b> 275 mg + 75 mg + 150 mg.
isoniazid	<b>Oral liquid:</b> 50 mg/5 ml [c]. <b>Tablet:</b> 100 mg to 300 mg. <b>Tablet (scored):</b> 50 mg.
isoniazid + pyrazinamide + rifampicin	<b>Tablet:</b> 75 mg + 400 mg + 150 mg. 150 mg + 500 mg + 150 mg ( <b>For intermittent use three times weekly</b> ).
isoniazid + rifampicin	<b>Tablet:</b> 75 mg + 150 mg; 150 mg + 300 mg. 60 mg + 60 mg ( <b>For intermittent use three times weekly</b> ). 150 mg + 150 mg ( <b>For intermittent use three times weekly</b> ).
pyrazinamide	<b>Oral liquid:</b> 30 mg/ml [c]. <b>Tablet:</b> 400 mg. <b>Tablet (dispersible):</b> 150 mg. <b>Tablet (scored):</b> 150 mg.
rifabutin	<b>Capsule:</b> 150 mg.* * For use only in patients with HIV receiving protease inhibitors.
rifampicin	<b>Oral liquid:</b> 20 mg/ml [c]. <b>Solid oral dosage form:</b> 150 mg; 300 mg.

**6. ANTI-INFECTIVE MEDICINES** (continued)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: 100 mg; 500 mg; 1 g (as sulfate) in vial.**capreomycin **Powder for injection: 1 g (as sulfate) in vial.**cycloserine **Solid oral dosage form: 250 mg.**ethionamide\* **Tablet: 125 mg; 250 mg.**

\* Protionamide may be an alternative.

kanamycin **Powder for injection: 1 g (as sulfate) in vial.**levofloxacin\* **Tablet: 250 mg; 500 mg; 750 mg.**

\* Ofloxacin and moxifloxacin may be alternatives based on availability and programme considerations.

*p*-aminosalicylic acid **Granules: 4 g in sachet.  
Tablet: 500 mg.**streptomycin [c] **Powder for injection: 1 g (as sulfate) in vial.****6.3 Antifungal medicines**amphotericin B **Powder for injection: 50 mg in vial (as sodium deoxycholate or liposomal complex).**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.**flucytosine **Capsule: 250 mg.  
Infusion: 2.5 g in 250 ml.**griseofulvin **Oral liquid: 125 mg/5 ml [c].  
Solid oral dosage form: 125 mg; 250 mg.**nystatin **Lozenge: 100 000 IU.  
Oral liquid: 50 mg/5 ml [c]; 100 000 IU/ml [c].  
Pessary: 100 000 IU.  
Tablet: 100 000 IU; 500 000 IU.**

## 6. ANTI-INFECTIVE MEDICINES (continued)

### Complementary List

*potassium iodide*

**Saturated solution.**

### 6.4 Antiviral medicines

#### 6.4.1 Antiherpes medicines

aciclovir

**Oral liquid:** 200 mg/5 ml [c].

**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). WHO emphasizes the importance of using these products in accordance with global and national guidelines. WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.

Scored tablets can be used in children and therefore can be considered for inclusion in the listing of tablets, provided that adequate quality products are available.

##### 6.4.2.1 Nucleoside/Nucleotide reverse transcriptase inhibitors

abacavir (ABC)

**Oral liquid:** 100 mg (as sulfate)/5 ml.

**Tablet:** 300 mg (as sulfate).

didanosine (ddl)

**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)\* [a]

**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.

[a] >3 months.

lamivudine (3TC)

**Oral liquid:** 50 mg/5 ml.

**Tablet:** 150 mg.



**6. ANTI-INFECTIVE MEDICINES** (*continued*)

stavudine (d4T)	<b>Capsule:</b> 15 mg; 20 mg; 30 mg. <b>Powder for oral liquid:</b> 5 mg/5 ml.
tenofovir disoproxil fumarate (TDF)	<b>Tablet:</b> 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil).
zidovudine (ZDV or AZT)	<b>Capsule:</b> 100 mg; 250 mg. <b>Oral liquid:</b> 50 mg/5 ml. <b>Solution for IV infusion injection:</b> 10 mg/ml in 20-ml vial. <b>Tablet:</b> 300 mg.

**6.4.2.2 Non-nucleoside reverse transcriptase inhibitors**

efavirenz (EFV or EFZ) [a]	<b>Capsule:</b> 50 mg; 100 mg; 200 mg. <b>Oral liquid:</b> 150 mg/5 ml. <b>Tablet:</b> 600 mg. [a] >3 years or >10 kg weight.
nevirapine (NVP)	<b>Oral liquid:</b> 50 mg/5 ml. <b>Tablet:</b> 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. All other protease inhibitors should be used in boosted forms (e.g. with ritonavir).

atazanavir [a]	<b>Solid oral dosage form:</b> 100 mg; 150 mg; 300 mg (as sulfate). [a] >25 kg.
indinavir (IDV)	<b>Solid oral dosage form:</b> 400 mg (as sulfate).
lopinavir + ritonavir (LPV/r)	<b>Capsule:</b> 133.3 mg + 33.3 mg. <b>Oral liquid:</b> 400 mg + 100 mg/5 ml. <b>Tablet (heat stable):</b> 100 mg + 25 mg; 200 mg + 50 mg.
ritonavir	<b>Oral liquid:</b> 400 mg/5 ml. <b>Solid oral dosage form:</b> 100 mg. <b>Tablet (heat stable):</b> 25 mg; 100 mg.
saquinavir (SQV) [a]	<b>Solid oral dosage form:</b> 200 mg; 500 mg (as mesilate). [a] >25 kg.

## 6. ANTI-INFECTIVE MEDICINES (continued)

### FIXED-DOSE COMBINATIONS

efavirenz + emtricitabine\* + tenofovir **Tablet:** 600 mg + 200 mg + 300 mg (disoproxil fumarate equivalent to 245 mg tenofovir disoproxil).

\* 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 (disoproxil fumarate equivalent to 245 mg tenofovir disoproxil).

\* FTC is an acceptable alternative to 3TC, based on knowledge of the pharmacology, the resistance patterns and clinical trials of antiretrovirals.

lamivudine + nevirapine + stavudine **Tablet:** 150 mg + 200 mg + 30 mg.

**Tablet (dispersible):** 30 mg + 50 mg + 6 mg [c]; 60 mg + 100 mg + 12 mg [c].

lamivudine + nevirapine + zidovudine **Tablet:** 30 mg + 50 mg + 60 mg [c]; 150 mg + 200 mg + 300 mg.

lamivudine + zidovudine **Tablet:** 30 mg + 60 mg [c]; 150 mg + 300 mg.

### 6.4.3 Other antivirals

oseltamivir\* **Capsule:** 30 mg; 45 mg; 75 mg (as phosphate).

**Oral powder:** 12 mg/ml.

\* Potentially severe or complicated illness due to confirmed or suspected influenza virus infection in accordance with WHO treatment guidelines.

ribavirin\* **Injection for intravenous administration:** 800 mg and 1 g in 10-ml phosphate buffer solution.

**Solid oral dosage form:** 200 mg; 400 mg; 600 mg.

\* For the treatment of viral haemorrhagic fevers and in combination with pegylated interferons for the treatment of hepatitis C.

### Complementary List

pegylated interferon alfa (2a or 2b)\*

**Vial or prefilled syringe:**

180 micrograms (peginterferon alfa-2a),

80 microgram, 100 microgram (peginterferon alfa-2b).

\* To be used in combination with ribavirin.

**6. ANTI-INFECTIVE MEDICINES** (*continued*)**6.5 Antiprotozoal medicines****6.5.1 Antiamoebic and anti giardiasis medicines**

diloxanide <b>[a]</b>	<b>Tablet:</b> 500 mg (furoate). <b>[a]</b> >25 kg.
<input type="checkbox"/> metronidazole	<b>Injection:</b> 500 mg in 100-ml vial. <b>Oral liquid:</b> 200 mg (as benzoate)/5 ml. <b>Tablet:</b> 200 mg to 500 mg.

**6.5.2 Antileishmaniasis medicines**

amphotericin B	<b>Powder for injection:</b> 50 mg in vial (as sodium deoxycholate <b>or</b> liposomal complex).
miltefosine	<b>Solid oral dosage form:</b> 10 mg; 50 mg.
paromomycin	<b>Solution for intramuscular injection:</b> 750 mg of paromomycin base (as the sulfate).
sodium stibogluconate <b>or</b> meglumine antimoniate	<b>Injection:</b> 100 mg/ml, 1 vial = 30 ml <b>or</b> 30%, equivalent to approximately 8.1% antimony (pentavalent) in 5-ml ampoule.

**6.5.3 Antimalarial medicines****6.5.3.1 For curative treatment**

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

amodiaquine*	<b>Tablet:</b> 153 mg <b>or</b> 200 mg (as hydrochloride). * To be used in combination with artesunate 50 mg.
artemether*	<b>Oily injection:</b> 80 mg/ml in 1-ml ampoule. * For use in the management of severe malaria.
artemether + lumefantrine*	<b>Tablet:</b> 20 mg + 120 mg. <b>Tablet (dispersible):</b> 20 mg + 120 mg <b>[c]</b> . * Not recommended in the first trimester of pregnancy <b>or</b> in children below 5 kg.

## 6. ANTI-INFECTIVE MEDICINES (continued)

artesunate*	<p><b>Injection:</b> ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution.</p> <p>For use in the management of severe malaria.</p> <p><b>Rectal dosage form:</b> 50 mg [C]; 200 mg capsules (for pre-referral treatment of severe malaria only; patients should be taken to an appropriate health facility for follow-up care) [C].</p> <p><b>Tablet:</b> 50 mg.</p> <p>* To be used in combination with either amodiaquine, mefloquine or sulfadoxine + pyrimethamine.</p>
artesunate + amodiaquine*	<p><b>Tablet:</b> 25 mg + 67.5 mg; 50 mg + 135 mg; 100 mg + 270 mg.</p> <p>* Other combinations that deliver the target doses required such as 153 mg or 200 mg (as hydrochloride) with 50 mg artesunate can be alternatives.</p>
artesunate + mefloquine	<p><b>Tablet:</b> 25 mg + 55 mg; 100 mg + 220 mg.</p>
chloroquine*	<p><b>Oral liquid:</b> 50 mg (as phosphate or sulfate)/5 ml.</p> <p><b>Tablet:</b> 100 mg; 150 mg (as phosphate or sulfate).</p> <p>* For use only for the treatment of <i>P. vivax</i> infection.</p>
doxycycline*	<p><b>Capsule:</b> 100 mg (as hydrochloride or hyclate).</p> <p><b>Tablet (dispersible):</b> 100 mg (as monohydrate).</p> <p>* For use only in combination with quinine.</p>
mefloquine*	<p><b>Tablet:</b> 250 mg (as hydrochloride).</p> <p>* To be used in combination with artesunate 50 mg.</p>
primaquine*	<p><b>Tablet:</b> 7.5 mg; 15 mg (as diphosphate).</p> <p>* Only for use to achieve radical cure of <i>P. vivax</i> and <i>P. ovale</i> infections, given for 14 days.</p>
quinine*	<p><b>Injection:</b> 300 mg quinine hydrochloride/ml in 2-ml ampoule.</p> <p><b>Tablet:</b> 300 mg (quinine sulfate) or 300 mg (quinine bisulfate).</p> <p>* For use only in the management of severe malaria, and should be used in combination with doxycycline.</p>
sulfadoxine + pyrimethamine*	<p><b>Tablet:</b> 500 mg + 25 mg.</p> <p>* Only in combination with artesunate 50 mg.</p>

**6. ANTI-INFECTIVE MEDICINES** (*continued*)**6.5.3.2 For prophylaxis**

chloroquine*	<b>Oral liquid:</b> 50 mg (as phosphate or sulfate)/5 ml. <b>Tablet:</b> 150 mg (as phosphate or sulfate). * For use only in central American regions, for <i>P. vivax</i> infections.
doxycycline [a]	<b>Solid oral dosage form:</b> 100 mg (as hydrochloride or hyclate). [a] >8 years.
mefloquine [a]	<b>Tablet:</b> 250 mg (as hydrochloride). [a] >5 kg or >3 months.
proguanil*	<b>Tablet:</b> 100 mg (as hydrochloride). * For use only in combination with chloroquine.

**6.5.4 Antipneumocystosis and antitoxoplasmosis medicines**

pyrimethamine	<b>Tablet:</b> 25 mg.
sulfadiazine	<b>Tablet:</b> 500 mg.
sulfamethoxazole + trimethoprim	<b>Injection:</b> 80 mg + 16 mg/ml in 5-ml ampoule; 80 mg + 16 mg/ml in 10-ml ampoule. <b>Oral liquid:</b> 200 mg + 40 mg/5 ml [c]. <b>Tablet:</b> 100 mg + 20 mg; 400 mg + 80 mg [c].

**Complementary List**

*pentamidine* **Tablet:** 200 mg; 300 mg (as isethionate).

**6.5.5 Antitrypanosomal medicines****6.5.5.1 African trypanosomiasis****Medicines for the treatment of 1st stage African trypanosomiasis**

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

**Medicines for the treatment of 2nd stage African trypanosomiasis**

eflornithine*	<b>Injection:</b> 200 mg (hydrochloride)/ml in 100-ml bottle. * To be used for the treatment of <i>Trypanosoma brucei gambiense</i> infection.
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## 6. ANTI-INFECTIVE MEDICINES (continued)

melarsoprol **Injection:** 3.6% solution, 5-ml ampoule (180 mg of active compound).

nifurtimox\* **Tablet:** 120 mg.

\* Only to be used in combination with eflornithine, for the treatment of *Trypanosoma brucei gambiense* infection.

### Complementary List [c]

melarsoprol **Injection:** 3.6% solution in 5-ml ampoule (180 mg of active compound).

### 6.5.5.2 American trypanosomiasis

benznidazole **Tablet:** 12.5 mg [c]; 100 mg.

**Tablet (scored):** 50 mg.

nifurtimox **Tablet:** 30 mg; 120 mg; 250 mg.

## 7. ANTIMIGRAINE MEDICINES

### 7.1 For treatment of acute attack

acetylsalicylic acid **Tablet:** 300 mg to 500 mg.

ibuprofen [c] **Tablet:** 200 mg; 400 mg.

paracetamol **Oral liquid:** 125 mg/5 ml [c].

**Tablet:** 300 mg to 500 mg.

### 7.2 For prophylaxis

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

## 8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES

This section will be reviewed and updated shortly. In view of this, no changes were made to this section during the meeting of the 19th Expert Committee.

### 8.1 Immunosuppressive medicines

#### Complementary List

azathioprine **Powder for injection:** 100 mg (as sodium salt) in vial.

**Tablet (scored):** 50 mg.

ciclosporin **Capsule:** 25 mg.

**Concentrate for injection:** 50 mg/ml in 1-ml ampoule for organ transplantation.

**8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES** (continued)**8.2 Cytotoxic and adjuvant medicines****Complementary List**

allopurinol [c]	<b>Tablet:</b> 100 mg; 300 mg.
asparaginase	<b>Powder for injection:</b> 10 000 IU in vial.
bleomycin	<b>Powder for injection:</b> 15 mg (as sulfate) in vial.
calcium folinate	<b>Injection:</b> 3 mg/ml in 10-ml ampoule. <b>Tablet:</b> 15 mg.
<input type="checkbox"/> carboplatin	<b>Injection:</b> 50 mg/5 ml; 150 mg/15 ml; 450 mg/45 ml; 600 mg/60 ml.
chlorambucil	<b>Tablet:</b> 2 mg.
cyclophosphamide	<b>Powder for injection:</b> 500 mg in vial. <b>Tablet:</b> 25 mg.
cytarabine	<b>Powder for injection:</b> 100 mg in vial.
dacarbazine	<b>Powder for injection:</b> 100 mg in vial.
dactinomycin	<b>Powder for injection:</b> 500 micrograms in vial.
daunorubicin	<b>Powder for injection:</b> 50 mg (hydrochloride) in vial.
docetaxel	<b>Injection:</b> 20 mg/ml; 40 mg/ml.
doxorubicin	<b>Powder for injection:</b> 10 mg; 50 mg (hydrochloride) in vial.
etoposide	<b>Capsule:</b> 100 mg. <b>Injection:</b> 20 mg/ml in 5-ml ampoule.
fluorouracil	<b>Injection:</b> 50 mg/ml in 5-ml ampoule.
hydroxycarbamide	<b>Solid oral dosage form:</b> 200 mg; 250 mg; 300 mg; 400 mg; 500 mg; 1 g.
ifosfamide	<b>Powder for injection:</b> 1-g vial; 2-g vial.
mercaptopurine	<b>Tablet:</b> 50 mg.
mesna	<b>Injection:</b> 100 mg/ml in 4-ml and 10-ml ampoules. <b>Tablet:</b> 400 mg; 600 mg.
methotrexate	<b>Powder for injection:</b> 50 mg (as sodium salt) in vial. <b>Tablet:</b> 2.5 mg (as sodium salt).

## 8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES (continued)

paclitaxel	<b>Powder for injection:</b> 6 mg/ml.
procarbazine	<b>Capsule:</b> 50 mg (as hydrochloride).
tioguanine [c]	<b>Solid oral dosage form:</b> 40 mg.
vinblastine	<b>Powder for injection:</b> 10 mg (sulfate) in vial.
vincristine	<b>Powder for injection:</b> 1 mg; 5 mg (sulfate) in vial.

### 8.3 Hormones and antihormones

#### Complementary List

dexamethasone	<b>Injection:</b> 4 mg/ml in 1-ml ampoule (as disodium phosphate salt). <b>Oral liquid:</b> 2 mg/5 ml [c].
hydrocortisone	<b>Powder for injection:</b> 100 mg (as sodium succinate) in vial.
methylprednisolone [c]	<b>Injection:</b> 40 mg/ml (as sodium succinate) in 1-ml single-dose vial and 5-ml multi-dose vials; 80 mg/ml (as sodium succinate) in 1-ml single-dose vial.
<input type="checkbox"/> prednisolone	<b>Oral liquid:</b> 5 mg/ml [c]. <b>Tablet:</b> 5 mg; 25 mg.
tamoxifen	<b>Tablet:</b> 10 mg; 20 mg (as citrate).

## 9. ANTIPARKINSONISM MEDICINES

<input type="checkbox"/> biperiden	<b>Injection:</b> 5 mg (lactate) in 1-ml ampoule. <b>Tablet:</b> 2 mg (hydrochloride).
levodopa + <input type="checkbox"/> carbidopa	<b>Tablet:</b> 100 mg + 10 mg; 100 mg + 25 mg; 250 mg + 25 mg.

## 10. MEDICINES AFFECTING THE BLOOD

### 10.1 Antianaemia medicines

ferrous salt	<b>Oral liquid:</b> equivalent to 25 mg iron (as sulfate)/ml. <b>Tablet:</b> equivalent to 60 mg iron.
ferrous salt + folic acid	<b>Tablet:</b> equivalent to 60 mg iron + 400 micrograms folic acid (nutritional supplement for use during pregnancy).
folic acid	<b>Tablet:</b> 1 mg; 5 mg.



**10. MEDICINES AFFECTING THE BLOOD** (*continued*)

hydroxocobalamin	<b>Injection:</b> 1 mg (as acetate, as hydrochloride or as sulfate) in 1-ml ampoule.
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**10.2 Medicines affecting coagulation**

heparin sodium	<b>Injection:</b> 1000 IU/ml; 5000 IU/ml; 20 000 IU/ml in 1-ml ampoule.
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phytomenadione	<b>Injection:</b> 1 mg/ml [c]; 10 mg/ml in 5-ml ampoule. <b>Tablet:</b> 10 mg.
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protamine sulfate	<b>Injection:</b> 10 mg/ml in 5-ml ampoule.
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tranexamic acid	<b>Injection:</b> 100 mg/ml in 10-ml ampoule.
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<input type="checkbox"/> warfarin	<b>Tablet:</b> 1 mg; 2 mg; 5 mg (sodium salt).
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**Complementary List** [c]

<i>heparin sodium</i>	<b>Injection:</b> 1000 IU/ml; 5000 IU/ml in 1-ml ampoule.
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<i>protamine sulfate</i>	<b>Injection:</b> 10 mg/ml in 5-ml ampoule.
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<input type="checkbox"/> <i>warfarin</i>	<b>Tablet:</b> 0.5 mg; 1 mg; 2 mg; 5 mg (sodium salt).
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**10.3 Other medicines for haemoglobinopathies****Complementary List**

<i>deferoxamine*</i>	<b>Powder for injection:</b> 500 mg (mesilate) in vial.
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\* *Deferasirox oral form may be an alternative, depending on cost and availability.*

<i>hydroxycarbamide</i>	<b>Solid oral dosage form:</b> 200 mg; 500 mg; 1 g.
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**11. BLOOD PRODUCTS OF HUMAN ORIGIN AND PLASMA SUBSTITUTES****11.1 Blood and blood components**

In accordance with the World Health Assembly resolution WHA63.12, WHO recognizes that achieving self-sufficiency, unless special circumstances preclude it, in the supply of safe blood components based on voluntary, non-remunerated blood donation, and the security of that supply are important national goals to prevent blood shortages and meet the transfusion requirements of the patient population. All preparations should comply with the WHO requirements.

fresh-frozen plasma

platelets

red blood cells

whole blood

## 11. BLOOD PRODUCTS OF HUMAN ORIGIN AND PLASMA SUBSTITUTES *(continued)*

### 11.2 Plasma-derived medicinales products

All human plasma-derived medicines should comply with the WHO requirements.

#### 11.2.1 Human immunoglobulins

##### *Complementary List*

human normal  
immunoglobulin

**Intramuscular administration:** 16% protein solution.\*

**Intravenous administration:** 5%; 10% protein solution.\*\*

**Subcutaneous administration:** 15%; 16% protein solution.\*

\* Indicated for primary immune deficiency.

\*\* Indicated for primary immune deficiency and Kawasaki disease.

#### 11.2.2 Blood coagulation factors

##### *Complementary List*

coagulation factor VIII

**Powder for injection:** 500 IU/vial.

coagulation factor IX

**Powder for injection:** 500 IU/vial, 1000 IU/vial.

### 11.3 Plasma substitutes

dextran 70\*

**Injectable solution:** 6%.

\* Polygeline, injectable solution, 3.5% is considered as equivalent.

## 12. CARDIOVASCULAR MEDICINES

### 12.1 Antianginal medicines

bisoprolol\*

**Tablet:** 1.25 mg; 5 mg.

\*  includes metoprolol and carvedilol as alternatives.

glyceryl trinitrate

**Tablet (sublingual):** 500 micrograms.

isosorbide dinitrate

**Tablet (sublingual):** 5 mg.

verapamil

**Tablet:** 40 mg; 80 mg (hydrochloride).

### 12.2 Antiarrhythmic medicines

bisoprolol\*

**Tablet:** 1.25 mg; 5 mg.

\*  includes metoprolol and carvedilol as alternatives.

digoxin

**Injection:** 250 micrograms/ml in 2-ml ampoule.

**Oral liquid:** 50 micrograms/ml.

**Tablet:** 62.5 micrograms; 250 micrograms.

**12. CARDIOVASCULAR MEDICINES** (*continued*)

epinephrine (adrenaline)	<b>Injection:</b> 100 micrograms/ml (as acid tartrate or hydrochloride) in 10-ml ampoule.
lidocaine	<b>Injection:</b> 20 mg (hydrochloride)/ml in 5-ml ampoule.
verapamil	<b>Injection:</b> 2.5 mg (hydrochloride)/ml in 2-ml ampoule. <b>Tablet:</b> 40 mg; 80 mg (hydrochloride).

**Complementary List**

<i>amiodarone</i>	<b>Injection:</b> 50 mg/ml in 3-ml ampoule (hydrochloride). <b>Tablet:</b> 100 mg; 200 mg; 400 mg (hydrochloride).
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**12.3 Antihypertensive medicines**

<input type="checkbox"/> amlodipine	<b>Tablet:</b> 5 mg (as maleate, mesylate or besylate).
<input type="checkbox"/> bisoprolol*	<b>Tablet:</b> 1.25 mg; 5 mg. * <input type="checkbox"/> includes metoprolol and carvedilol as alternatives.
<input type="checkbox"/> enalapril	<b>Tablet:</b> 2.5 mg; 5 mg (as hydrogen maleate).
hydralazine*	<b>Powder for injection:</b> 20 mg (hydrochloride) in ampoule. <b>Tablet:</b> 25 mg; 50 mg (hydrochloride). * Hydralazine is listed for use only in the acute management of severe pregnancy-induced hypertension. Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines.
<input type="checkbox"/> hydrochlorothiazide	<b>Oral liquid:</b> 50 mg/5 ml. <b>Solid oral dosage form:</b> 12.5 mg; 25 mg.
methyldopa*	<b>Tablet:</b> 250 mg. * Methyldopa is listed for use only in the management of pregnancy-induced hypertension. Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines.

**Complementary List**

<i>sodium nitroprusside</i>	<b>Powder for infusion:</b> 50 mg in ampoule.
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**12.4 Medicines used in heart failure**

<input type="checkbox"/> bisoprolol*	<b>Tablet:</b> 1.25 mg; 5 mg. * <input type="checkbox"/> includes metoprolol and carvedilol as alternatives.
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## 12. CARDIOVASCULAR MEDICINES (continued)

digoxin	<b>Injection:</b> 250 micrograms/ml in 2-ml ampoule. <b>Oral liquid:</b> 50 micrograms/ml. <b>Tablet:</b> 62.5 micrograms; 250 micrograms.
<input type="checkbox"/> enalapril	<b>Tablet:</b> 2.5 mg; 5 mg (as hydrogen maleate).
<input type="checkbox"/> furosemide	<b>Injection:</b> 10 mg/ml in 2-ml ampoule. <b>Oral liquid:</b> 20 mg/5 ml [c]. <b>Tablet:</b> 40 mg.
<input type="checkbox"/> hydrochlorothiazide	<b>Oral liquid:</b> 50 mg/5 ml. <b>Solid oral dosage form:</b> 25 mg.
spironolactone	<b>Tablet:</b> 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

<input type="checkbox"/> miconazole	<b>Cream or ointment:</b> 2% (nitrate).
selenium sulfide	<b>Detergent-based suspension:</b> 2%.
sodium thiosulfate	<b>Solution:</b> 15%.
terbinafine	<b>Cream:</b> 1% <b>or Ointment:</b> 1% terbinafine hydrochloride.

### 13.2 Anti-infective medicines

mupirocin	<b>Cream (as mupirocin calcium):</b> 2%. <b>Ointment:</b> 2%.
potassium permanganate	<b>Aqueous solution:</b> 1:10 000.

**13. DERMATOLOGICAL MEDICINES (topical) (continued)**

silver sulfadiazine  **a**                      **Cream:** 1%.  
 **a** >2 months.

**13.3 Anti-inflammatory and antipruritic medicines**

betamethasone  **a**                      **Cream or ointment:** 0.1% (as valerate).  
 **a** Hydrocortisone preferred in neonates.

calamine                                      **Lotion.**

hydrocortisone                              **Cream or ointment:** 1% (acetate).

**13.4 Medicines affecting skin differentiation and proliferation**

benzoyl peroxide                              **Cream or lotion:** 5%.

coal tar    **Solution:** 5%.

fluorouracil                                      **Ointment:** 5%.

podophyllum resin                              **Solution:** 10% to 25%.

salicylic acid                                      **Solution:** 5%.

urea    **Cream or ointment:** 5%; 10%.

**13.5 Scabicides and pediculicides**

benzyl benzoate  **a**                      **Lotion:** 25%.  
 **a** >2 years.

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 mg to 420 mg iodine (as sodium or meglumine salt)/ml in 20-ml ampoule.

barium sulfate                                      **Aqueous suspension.**

iohexol    **Injection:** 140 mg to 350 mg iodine/ml in 5-ml; 10-ml; 20-ml ampoules.

## 14. DIAGNOSTIC AGENTS (continued)

### Complementary List [c]

- |  |   |
|--|---|
| barium sulfate [c]                           | <b>Aqueous suspension.</b>                              |
| <input type="checkbox"/> meglumine iotroxate | <b>Solution: 5 g to 8 g iodine in 100 ml to 250 ml.</b> |

## 15. DISINFECTANTS AND ANTISEPTICS

### 15.1 Antiseptics

- |  |   |
|--|---|
| <input type="checkbox"/> chlorhexidine   | <b>Solution: 5% (digluconate).</b>                        |
| <input type="checkbox"/> ethanol         | <b>Solution: 70% (denatured).</b>                         |
| <input type="checkbox"/> povidone iodine | <b>Solution: 10% (equivalent to 1% available iodine).</b> |

### 15.2 Disinfectants

- |   |  |
|---|--|
| <input type="checkbox"/> chlorine base compound | <b>Powder: (0.1% available chlorine) for solution.</b> |
| <input type="checkbox"/> chloroxylonol          | <b>Solution: 4.8%.</b>                                 |
| glutaral  | <b>Solution: 2%.</b>                                   |

## 16. DIURETICS

- |  |   |
|--|---|
| amiloride                                    | <b>Tablet: 5 mg (hydrochloride).</b>  |
| <input type="checkbox"/> furosemide          | <b>Injection: 10 mg/ml in 2-ml ampoule.</b><br><b>Oral liquid: 20 mg/5 ml [c].</b><br><b>Tablet: 10 mg [c]; 20 mg [c]; 40 mg.</b> |
| <input type="checkbox"/> hydrochlorothiazide | <b>Solid oral dosage form: 25 mg.</b>   |
| mannitol                                     | <b>Injectable solution: 10%; 20%.</b>   |
| spironolactone                               | <b>Tablet: 25 mg.</b>   |
| <b>Complementary List [c]</b>                |   |
| <input type="checkbox"/> hydrochlorothiazide | <b>Tablet (scored): 25 mg.</b>  |
| mannitol                                     | <b>Injectable solution: 10%; 20%.</b>   |
| spironolactone                               | <b>Oral liquid: 5 mg/5 ml; 10 mg/5 ml; 25 mg/5 ml.</b><br><b>Tablet: 25 mg.</b>   |

## 17. GASTROINTESTINAL MEDICINES

### Complementary List [c]

- |   |   |
|---|---|
| <input type="checkbox"/> pancreatic enzymes | <b>Age-appropriate formulations and doses including lipase, protease and amylase.</b> |
|---|---|

**17. GASTROINTESTINAL MEDICINES** *(continued)***17.1 Antiulcer medicines**

- omeprazole                      **Powder for oral liquid:** 20 mg; 40 mg sachets.  
**Solid oral dosage form:** 10 mg; 20 mg; 40 mg.
- ranitidine                        **Injection:** 25 mg/ml (as hydrochloride) in  
2-ml ampoule.  
**Oral liquid:** 75 mg/5 ml (as hydrochloride).  
**Tablet:** 150 mg (as hydrochloride).

**17.2 Antiemetic medicines**

- dexamethasone                      **Injection:** 4 mg/ml in 1-ml ampoule (as disodium  
phosphate salt).  
**Oral liquid:** 0.5 mg/5 ml; 2 mg/5 ml.  
**Solid oral dosage form:** 0.5 mg; 0.75 mg; 1.5 mg;  
4 mg.
- metoclopramide  **a**                      **Injection:** 5 mg (hydrochloride)/ml in 2-ml ampoule.  
**Oral liquid:** 5 mg/5 ml  **c**].  
**Tablet:** 10 mg (hydrochloride).  
 **a** Not in neonates.
- ondansetron  **a**                      **Injection:** 2 mg base/ml in 2-ml ampoule  
(as hydrochloride).  
**Oral liquid:** 4 mg base/5 ml.  
**Solid oral dosage form:** Eq 4 mg base; Eq 8 mg base;  
Eq 24 mg base.  
 **a** >1 month.

**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. GASTROINTESTINAL MEDICINES (continued)

### 17.5 Medicines used in diarrhoea

#### 17.5.1 Oral rehydration

oral rehydration salts	<b>Powder for dilution</b> in 200 ml; 500 ml; 1 L.
	glucose: 75 mEq
	sodium: 75 mEq <b>or</b> mmol/L
	chloride: 65 mEq <b>or</b> mmol/L
	potassium: 20 mEq <b>or</b> mmol/L
	citrate: 10 mmol/L
	osmolarity: 245 mOsm/L
	glucose: 13.5 g/L
	sodium chloride: 2.6 g/L
	potassium chloride: 1.5 g/L
	trisodium citrate dihydrate*: 2.9 g/L

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

#### 17.5.2 Medicines for diarrhoea

zinc sulfate*	<b>Solid oral dosage form:</b> 20 mg.
	* In acute diarrhoea zinc sulfate should be used as an adjunct to oral rehydration salts.

## 18. HORMONES, OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES

### 18.1 Adrenal hormones and synthetic substitutes

fludrocortisone	<b>Tablet:</b> 100 micrograms (acetate).
hydrocortisone	<b>Tablet:</b> 5 mg; 10 mg; 20 mg.

### 18.2 Androgens

#### Complementary List

testosterone	<b>Injection:</b> 200 mg (enanthate) in 1-ml ampoule.
--------------	---

### 18.3 Contraceptives

#### 18.3.1 Oral hormonal contraceptives

<input type="checkbox"/> ethinylestradiol +	<b>Tablet:</b> 30 micrograms + 150 micrograms.
<input type="checkbox"/> levonorgestrel	



**18. HORMONES, OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES** (*continued*)

ethinylestradiol +  
 norethisterone

**Tablet:** 35 micrograms + 1 mg.

levonorgestrel

**Tablet:** 30 micrograms; 750 micrograms (pack of two); 1.5 mg.

**18.3.2 Injectable hormonal contraceptives**

estradiol cypionate +  
medroxyprogesterone acetate

**Injection:** 5 mg + 25 mg.

medroxyprogesterone acetate

**Depot injection:** 150 mg/ml in 1-ml vial.

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).

**18.4 Estrogens****18.5 Insulins and other medicines used for diabetes**

gliclazide\*

**Solid oral dosage form:** (controlled-release tablets)  
30 mg; 60 mg; 80 mg.

\* glibenclamide not suitable above 60 years.

glucagon

**Injection:** 1 mg/ml.

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).

**Complementary List** [c]

*metformin*

**Tablet:** 500 mg (hydrochloride).

## 18. HORMONES, OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES (continued)

### 18.6 Ovulation inducers

#### Complementary List

*clomifene* **Tablet:** 50 mg (citrate).

### 18.7 Progestogens

medroxyprogesterone acetate **Tablet:** 5 mg.

### 18.8 Thyroid hormones and antithyroid medicines

levothyroxine **Tablet:** 25 micrograms [c]; 50 micrograms; 100 micrograms (sodium salt).

potassium iodide **Tablet:** 60 mg.

propylthiouracil **Tablet:** 50 mg.

#### Complementary List [c]

*Lugol's solution* **Oral liquid:** about 130 mg total iodine/ml.

*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.

tuberculin, purified protein derivative (PPD) **Injection.**

### 19.2 Sera and immunoglobulins

All plasma fractions should comply with the WHO requirements.

anti-D immunoglobulin (human) **Injection:** 250 micrograms in single-dose vial.

anti-rabies immunoglobulin (human) **Injection:** 150 IU/ml in vial.

anti-tetanus immunoglobulin (human) **Injection:** 500 IU in vial.

anti-venom immunoglobulin\* **Injection.**  
\* Exact type to be defined locally.

diphtheria antitoxin **Injection:** 10 000 IU; 20 000 IU in vial.

**19. IMMUNOLOGICALS** (*continued*)**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](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. WHO noted the need for vaccines used in children to be polyvalent.

BCG vaccine

cholera vaccine

diphtheria vaccine

*Haemophilus influenzae* type b vaccine

hepatitis A vaccine

hepatitis B vaccine

influenza vaccine

Japanese encephalitis vaccine

measles vaccine

meningococcal meningitis vaccine

mumps vaccine

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

<input type="checkbox"/> atracurium	<b>Injection:</b> 10 mg/ml (besylate).
neostigmine	<b>Injection:</b> 500 micrograms in 1-ml ampoule; 2.5 mg (metilsulfate) in 1-ml ampoule. <b>Tablet:</b> 15 mg (bromide).
suxamethonium	<b>Injection:</b> 50 mg (chloride)/ml in 2-ml ampoule. <b>Powder for injection</b> (chloride), in vial.
<input type="checkbox"/> vecuronium <b>[c]</b>	<b>Powder for injection:</b> 10 mg (bromide) in vial.
<b>Complementary List</b>	
<i>pyridostigmine</i>	<b>Injection:</b> 1 mg in 1-ml ampoule. <b>Tablet:</b> 60 mg (bromide).
<input type="checkbox"/> <i>vecuronium</i>	<b>Powder for injection:</b> 10 mg (bromide) in vial.

## 21. OPHTHALMOLOGICAL PREPARATIONS

### 21.1 Anti-infective agents

aciclovir	<b>Ointment:</b> 3% W/W.
azithromycin	<b>Solution (eye drops):</b> 1.5%.
<input type="checkbox"/> gentamicin	<b>Solution (eye drops):</b> 0.3% (sulfate).
<input type="checkbox"/> ofloxacin	<b>Solution (eye drops):</b> 0.3%.
<input type="checkbox"/> tetracycline	<b>Eye ointment:</b> 1% (hydrochloride).

### 21.2 Anti-inflammatory agents

<input type="checkbox"/> prednisolone	<b>Solution (eye drops):</b> 0.5% (sodium phosphate).
---------------------------------------	---

### 21.3 Local anaesthetics

<input type="checkbox"/> tetracaine <b>[a]</b>	<b>Solution (eye drops):</b> 0.5% (hydrochloride). <b>[a]</b> Not in preterm neonates.
--	---

### 21.4 Miotics and antiglaucoma medicines

acetazolamide	<b>Tablet:</b> 250 mg.
latanoprost	<b>Solution (eye drops):</b> latanoprost 50 micrograms/mL
<input type="checkbox"/> pilocarpine	<b>Solution (eye drops):</b> 2%; 4% (hydrochloride or nitrate).
<input type="checkbox"/> timolol	<b>Solution (eye drops):</b> 0.25%; 0.5% (as hydrogen maleate).

**21. OPHTHALMOLOGICAL PREPARATIONS** (*continued*)**21.5 Mydriatics**atropine\* **[a]****Solution (eye drops):** 0.1%; 0.5%; 1% (sulfate).\* **[c]** Or homatropine (hydrobromide) or cyclopentolate (hydrochloride).**[a]** >3 months.**Complementary List***epinephrine (adrenaline)***Solution (eye drops):** 2% (as hydrochloride).**21.6 Anti-vascular endothelial growth factor (VEGF) preparations****Complementary List***bevacizumab***Injection:** 25 mg/ml.**22. OXYTOCICS AND ANTIOXYTOCICS****22.1 Oxytocics** ergometrine**Injection:** 200 micrograms (hydrogen maleate) in 1-ml ampoule.

misoprostol

**Tablet:** 200 micrograms.\*

\* For management of incomplete abortion and miscarriage, and for prevention of postpartum haemorrhage where oxytocin is not available or cannot be safely used.

**Vaginal tablet:** 25 micrograms.\*

\* Only for use for induction of labour where appropriate facilities are available.

oxytocin

**Injection:** 10 IU in 1-ml.**Complementary List***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. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS

### 24.1 Medicines used in psychotic disorders

- |   |  |
|---|--|
| <input type="checkbox"/> chlorpromazine | <b>Injection:</b> 25 mg (hydrochloride)/ml in 2-ml ampoule.<br><b>Oral liquid:</b> 25 mg (hydrochloride)/5 ml.<br><b>Tablet:</b> 100 mg (hydrochloride). |
| <input type="checkbox"/> fluphenazine   | <b>Injection:</b> 25 mg (decanoate or enantate) in 1-ml ampoule.   |
| <input type="checkbox"/> haloperidol    | <b>Injection:</b> 5 mg in 1-ml ampoule.<br><b>Tablet:</b> 2 mg; 5 mg.  |
| risperidone                             | <b>Solid oral dosage form:</b> 0.25 mg to 6.0 mg.  |

#### Complementary List

- |                           |   |
|---------------------------|---|
| <i>chlorpromazine</i> [c] | <b>Injection:</b> 25 mg (hydrochloride)/ml in 2-ml ampoule.<br><b>Oral liquid:</b> 25 mg (hydrochloride)/5 ml.<br><b>Tablet:</b> 10 mg; 25 mg; 50 mg; 100 mg (hydrochloride). |
| <i>clozapine</i>          | <b>Solid oral dosage form:</b> 25 to 200 mg.  |
| <i>haloperidol</i> [c]    | <b>Injection:</b> 5 mg in 1-ml ampoule.<br><b>Oral liquid:</b> 2 mg/ml.<br><b>Solid oral dosage form:</b> 0.5 mg; 2 mg; 5 mg.   |

### 24.2 Medicines used in mood disorders

#### 24.2.1 Medicines used in depressive disorders

- |  |  |
|--|--|
| <input type="checkbox"/> amitriptyline | <b>Tablet:</b> 25 mg; 75 mg. (hydrochloride).            |
| fluoxetine                             | <b>Solid oral dosage form:</b> 20 mg (as hydrochloride). |

#### Complementary List [c]

- |                       |   |
|-----------------------|---|
| <i>fluoxetine</i> [a] | <b>Solid oral dosage form:</b> 20 mg (as hydrochloride).<br>[a] >8 years. |
|-----------------------|---|

#### 24.2.2 Medicines used in bipolar disorders

- |                                     |   |
|-------------------------------------|---|
| carbamazepine                       | <b>Tablet (scored):</b> 100 mg; 200 mg.                               |
| lithium carbonate                   | <b>Solid oral dosage form:</b> 300 mg.                                |
| valproic acid<br>(sodium valproate) | <b>Tablet (enteric-coated):</b> 200 mg; 500 mg<br>(sodium valproate). |

### 24.3 Medicines for anxiety disorders

- |                                   |                                     |
|-----------------------------------|-------------------------------------|
| <input type="checkbox"/> diazepam | <b>Tablet (scored):</b> 2 mg; 5 mg. |
|-----------------------------------|-------------------------------------|

**24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS** (*continued*)**24.4 Medicines used for obsessive compulsive disorders**

clomipramine	<b>Capsule:</b> 10 mg; 25 mg (hydrochloride).
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**24.5 Medicines for disorders due to psychoactive substance use**

nicotine replacement therapy (NRT)	<b>Chewing gum:</b> 2 mg; 4 mg (as polacrilex). <b>Transdermal patch:</b> 5 mg to 30 mg/16 hrs; 7 mg to 21 mg/24 hrs.
------------------------------------	--

**Complementary List**

<input type="checkbox"/> methadone*	<b>Concentrate for oral liquid:</b> 5 mg/ml; 10 mg/ml (hydrochloride). <b>Oral liquid:</b> 5 mg/5 ml; 10 mg/5 ml (hydrochloride).
-------------------------------------	--

\* 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**

<input type="checkbox"/> beclometasone	<b>Inhalation (aerosol):</b> 50 micrograms (dipropionate) per dose; 100 micrograms (dipropionate) per dose (as CFC free forms).
--	---

<input type="checkbox"/> budesonide <span style="border: 1px solid black; padding: 0 2px;">c</span>	<b>Inhalation (aerosol):</b> 100 micrograms per dose; 200 micrograms per dose.
---	--

epinephrine (adrenaline)	<b>Injection:</b> 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule.
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ipratropium bromide	<b>Inhalation (aerosol):</b> 20 micrograms/metered dose.
---------------------	--

<input type="checkbox"/> salbutamol	<b>Inhalation (aerosol):</b> 100 micrograms (as sulfate) per dose. <b>Injection:</b> 50 micrograms (as sulfate)/ml in 5-ml ampoule. <b>Metered dose inhaler (aerosol):</b> 100 micrograms (as sulfate) per dose. <b>Respirator solution for use in nebulizers:</b> 5 mg (as sulfate)/ml.
-------------------------------------	---

**26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID-BASE DISTURBANCES****26.1 Oral**

oral rehydration salts	See section 17.5.1.
------------------------	---------------------

## 26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID-BASE DISTURBANCES (continued)

potassium chloride                      **Powder for solution.**

### 26.2 Parenteral

glucose                                      **Injectable solution:** 5% (isotonic); 10% (hypertonic); 50% (hypertonic).

glucose with sodium chloride        **Injectable solution:** 4% glucose, 0.18% sodium chloride (equivalent to Na<sup>+</sup> 30 mmol/L, Cl<sup>-</sup> 30 mmol/L).

**Injectable solution:** 5% glucose, 0.9% sodium chloride (equivalent to Na<sup>+</sup> 150 mmol/L and Cl<sup>-</sup> 150 mmol/L); 5% glucose, 0.45% sodium chloride (equivalent to Na<sup>+</sup> 75 mmol/L and Cl<sup>-</sup> 75 mmol/L) [c].

potassium chloride                      **Solution:** 11.2% in 20-ml ampoule (equivalent to K<sup>+</sup> 1.5 mmol/ml, Cl<sup>-</sup> 1.5 mmol/ml).

**Solution for dilution:** 7.5% (equivalent to K 1 mmol/ml and Cl 1 mmol/ml) [c]; 15% (equivalent to K 2 mmol/ml and Cl 2 mmol/ml) [c].

sodium chloride                            **Injectable solution:** 0.9% isotonic (equivalent to Na<sup>+</sup> 154 mmol/L, Cl<sup>-</sup> 154 mmol/L).

sodium hydrogen carbonate            **Injectable solution:** 1.4% isotonic (equivalent to Na<sup>+</sup> 167 mmol/L, HCO<sub>3</sub><sup>-</sup> 167 mmol/L).

**Solution:** 8.4% in 10-ml ampoule (equivalent to Na<sup>+</sup> 1000 mmol/L, HCO<sub>3</sub><sup>-</sup> 1000 mmol/L).

□ sodium lactate, compound solution      **Injectable solution.**

### 26.3 Miscellaneous

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

## 27. VITAMINS AND MINERALS

ascorbic acid                                **Tablet:** 50 mg.

calcium                                        **Tablet:** 500 mg (elemental).

cholecalciferol\* [c]                        **Oral liquid:** 400 IU/ml.

**Solid oral dosage form:** 400 IU; 1000 IU.

\* Ergocalciferol can be used as an alternative.



**27. VITAMINS AND MINERALS** *(continued)*

<input type="checkbox"/> ergocalciferol	<b>Oral liquid:</b> 250 micrograms/ml (10 000 IU/ml). <b>Solid oral dosage form:</b> 1.25 mg (50 000 IU).
iodine	<b>Capsule:</b> 200 mg. <b>Iodized oil:</b> 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.
<input type="checkbox"/> nicotinamide	<b>Tablet:</b> 50 mg.
pyridoxine	<b>Tablet:</b> 25 mg (hydrochloride).
retinol	<b>Capsule:</b> 50 000 IU; 100 000 IU; 200 000 IU (as palmitate). <b>Oral oily solution:</b> 100 000 IU (as palmitate)/ml in multidose dispenser. <b>Tablet (sugar-coated):</b> 10 000 IU (as palmitate). <b>Water-miscible injection:</b> 100 000 IU (as palmitate) in 2-ml ampoule.
riboflavin	<b>Tablet:</b> 5 mg.
sodium fluoride	In any appropriate topical formulation.
thiamine	<b>Tablet:</b> 50 mg (hydrochloride).

**Complementary List**

*calcium gluconate*      **Injection:** 100 mg/ml in 10-ml ampoule.

**28. EAR, NOSE AND THROAT MEDICINES** [c]

acetic acid	<b>Topical:</b> 2%, in alcohol.
<input type="checkbox"/> budesonide	<b>Nasal spray:</b> 100 micrograms per dose.
<input type="checkbox"/> ciprofloxacin	<b>Topical:</b> 0.3% drops (as hydrochloride).
<input type="checkbox"/> xylometazoline [a]	<b>Nasal spray:</b> 0.05%. [a] Not in children less than 3 months.

**29. SPECIFIC MEDICINES FOR NEONATAL CARE****29.1 Medicines administered to the neonate** [c]

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

## 29. SPECIFIC MEDICINES FOR NEONATAL CARE (continued)

Chlorhexidine **Solution or gel:** 7.1% (digluconate) delivering 4% chlorhexidine (for umbilical cord care) [c].

### Complementary List

*ibuprofen* **Solution for injection:** 5 mg/ml.

*prostaglandin E* **Solution for injection:**  
*Prostaglandin E1:* 0.5 mg/ml in alcohol.  
*Prostaglandin E2:* 1 mg/ml.

*surfactant* **Suspension for intratracheal instillation:** 25 mg/ml or 80 mg/ml.

## 29.2 Medicines administered to the mother

dexamethasone **Injection:** 4 mg/ml dexamethasone phosphate (as disodium salt).

## 30. MEDICINES FOR DISEASES OF JOINTS

### 30.1 Medicines used to treat gout

allopurinol **Tablet:** 100 mg.

### 30.2 Disease-modifying agents used in rheumatoid disorders (DMARDs)

chloroquine **Tablet:** 100 mg; 150 mg (as phosphate or sulfate).

#### Complementary List

*azathioprine* **Tablet:** 50 mg.

*hydroxychloroquine* [c] **Solid oral dosage form:** 200 mg (as sulfate).

*methotrexate* **Tablet:** 2.5 mg (as sodium salt).

*penicillamine* **Solid oral dosage form:** 250 mg.

*sulfasalazine* **Tablet:** 500 mg.

### 30.3 Juvenile joint diseases

acetylsalicylic acid\* (acute or chronic use) **Suppository:** 50 mg to 150 mg.  
**Tablet:** 100 mg to 500 mg.

\* For use for rheumatic fever, juvenile arthritis, Kawasaki disease.

**Table 1.1: Medicines with age or weight restrictions**

atazanavir	>25 kg
atropine	>3 months
benzyl benzoate	>2 years
betamethasone topical preparations	hydrocortisone preferred in neonates
cefazolin	>1 month
ceftriaxone	>41 weeks corrected gestational age
diloxanide	>25 kg
doxycycline	>8 years (except for serious infections e.g. cholera)
efavirenz	>3 years or >10 kg
emtricitabine	>3 months
fluoxetine	>8 years
ibuprofen	>3 months (except IV form for patent ductus arteriosus)
mefloquine	>5 kg or >3 months
metoclopramide	Not in neonates
ondansetron	>1 month
saquinavir	>25 kg
silver sulfadiazine	>2 months
tetracaine	Not in preterm neonates
trimethoprim	>6 months
xylometazoline	>3 months

## Table 1.2: Explanation of dosage forms

### A. Principal dosage forms used in EML – oral administration

Term	Definition
<b>Solid oral dosage form</b>	<p>Refers to tablets or capsules or other solid dosage forms such as 'melts' that are immediate-release preparations. It implies that there is no difference in clinical efficacy or safety between the available dosage forms, and countries should therefore choose the form(s) to be listed depending on quality and availability.</p> <p>The term 'solid oral dosage form' is <i>never</i> intended to allow any type of modified-release tablet.</p>
<b>Tablets</b>	<p>Refers to:</p> <ul style="list-style-type: none"> <li>• uncoated or coated (film-coated or sugar-coated) tablets that are intended to be swallowed whole;</li> <li>• unscored and scored*;</li> <li>• tablets that are intended to be chewed before being swallowed;</li> <li>• tablets that are intended to be dispersed or dissolved in water or another suitable liquid before being swallowed;</li> <li>• tablets that are intended to be crushed before being swallowed.</li> </ul> <p>The term 'tablet' without qualification is <i>never</i> intended to allow any type of modified-release tablet.</p>
<b>Tablets (qualified)</b>	<p>Refers to a specific type of tablet:</p> <p><b>chewable</b> – tablets that are intended to be chewed before being swallowed;</p> <p><b>dispersible</b> – tablets that are intended to be dispersed in water or another suitable liquid before being swallowed;</p> <p><b>soluble</b> – tablets that are intended to be dissolved in water or another suitable liquid before being swallowed;</p> <p><b>crushable</b> – tablets that are intended to be crushed before being swallowed;</p> <p><b>scored</b> – tablets bearing a break mark or marks where sub-division is intended in order to provide doses of less than one tablet;</p> <p><b>sublingual</b> – tablets that are intended to be placed beneath the tongue.</p>

\* Scored tablets may be divided for ease of swallowing, provided that dose is a whole number of tablets.

Table 1.2 *continued*

Term	Definition
	The term 'tablet' is <i>always</i> qualified with an additional term (in parentheses) in entries where one of the following types of tablet is intended: <b>gastro-resistant</b> (such tablets may sometimes be described as enteric-coated or as delayed-release), <b>prolonged-release</b> or another modified-release form.
<b>Capsules</b>	Refers to hard or soft capsules. The term 'capsule' without qualification is <i>never</i> intended to allow any type of modified-release capsule.
<b>Capsules (qualified)</b>	The term 'capsule' with qualification refers to <b>gastro-resistant</b> (such capsules may sometimes be described as enteric-coated or as delayed-release), <b>prolonged-release</b> or another modified-release form.
<b>Granules</b>	Preparations that are issued to patient as granules to be swallowed without further preparation, to be chewed, or to be taken in or with water or another suitable liquid. The term 'granules' without further qualification is <i>never</i> intended to allow any type of modified-release granules.
<b>Oral powder</b>	Preparations that are issued to patient as powder (usually as single-dose) to be taken in or with water or another suitable liquid.
<b>Oral liquid</b>	Liquid preparations intended to be <i>swallowed</i> i.e. oral solutions, suspensions, emulsions and oral drops, including those constituted from powders or granules, but not those preparations intended for <i>oromucosal administration</i> e.g. gargles and mouthwashes. Oral liquids presented as powders or granules may offer benefits in the form of better stability and lower transport costs. If more than one type of oral liquid is available on the same market (e.g. solution, suspension, granules for reconstitution), they may be interchanged and in such cases should be bioequivalent. It is preferable that oral liquids do not contain sugar and that solutions for children do not contain alcohol.

## B. Principal dosage forms used in EMLc – parenteral administration

Term	Definition
<b>Injection</b>	Refers to solutions, suspensions and emulsions including those constituted from powders or concentrated solutions.
<b>Injection (qualified)</b>	Route of administration is indicated in parentheses where relevant.
<b>Injection (oily)</b>	The term 'injection' is qualified by '(oily)' in relevant entries.
<b>Intravenous infusion</b>	Refers to solutions and emulsions including those constituted from powders or concentrated solutions.

## C. Other dosage forms

Mode of administration	Term to be used
<b>To the eye</b>	Eye drops, eye ointments.
<b>Topical</b>	For liquids: lotions, paints. For semi-solids: cream, ointment.
<b>Rectal</b>	Suppositories, gel or solution.
<b>Vaginal</b>	Pessaries or vaginal tablets.
<b>Inhalation</b>	Powder for inhalation, pressurized inhalation, nebulizer.

# Annex 2

## 4th WHO Model List of Essential Medicines for Children (April 2013)

### Explanatory notes

**This Model List is intended for use for children up to 12 years of age.**

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

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

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

Therapeutic equivalence is indicated only on the basis of reviews of efficacy and safety and when consistent with WHO clinical guidelines. National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price.

The format and numbering of the 18th WHO Model List of Essential Medicines have been retained but, as indicated in the text, some sections have been deleted because they contain medicines that are not relevant for children.

**a** indicates that there is an age or weight restriction on use of the medicines; the details for each medicine are in Table 1.1 of Annex 1.

The presence of an entry on the Essential Medicines List carries no assurance as to pharmaceutical quality. It is the responsibility of the relevant national or regional drug regulatory authority to ensure that each product is of appropriate pharmaceutical quality (including stability) and that when relevant, different products are interchangeable.

For recommendations and advice concerning all aspects of the quality assurance of medicines see the WHO Medicines web site [http://www.who.int/medicines/areas/quality\\_assurance](http://www.who.int/medicines/areas/quality_assurance).

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

The main terms used for dosage forms in the Essential Medicines List can be found in Table 1.2 of Annex 1.

Definitions of many of these terms and pharmaceutical quality requirements applicable to the different categories are published in the current edition of *The International Pharmacopoeia* <http://www.who.int/medicines/publications/pharmacopoeia>.



## 1. ANAESTHETICS

### 1.1 General anaesthetics and oxygen

#### 1.1.1 Inhalational medicines

halothane	<b>Inhalation.</b>
isoflurane	<b>Inhalation.</b>
nitrous oxide	<b>Inhalation.</b>
oxygen	<b>Inhalation</b> (medicinal gas).

#### 1.1.2 Injectable medicines

ketamine	<b>Injection:</b> 50 mg (as hydrochloride)/ml in 10-ml vial.
propofol *	<b>Injection:</b> 10 mg/ml; 20 mg/ml.

\* Thiopental may be used as an alternative depending on local availability and cost.

### 1.2 Local anaesthetics

<input type="checkbox"/> bupivacaine	<b>Injection:</b> 0.25%; 0.5% (hydrochloride) in vial. <b>Injection for spinal anaesthesia:</b> 0.5% (hydrochloride) in 4-ml ampoule to be mixed with 7.5% glucose solution.
<input type="checkbox"/> lidocaine	<b>Injection:</b> 1%; 2% (hydrochloride) in vial. <b>Injection for spinal anaesthesia:</b> 5% (hydrochloride) in 2-ml ampoule to be mixed with 7.5% glucose solution. <b>Topical forms:</b> 2% to 4% (hydrochloride).
lidocaine + epinephrine (adrenaline)	<b>Dental cartridge:</b> 2% (hydrochloride) + epinephrine 1:80 000. <b>Injection:</b> 1%; 2% (hydrochloride or sulfate) + epinephrine 1:200 000 in vial.

### 1.3 Preoperative medication and sedation for short-term procedures

atropine	<b>Injection:</b> 1 mg (sulfate) in 1-ml ampoule.
<input type="checkbox"/> midazolam	<b>Injection:</b> 1 mg/ml. <b>Oral liquid:</b> 2 mg/ml. <b>Tablet:</b> 7.5 mg; 15 mg.
morphine	<b>Injection:</b> 10 mg (sulfate or hydrochloride) in 1-ml ampoule.

## 2. MEDICINES FOR PAIN AND PALLIATIVE CARE

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

ibuprofen <input type="checkbox"/> <sup>a</sup>	<b>Oral liquid:</b> 200 mg/5 ml. <b>Tablet:</b> 200 mg; 400 mg; 600 mg. <input type="checkbox"/> <sup>a</sup> Not in children less than 3 months.
paracetamol*	<b>Oral liquid:</b> 125 mg/5 ml. <b>Suppository:</b> 100 mg. <b>Tablet:</b> 100 mg to 500 mg. * Not recommended for anti-inflammatory use due to lack of proven benefit to that effect.

### 2.2 Opioid analgesics

<input type="checkbox"/> morphine*	<b>Granules (slow release; to mix with water):</b> 20 mg to 200 mg (morphine sulfate). <b>Injection:</b> 10 mg (morphine hydrochloride or morphine sulfate) in 1-ml ampoule. <b>Oral liquid:</b> 10 mg (morphine hydrochloride or morphine sulfate)/5 ml. <b>Tablet (slow release):</b> 10 mg – 200mg (morphine hydrochloride or morphine sulfate). <b>Tablet (immediate release):</b> 10 mg (morphine sulfate). * Alternatives limited to hydromorphone and oxycodone.
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### 2.3 Medicines for other symptoms common in palliative care

amitriptyline	<b>Tablet:</b> 10 mg; 25 mg.
cyclizine	<b>Injection:</b> 50 mg/ml. <b>Tablet:</b> 50 mg.
dexamethasone	<b>Injection:</b> 4 mg/ml in 1-ml ampoule (as disodium phosphate salt). <b>Oral liquid:</b> 2 mg/5 ml. <b>Tablet:</b> 2 mg.
diazepam	<b>Injection:</b> 5 mg/ml. <b>Oral liquid:</b> 2 mg/5 ml. <b>Rectal solution:</b> 2.5 mg; 5 mg; 10 mg. <b>Tablet:</b> 5 mg; 10 mg.
docusate sodium	<b>Capsule:</b> 100 mg. <b>Oral liquid:</b> 50 mg/5 ml.

**2. MEDICINES FOR PAIN AND PALLIATIVE CARE** (*continued*)

fluoxetine <input type="checkbox"/> a	<b>Solid oral dosage form:</b> 20 mg (as hydrochloride). <input type="checkbox"/> a >8 years.
hyoscine hydrobromide	<b>Injection:</b> 400 micrograms/ml; 600 micrograms/ml. <b>Transdermal patches:</b> 1 mg/72 hours.
lactulose	<b>Oral liquid:</b> 3.1–3.7 g/5 ml.
midazolam	<b>Injection:</b> 1 mg/ml; 5 mg/ml. <b>Oral liquid:</b> 2mg/ml. <b>Solid oral dosage form:</b> 7.5 mg; 15 mg.
ondansetron <input type="checkbox"/> a	<b>Injection:</b> 2 mg base/ml in 2-ml ampoule (as hydrochloride). <b>Oral liquid:</b> 4 mg base/5 ml. <b>Solid oral dosage form:</b> Eq 4 mg base; Eq 8 mg base. <input type="checkbox"/> a >1 month.
senna	<b>Oral liquid:</b> 7.5 mg/5 ml.

**3. ANTIALLERGICS AND MEDICINES USED IN ANAPHYLAXIS**

dexamethasone	<b>Injection:</b> 4 mg/ml in 1-ml ampoule (as disodium phosphate salt).
epinephrine (adrenaline)	<b>Injection:</b> 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule.
hydrocortisone	<b>Powder for injection:</b> 100 mg (as sodium succinate) in vial.
<input type="checkbox"/> loratadine *	<b>Oral liquid:</b> 1 mg/ml. <b>Tablet:</b> 10 mg. * There may be a role for sedating antihistamines for limited indications.
<input type="checkbox"/> prednisolone	<b>Oral liquid:</b> 5 mg/ml. <b>Tablet:</b> 5 mg; 25 mg.

**4. ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS****4.1 Non-specific**

charcoal, activated	<b>Powder.</b>
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**4.2 Specific**

acetylcysteine	<b>Injection:</b> 200 mg/ml in 10-ml ampoule. <b>Oral liquid:</b> 10%; 20%.
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#### 4. ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS *(continued)*

atropine	<b>Injection:</b> 1 mg (sulfate) in 1-ml ampoule.
calcium gluconate	<b>Injection:</b> 100 mg/ml in 10-ml ampoule.
naloxone	<b>Injection:</b> 400 micrograms (hydrochloride) in 1-ml ampoule.

##### *Complementary List*

<i>deferoxamine</i>	<b>Powder for injection:</b> 500 mg (mesilate) in vial.
<i>dimercaprol</i>	<b>Injection in oil:</b> 50 mg/ml in 2-ml ampoule.
<i>fomepizole</i>	<b>Injection:</b> 5 mg/ml (sulfate) in 20-ml ampoule or 1 g/ml (base) in 1.5-ml ampoule.
<i>sodium calcium edetate</i>	<b>Injection:</b> 200 mg/ml in 5-ml ampoule.
<i>succimer</i>	<b>Solid oral dosage form:</b> 100 mg.

#### 5. ANTICONVULSANTS/ANTIEPILEPTICS

carbamazepine	<b>Oral liquid:</b> 100 mg/5 ml. <b>Tablet (chewable):</b> 100 mg; 200 mg. <b>Tablet (scored):</b> 100 mg; 200 mg.
diazepam	<b>Gel or rectal solution:</b> 5 mg/ml in 0.5 ml; 2-ml; 4-ml tubes.
<input type="checkbox"/> lorazepam	<b>Parenteral formulation:</b> 2 mg/ml in 1-ml ampoule; 4 mg/ml in 1-ml ampoule.
phenobarbital	<b>Injection:</b> 200 mg/ml (sodium). <b>Oral liquid:</b> 15 mg/5 ml. <b>Tablet:</b> 15 mg to 100 mg.
phenytoin	<b>Injection:</b> 50 mg/ml in 5-ml vial (sodium salt). <b>Oral liquid:</b> 25 mg to 30 mg/5 ml.* <b>Solid oral dosage form:</b> 25 mg; 50 mg; 100 mg (sodium salt). <b>Tablet (chewable):</b> 50 mg.
valproic acid (sodium valproate)	<b>Oral liquid:</b> 200 mg/5 ml. <b>Tablet (crushable):</b> 100 mg. <b>Tablet (enteric-coated):</b> 200 mg; 500 mg (sodium valproate).

\* 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.

**5. ANTICONVULSANTS/ANTIEPILEPTICS** (*continued*)**Complementary List**

*ethosuximide*                      **Capsule:** 250 mg.  
**Oral liquid:** 250 mg/5 ml.

**6. ANTI-INFECTIVE MEDICINES****6.1 Anthelmintics****6.1.1 Intestinal anthelmintics**

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.  
praziquantel                      **Tablet:** 150 mg; 600 mg.  
pyrantel                      **Oral liquid:** 50 mg (as embonate or pamoate)/ml.  
**Tablet (chewable):** 250 mg (as embonate or pamoate).

**6.1.2 Antifilarials**

albendazole                      **Tablet (chewable):** 400 mg.  
diethylcarbamazine              **Tablet:** 50 mg; 100 mg (dihydrogen citrate).  
ivermectin                      **Tablet (scored):** 3 mg.

**6.1.3 Antischistosomal and other antitrepatode medicines**

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                      **Powder for oral liquid:** 125 mg (as trihydrate)/5 ml;  
250 mg (as trihydrate)/5 ml.  
**Solid oral dosage form:** 250 mg; 500 mg  
(as trihydrate).

## 6. ANTI-INFECTIVE MEDICINES (continued)

amoxicillin + clavulanic acid	<p><b>Oral liquid:</b> 125 mg amoxicillin + 31.25 mg clavulanic acid/5 ml AND 250 mg amoxicillin + 62.5 mg clavulanic acid/5 ml.</p> <p><b>Tablet:</b> 500 mg (as trihydrate) + 125 mg (as potassium salt).</p>
ampicillin	<p><b>Powder for injection:</b> 500 mg; 1 g (as sodium salt) in vial.</p>
benzathine benzylpenicillin	<p><b>Powder for injection:</b> 900 mg benzylpenicillin (= 1.2 million IU) in 5-ml vial; 1.44 g benzylpenicillin (= 2.4 million IU) in 5-ml vial.</p>
benzylpenicillin	<p><b>Powder for injection:</b> 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial.</p>
cefalexin	<p><b>Powder for reconstitution with water:</b> 125 mg/5 ml; 250 mg/5 ml (anhydrous).</p> <p><b>Solid oral dosage form:</b> 250 mg (as monohydrate).</p>
<input type="checkbox"/> cefazolin* <span style="border: 1px solid black; padding: 0 2px;">a</span>	<p><b>Powder for injection:</b> 1 g (as sodium salt) in vial.</p> <p>* For surgical prophylaxis.</p> <p><span style="border: 1px solid black; padding: 0 2px;">a</span> &gt;1 month.</p>
ceftriaxone* <span style="border: 1px solid black; padding: 0 2px;">a</span>	<p><b>Powder for injection:</b> 250 mg; 1 g (as sodium salt) in vial.</p> <p>* Do not administer with calcium and avoid in infants with hyperbilirubinaemia.</p> <p><span style="border: 1px solid black; padding: 0 2px;">a</span> &gt;41 weeks corrected gestational age.</p>
<input type="checkbox"/> cloxacillin	<p><b>Capsule:</b> 500 mg; 1 g (as sodium salt).</p> <p><b>Powder for injection:</b> 500 mg (as sodium salt) in vial.</p> <p><b>Powder for oral liquid:</b> 125 mg (as sodium salt)/5 ml.</p>
phenoxymethylpenicillin	<p><b>Powder for oral liquid:</b> 250 mg (as potassium salt)/5 ml.</p> <p><b>Tablet:</b> 250 mg (as potassium salt).</p>
procaine benzylpenicillin*	<p><b>Powder for injection:</b> 1 g (=1 million IU); 3 g (=3 million IU) in vial.</p> <p>* Procaine benzylpenicillin is not recommended as first-line treatment for neonatal sepsis except in settings with high neonatal mortality, when given by trained health workers in cases where hospital care is not achievable.</p>

**6. ANTI-INFECTIVE MEDICINES** (continued)**Complementary List**

*cefotaxime*\* **Powder for injection:** 250 mg per vial (as sodium salt).  
\* 3rd generation cephalosporin of choice for use in hospitalized neonates.

*ceftazidime* **Powder for injection:** 250 mg or 1 g (as pentahydrate) 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. Meropenem is indicated for the treatment of meningitis and is licensed for use in children over the age of 3 months.

**6.2.2 Other antibacterials**

*azithromycin*\* **Capsule:** 250 mg; 500 mg (anhydrous).  
**Oral liquid:** 200 mg/5 ml.  
\* Listed only for trachoma.

*chloramphenicol* **Capsule:** 250 mg.  
**Oily suspension for injection**\*: 0.5 g (as sodium succinate)/ml in 2-ml ampoule.  
\* Only for the presumptive treatment of epidemic meningitis in children older than 2 years.  
**Oral liquid:** 150 mg (as palmitate)/5 ml.  
**Powder for injection:** 1 g (sodium succinate) in vial.

*ciprofloxacin* **Oral liquid:** 250 mg/5 ml (anhydrous).  
**Solution for IV infusion:** 2 mg/ml (as hyclate).  
**Tablet:** 250 mg (as hydrochloride).

*doxycycline* **a** **Oral liquid:** 25 mg/5 ml; 50 mg/5 ml (anhydrous).  
**Solid oral dosage form:** 50 mg; 100 mg (as hyclate).  
**a** Use in children <8 years only for life-threatening infections when no alternative exists.

*erythromycin* **Powder for oral liquid:** 125 mg/5 ml (as stearate or estolate or ethyl succinate).  
**Solid oral dosage form:** 250 mg (as stearate or estolate or ethyl succinate).

*gentamicin* **Injection:** 10 mg; 40 mg (as sulfate)/ml in 2-ml vial.

## 6. ANTI-INFECTIVE MEDICINES (continued)

metronidazole	<b>Injection:</b> 500 mg in 100-ml vial. <b>Oral liquid:</b> 200 mg (as benzoate)/5 ml. <b>Tablet:</b> 200 mg to 500 mg.
nitrofurantoin	<b>Oral liquid:</b> 25 mg/5 ml. <b>Tablet:</b> 100 mg.
sulfamethoxazole + trimethoprim	<b>Injection:</b> 80 mg + 16 mg/ml in 5-ml ampoule; 80 mg + 16 mg/ml in 10-ml ampoule. <b>Oral liquid:</b> 200 mg + 40 mg/5 ml. <b>Tablet:</b> 100 mg + 20 mg; 400 mg + 80 mg.
trimethoprim <sup>a</sup>	<b>Oral liquid:</b> 50 mg/5 ml. <b>Tablet:</b> 100 mg; 200 mg. <sup>a</sup> >6 months.

### Complementary List

clindamycin	<b>Capsule:</b> 150 mg (as hydrochloride). <b>Injection:</b> 150 mg (as phosphate)/ml. <b>Oral liquid:</b> 75 mg/5 ml (as palmitate).
vancomycin	<b>Powder for injection:</b> 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	<b>Capsule:</b> 50 mg; 100 mg.
dapsone	<b>Tablet:</b> 25 mg; 50 mg; 100 mg.
rifampicin	<b>Solid oral dosage form:</b> 150 mg; 300 mg.

### 6.2.4 Antituberculosis medicines

WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.

ethambutol	<b>Oral liquid:</b> 25 mg/ml. <b>Tablet:</b> 100 mg; 400 mg (hydrochloride).
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**6. ANTI-INFECTIVE MEDICINES** *(continued)*

isoniazid	<b>Oral liquid:</b> 50 mg/5 ml. <b>Tablet:</b> 100 mg to 300 mg. <b>Tablet (scored):</b> 50 mg.
pyrazinamide	<b>Oral liquid:</b> 30 mg/ml. <b>Tablet:</b> 400 mg. <b>Tablet (dispersible):</b> 150 mg. <b>Tablet (scored):</b> 150 mg.
rifampicin	<b>Oral liquid:</b> 20 mg/ml. <b>Solid oral dosage form:</b> 150 mg; 300 mg.

**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.*

<i>amikacin</i>	<b>Powder for injection:</b> 100 mg; 500 mg; 1 g (as sulfate) in vial.
<i>capreomycin</i>	<b>Powder for injection:</b> 1 g (as sulfate) in vial.
<i>cycloserine</i>	<b>Solid oral dosage form:</b> 250 mg.
<i>ethionamide*</i>	<b>Tablet:</b> 125 mg; 250 mg. * <i>Protionamide may be used as an alternative.</i>
<i>kanamycin</i>	<b>Powder for injection:</b> 1 g (as sulfate) in vial.
<i>levofloxacin*</i>	<b>Tablet:</b> 250 mg; 500 mg. * <i>Ofloxacin and moxifloxacin may be used as alternatives based on availability and programme considerations.</i>
<i>p-aminosalicylic acid</i>	<b>Granules:</b> 4 g in sachet. <b>Tablet:</b> 500 mg.
<i>streptomycin</i>	<b>Powder for injection:</b> 1 g (as sulfate) in vial.

**6.3 Antifungal medicines**

amphotericin B	<b>Powder for injection:</b> 50 mg in vial (as sodium deoxycholate or liposomal complex).
<input type="checkbox"/> fluconazole	<b>Capsule:</b> 50 mg. <b>Injection:</b> 2 mg/ml in vial. <b>Oral liquid:</b> 50 mg/5 ml.
flucytosine	<b>Capsule:</b> 250 mg. <b>Infusion:</b> 2.5 g in 250 ml.

**6. ANTI-INFECTIVE MEDICINES** (*continued*)

griseofulvin	<b>Oral liquid:</b> 125 mg/5 ml. <b>Solid oral dosage form:</b> 125 mg; 250 mg.
nystatin	<b>Lozenge:</b> 100 000 IU. <b>Oral liquid:</b> 50 mg/5 ml; 100 000 IU/ml. <b>Tablet:</b> 100 000 IU; 500 000 IU.

**Complementary List**

<i>potassium iodide</i>	<b>Saturated solution.</b>
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**6.4 Antiviral medicines****6.4.1 Antiherpes medicines**

aciclovir	<b>Oral liquid:</b> 200 mg/5 ml. <b>Powder for injection:</b> 250 mg (as sodium salt) in vial. <b>Tablet:</b> 200 mg.
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**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). WHO emphasizes the importance of using these products in accordance with global and national guidelines. WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.

Scored tablets can be used in children and therefore can be considered for inclusion in the listing of tablets, provided that adequate quality products are available.

**6.4.2.1 Nucleoside/Nucleotide reverse transcriptase inhibitors**

abacavir (ABC)	<b>Oral liquid:</b> 100 mg (as sulfate)/5 ml. <b>Tablet:</b> 300 mg (as sulfate).
didanosine (ddI)	<b>Buffered powder for oral liquid:</b> 100-mg; 167-mg; 250-mg packets. <b>Capsule (unbuffered enteric-coated):</b> 125 mg; 200 mg; 250 mg; 400 mg. <b>Tablet (buffered chewable, dispersible):</b> 25 mg; 50 mg; 100 mg; 150 mg; 200 mg.

**6. ANTI-INFECTIVE MEDICINES** (*continued*)

emtricitabine (FTC)* <b>[a]</b>	<b>Capsule:</b> 200 mg. <b>Oral liquid:</b> 10 mg/ml. * FTC is an acceptable alternative to 3TC, based on knowledge of the pharmacology, the resistance patterns and clinical trials of antiretrovirals. <b>[a]</b> >3 months.
lamivudine (3TC)	<b>Oral liquid:</b> 50 mg/5 ml. <b>Tablet:</b> 150 mg.
stavudine (d4T)	<b>Capsule:</b> 15 mg; 20 mg; 30 mg. <b>Powder for oral liquid:</b> 5 mg/5 ml.
zidovudine (ZDV or AZT)	<b>Capsule:</b> 100 mg; 250 mg. <b>Oral liquid:</b> 50 mg/5 ml. <b>Solution for IV infusion injection:</b> 10 mg/ml in 20-ml vial. <b>Tablet:</b> 300 mg.

**6.4.2.2 Non-nucleoside reverse transcriptase inhibitors**

efavirenz (EFV or EFZ) <b>[a]</b>	<b>Capsule:</b> 50 mg; 100 mg; 200 mg. <b>Oral liquid:</b> 150 mg/5 ml. <b>Tablet:</b> 600 mg. <b>[a]</b> >3 years or >10 kg.
nevirapine (NVP)	<b>Oral liquid:</b> 50 mg/5 ml. <b>Tablet:</b> 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. All other protease inhibitors should be used in boosted forms (e.g. with ritonavir).

atazanavir <b>[a]</b>	<b>Solid oral dosage form:</b> 100 mg; 150 mg; 300 mg (as sulfate). <b>[a]</b> >25 kg.
lopinavir + ritonavir (LPV/r)	<b>Capsule:</b> 133.3 mg + 33.3 mg. <b>Oral liquid:</b> 400 mg + 100 mg/5 ml. <b>Tablet (heat stable):</b> 100 mg + 25 mg; 200 mg + 50 mg.

## 6. ANTI-INFECTIVE MEDICINES (continued)

ritonavir	<b>Oral liquid:</b> 400 mg/5 ml. <b>Solid oral dosage form:</b> 100 mg. <b>Tablet (heat stable):</b> 25 mg; 100 mg.
saquinavir (SQV) <span style="border: 1px solid black; padding: 0 2px;">a</span>	<b>Solid oral dosage form:</b> 200 mg (as mesilate). <span style="border: 1px solid black; padding: 0 2px;">a</span> >25 kg.

### FIXED-DOSE COMBINATIONS

lamivudine + nevirapine + stavudine	<b>Tablet:</b> 150 mg + 200 mg + 30 mg. <b>Tablet (dispersible):</b> 30 mg + 50 mg + 6 mg; 60 mg + 100 mg + 12 mg.
lamivudine + nevirapine + zidovudine	<b>Tablet:</b> 30 mg + 50 mg + 60 mg; 150 mg + 200 mg + 300 mg.
lamivudine + zidovudine	<b>Tablet:</b> 30 mg + 60 mg; 150 mg + 300 mg.

### 6.4.3 Other antivirals

oseltamivir*	<b>Capsule:</b> 30 mg; 45 mg; 75 mg (as phosphate). <b>Oral powder:</b> 12 mg/ml. * Potentially severe or complicated illness due to confirmed or suspected influenza virus infection in accordance with WHO treatment guidelines.
ribavirin*	<b>Injection for intravenous administration:</b> 800 mg and 1 g in 10-ml phosphate buffer solution. <b>Solid oral dosage form:</b> 200 mg; 400 mg; 600 mg. * For the treatment of viral haemorrhagic fevers only.

## 6.5 Antiprotozoal medicines

### 6.5.1 Antiamoebic and anti giardiasis medicines

diloxanide <span style="border: 1px solid black; padding: 0 2px;">a</span>	<b>Tablet:</b> 500 mg (furoate). <span style="border: 1px solid black; padding: 0 2px;">a</span> >25 kg.
<span style="border: 1px solid black; padding: 0 2px;">□</span> metronidazole	<b>Injection:</b> 500 mg in 100-ml vial. <b>Oral liquid:</b> 200 mg (as benzoate)/5 ml. <b>Tablet:</b> 200 mg to 500 mg.

### 6.5.2 Antileishmaniasis medicines

amphotericin B	<b>Powder for injection:</b> 50 mg in vial. As sodium deoxycholate or liposomal complex.
miltefosine	<b>Solid oral dosage form:</b> 10 mg; 50 mg.



## 6. ANTI-INFECTIVE MEDICINES (continued)

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

### 6.5.3.2 For prophylaxis

chloroquine*	<b>Oral liquid:</b> 50 mg (as phosphate or sulfate)/5 ml. <b>Tablet:</b> 150 mg (as phosphate or sulfate). * For use only for the treatment of <i>P. vivax</i> infection.
doxycycline <sup>a</sup>	<b>Solid oral dosage form:</b> 100 mg (as hydrochloride or hyclate). <sup>a</sup> >8 years.
mefloquine <sup>a</sup>	<b>Tablet:</b> 250 mg (as hydrochloride). <sup>a</sup> >5 kg or >3 months.
proguanil*	<b>Tablet:</b> 100 mg (as hydrochloride). * For use only in combination with chloroquine.

### 6.5.4 Antipneumocystosis and antitoxoplasmosis medicines

pyrimethamine	<b>Tablet:</b> 25 mg.
sulfadiazine	<b>Tablet:</b> 500 mg.

**6. ANTI-INFECTIVE MEDICINES** (continued)

sulfamethoxazole + trimethoprim	<p><b>Injection:</b> 80 mg + 16 mg/ml in 5-ml ampoule; 80 mg + 16 mg/ml in 10-ml ampoule.</p> <p><b>Oral liquid:</b> 200 mg + 40 mg/5 ml.</p> <p><b>Tablet:</b> 100 mg + 20 mg; 400 mg + 80 mg.</p>
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**6.5.5 Antitrypanosomal medicines****6.5.5.1 African trypanosomiasis****Medicines for the treatment of 1st stage African trypanosomiasis.**

pentamidine*	<p><b>Powder for injection:</b> 200 mg (as isetionate) in vial.</p> <p>* To be used for the treatment of <i>Trypanosoma brucei gambiense</i> infection.</p>
suramin sodium*	<p><b>Powder for injection:</b> 1 g in vial.</p> <p>* To be used for the treatment of the initial phase of <i>Trypanosoma brucei rhodesiense</i> infection.</p>

**Medicines for the treatment of 2nd stage African trypanosomiasis**

eflornithine*	<p><b>Injection:</b> 200 mg (hydrochloride)/ml in 100-ml bottle.</p> <p>* To be used for the treatment of <i>Trypanosoma brucei gambiense</i> infection.</p>
nifurtimox*	<p><b>Tablet:</b> 120 mg.</p> <p>* Only to be used in combination with eflornithine, for the treatment of <i>Trypanosoma brucei gambiense</i> infection.</p>

**Complementary List**

melarsoprol	<b>Injection:</b> 3.6% solution in 5-ml ampoule (180 mg of active compound).
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**6.5.5.2 American trypanosomiasis**

benznidazole	<p><b>Tablet:</b> 12.5 mg; 100 mg.</p> <p><b>Tablet (scored):</b> 50 mg.</p>
nifurtimox	<b>Tablet:</b> 30 mg; 120 mg; 250 mg.

**7. ANTIMIGRAINE MEDICINES****7.1 For treatment of acute attack**

ibuprofen	<b>Tablet:</b> 200 mg; 400 mg.
paracetamol	<p><b>Oral liquid:</b> 125 mg/5 ml.</p> <p><b>Tablet:</b> 300 mg to 500 mg.</p>

## 7. ANTIMIGRAINE MEDICINES (continued)

### 7.2 For prophylaxis

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

## 8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES

### 8.1 Immunosuppressive medicines

#### *Complementary List*

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

### 8.2 Cytotoxic and adjuvant medicines

Medicines listed below should be used according to protocols for treatment of the diseases.

#### *Complementary List*

#### ACUTE LYMPHOBLASTIC LEUKAEMIA

##### STEP 1

<i>asparaginase</i>	<b>Powder for injection:</b> 10 000 IU in vial.
<i>dexamethasone</i>	<b>Oral liquid:</b> 2 mg/5 ml.
<i>mercaptopurine</i>	<b>Tablet:</b> 50 mg.
<i>methotrexate</i>	<b>Powder for injection:</b> 50 mg (as sodium salt) in vial. <b>Tablet:</b> 2.5 mg (as sodium salt).
<i>methylprednisolone</i>	<b>Injection:</b> 40 mg/ml (as sodium succinate) in 1-ml single dose vial and 5-ml multidose vials; 80 mg/ml (as sodium succinate) in 1-ml single dose vial.
<i>prednisolone</i>	<b>Oral liquid:</b> 5 mg/ml.
<i>vincristine</i>	<b>Powder for injection:</b> 1 mg; 5 mg (sulfate) in vial.

##### STEP 2

<i>cyclophosphamide</i>	<b>Powder for injection:</b> 500 mg in vial.
<i>cytarabine</i>	<b>Powder for injection:</b> 100 mg in vial.
<i>daunorubicin</i>	<b>Powder for injection:</b> 50 mg (hydrochloride) in vial.



**8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES** (*continued*)

<i>doxorubicin</i>	<b>Powder for injection:</b> 10 mg; 50 mg (hydrochloride) in vial.
<i>hydrocortisone</i>	<b>Powder for injection:</b> 100 mg (as sodium succinate) in vial.
<i>methotrexate</i>	<b>Powder for injection:</b> 50 mg (as sodium salt) in vial.
<i>tioguanine</i>	<b>Solid oral dosage form:</b> 40 mg.

**WILMS TUMOUR (NEPHROBLASTOMA)****STEP 1 & STEP 2**

<i>dactinomycin</i>	<b>Powder for injection:</b> 500 micrograms in vial.
<i>daunorubicin</i>	<b>Powder for injection:</b> 50 mg (hydrochloride) in vial.
<i>vincristine</i>	<b>Powder for injection:</b> 1 mg; 5 mg (sulfate) in vial.

**BURKITT LYMPHOMA****STEP 1 & STEP 2**

<i>cyclophosphamide</i>	<b>Powder for injection:</b> 500 mg in vial.
<i>cytarabine</i>	<b>Powder for injection:</b> 100 mg in vial.
<i>doxorubicin</i>	<b>Powder for injection:</b> 10 mg; 50 mg (hydrochloride) in vial.
<i>prednisolone</i>	<b>Oral liquid:</b> 5 mg/ml.
<i>vincristine</i>	<b>Powder for injection:</b> 1 mg; 5 mg (sulfate) in vial.

**ADJUVANT MEDICINES**

<i>allopurinol</i>	<b>Tablet:</b> 100 mg; 300 mg.
<i>mesna</i>	<b>Injection:</b> 100 mg/ml in 4-ml and 10-ml ampoules. <b>Tablet:</b> 400 mg; 600 mg.

**8.3 Hormones and antihormones****9. ANTIPARKINSONISM MEDICINES****10. MEDICINES AFFECTING THE BLOOD****10.1 Antianaemia medicines**

<i>ferrous salt</i>	<b>Oral liquid:</b> equivalent to 25 mg iron (as sulfate)/ml. <b>Tablet:</b> equivalent to 60 mg iron.
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**10. MEDICINES AFFECTING THE BLOOD** (*continued*)

folic acid	<b>Tablet:</b> 1 mg; 5 mg.
hydroxocobalamin	<b>Injection:</b> 1 mg (as acetate, as hydrochloride or as sulfate) in 1-ml ampoule.

**10.2 Medicines affecting coagulation**

phytomenadione	<b>Injection:</b> 1 mg/ml; 10 mg/ml in 5-ml ampoule. <b>Tablet:</b> 10 mg.
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**Complementary List**

*heparin sodium* **Injection:** 1000 IU/ml; 5000 IU/ml in 1-ml ampoule.

*protamine sulfate* **Injection:** 10 mg/ml in 5-ml ampoule.

*warfarin* **Tablet:** 0.5 mg; 1 mg; 2 mg; 5 mg (sodium salt).

**10.3 Other medicines for haemoglobinopathies****Complementary List**

*deferoxamine\** **Powder for injection:** 500 mg (mesilate) in vial.

\* *Deferasirox oral form may be an alternative, depending on cost and availability.*

*hydroxycarbamide* **Solid oral dosage form:** 200 mg; 500 mg; 1 g.

**11. BLOOD PRODUCTS OF HUMAN ORIGIN AND PLASMA SUBSTITUTES****11.1 Blood and blood components**

In accordance with the World Health Assembly resolution WHA63.12, WHO recognizes that achieving self-sufficiency, unless special circumstances preclude it, in the supply of safe blood components based on voluntary, non-remunerated blood donation, and the security of that supply are important national goals to prevent blood shortages and meet the transfusion requirements of the patient population. All preparations should comply with the WHO requirements.

fresh-frozen plasma

platelets

red blood cells

whole blood

**11.2 Plasma-derived medicinal products**

All human plasma-derived medicines should comply with the WHO requirements.

**11. BLOOD PRODUCTS OF HUMAN ORIGIN AND PLASMA SUBSTITUTES** *(continued)***11.2.1 Human immunoglobulins****Complementary List***human normal immunoglobulin***Intramuscular administration:** 16% protein solution.\***Intravenous administration:** 5%; 10% protein solution.\*\***Subcutaneous administration:** 15%; 16% protein solution.\*

\* Indicated for primary immune deficiency.

\*\* Indicated for primary immune deficiency and Kawasaki disease.

**11.2.2 Blood coagulation factors****Complementary List** *coagulation factor VIII***Powder for injection:** 500 IU/vial. *coagulation factor IX***Powder for injection:** 500 IU/vial, 1000 IU/vial.**11.3 Plasma substitutes** *dextran 70\****Injectable solution:** 6%.

\* Polygeline, injectable solution, 3.5% is considered as equivalent.

**12. CARDIOVASCULAR MEDICINES**~~12.1 Antianginal medicines~~~~12.2 Antiarrhythmic medicines~~**12.3 Antihypertensive medicines** *enalapril***Tablet:** 2.5 mg; 5 mg (as hydrogen maleate).**12.4 Medicines used in heart failure***digoxin***Injection:** 250 micrograms/ml in 2-ml ampoule.**Oral liquid:** 50 micrograms/ml.**Tablet:** 62.5 micrograms; 250 micrograms.*furosemide***Injection:** 10 mg/ml in 2-ml ampoule.**Oral liquid:** 20 mg/5 ml.**Tablet:** 40 mg.**Complementary List***dopamine***Injection:** 40 mg (hydrochloride) in 5-ml vial.

## 12. CARDIOVASCULAR MEDICINES (continued)

### 12.5 Antithrombotic medicines

### 12.6 Lipid-lowering agents

## 13. DERMATOLOGICAL MEDICINES (topical)

### 13.1 Antifungal medicines

<input type="checkbox"/> miconazole	<b>Cream or ointment:</b> 2% (nitrate).
terbinafine	<b>Cream:</b> 1% <b>or Ointment:</b> 1% terbinafine hydrochloride.

### 13.2 Anti-infective medicines

mupirocin	<b>Cream (as mupirocin calcium):</b> 2%. <b>Ointment:</b> 2%.
potassium permanganate	<b>Aqueous solution:</b> 1:10 000.
silver sulfadiazine <input type="checkbox"/> <b>a</b>	<b>Cream:</b> 1%. <b>a</b> >2 months.

### 13.3 Anti-inflammatory and antipruritic medicines

<input type="checkbox"/> betamethasone <input type="checkbox"/> <b>a</b>	<b>Cream or ointment:</b> 0.1% (as valerate). <b>a</b> Hydrocortisone preferred in neonates.
calamine	<b>Lotion.</b>
hydrocortisone	<b>Cream or ointment:</b> 1% (acetate).

### 13.4 Medicines affecting skin differentiation and proliferation

benzoyl peroxide	<b>Cream or lotion:</b> 5%.
coal tar	<b>Solution:</b> 5%.
<input type="checkbox"/> podophyllum resin	<b>Solution:</b> 10% to 25%.
salicylic acid	<b>Solution:</b> 5%.
urea	<b>Cream or ointment:</b> 5%; 10%.

### 13.5 Scabicides and pediculicides

<input type="checkbox"/> benzyl benzoate <input type="checkbox"/> <b>a</b>	<b>Lotion:</b> 25%. <b>a</b> >2 years.
permethrin	<b>Cream:</b> 5%. <b>Lotion:</b> 1%.

**14. DIAGNOSTIC AGENTS****14.1 Ophthalmic medicines**

- fluorescein **Eye drops:** 1% (sodium salt).
- tropicamide **Eye drops:** 0.5%.

**14.2 Radiocontrast media*****Complementary List***

*barium sulfate* **Aqueous suspension.**

**15. DISINFECTANTS AND ANTISEPTICS****15.1 Antiseptics**

- chlorhexidine **Solution:** 5% (digluconate).  
**Gel:** 4%.
- ethanol **Solution:** 70% (denatured).
- povidone iodine **Solution:** 10% (equivalent to 1% available iodine).

**15.2 Disinfectants**

- chlorine base compound **Powder:** (0.1% available chlorine) for solution.
- chloroxylenol **Solution:** 4.8%.
- glutaral **Solution:** 2%.

**16. DIURETICS**

- furosemide **Injection:** 10 mg/ml in 2-ml ampoule.  
**Oral liquid:** 20 mg/5 ml.  
**Tablet:** 10 mg; 20 mg; 40 mg.

***Complementary List***

- hydrochlorothiazide **Tablet (scored):** 25 mg.
- mannitol* **Injectable solution:** 10%; 20%.
- spironolactone* **Oral liquid:** 5 mg/5 ml; 10 mg/5 ml; 25 mg/5 ml.  
**Tablet:** 25 mg.

**17. GASTROINTESTINAL MEDICINES*****Complementary List***

- pancreatic enzymes **Age-appropriate formulations and doses including lipase, protease and amylase.**

## 17. GASTROINTESTINAL MEDICINES *(continued)*

### 17.1 Antiulcer medicines

- |                                     |   |
|-------------------------------------|---|
| <input type="checkbox"/> omeprazole | <b>Powder for oral liquid:</b> 20-mg; 40-mg sachets.<br><b>Solid oral dosage form:</b> 10 mg; 20 mg; 40 mg.   |
| <input type="checkbox"/> ranitidine | <b>Injection:</b> 25 mg/ml (as hydrochloride) in 2-ml ampoule.<br><b>Oral liquid:</b> 75 mg/5 ml (as hydrochloride).<br><b>Tablet:</b> 150 mg (as hydrochloride). |

### 17.2 Antiemetic medicines

- |  |  |
|--|--|
| dexamethasone                                    | <b>Injection:</b> 4 mg/ml in 1-ml ampoule (as disodium phosphate salt).<br><b>Oral liquid:</b> 0.5 mg/5 ml; 2 mg/5 ml.<br><b>Solid oral dosage form:</b> 0.5 mg; 0.75 mg; 1.5 mg; 4 mg.                                |
| metoclopramide <input type="checkbox"/> <b>a</b> | <b>Injection:</b> 5 mg (hydrochloride)/ml in 2-ml ampoule.<br><b>Oral liquid:</b> 5 mg/5 ml.<br><b>Tablet:</b> 10 mg (hydrochloride).<br><input type="checkbox"/> <b>a</b> Not in neonates.                            |
| ondansetron <input type="checkbox"/> <b>a</b>    | <b>Injection:</b> 2 mg base/ml in 2-ml ampoule (as hydrochloride).<br><b>Oral liquid:</b> 4 mg base/5 ml.<br><b>Solid oral dosage form:</b> Eq 4 mg base; Eq 8 mg base.<br><input type="checkbox"/> <b>a</b> >1 month. |

### ~~17.3 Anti-inflammatory medicines~~

### 17.4 Laxatives

**17. GASTROINTESTINAL MEDICINES** (*continued*)**17.5 Medicines used in diarrhoea****17.5.1 Oral rehydration**

oral rehydration salts

**Powder for dilution** in 200 ml; 500 ml; 1 L.

glucose:	75 mEq
sodium:	75 mEq <b>or</b> mmol/L
chloride:	65 mEq <b>or</b> mmol/L
potassium:	20 mEq <b>or</b> mmol/L
citrate:	10 mmol/L
osmolarity:	245 mOsm/L
glucose:	13.5 g/L
sodium chloride:	2.6 g/L
potassium chloride:	1.5 g/L
trisodium citrate dihydrate*:	2.9 g/L

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

**17.5.2 Medicines for diarrhoea**

zinc sulfate\*

**Solid oral dosage form:** 20 mg. [C].

\* In acute diarrhoea zinc sulfate should be used as an adjunct to oral rehydration salts.

**18. HORMONES, OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES****18.1 Adrenal hormones and synthetic substitutes**

fludrocortisone

**Tablet:** 100 micrograms (acetate).

hydrocortisone

**Tablet:** 5 mg; 10 mg; 20 mg.~~**18.2 Androgens**~~~~**18.3 Contraceptives**~~~~**18.3.1 Oral hormonal contraceptives**~~~~**18.3.2 Injectable hormonal contraceptives**~~~~**18.3.3 Intrauterine devices**~~~~**18.3.4 Barrier methods**~~~~**18.3.5 Implantable contraceptives**~~

## 18. HORMONES, OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES (continued)

### 18.4 Estrogens

#### 18.5 Insulins and other medicines used for diabetes

glucagon	<b>Injection:</b> 1 mg/ml.
insulin injection (soluble)	<b>Injection:</b> 100 IU/ml in 10-ml vial.
intermediate-acting insulin	<b>Injection:</b> 100 IU/ml in 10-ml vial (as compound insulin zinc suspension or isophane insulin).

#### *Complementary List*

<i>metformin</i>	<b>Tablet:</b> 500 mg (hydrochloride).
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### 18.6 Ovulation inducers

### 18.7 Progestogens

#### 18.8 Thyroid hormones and antithyroid medicines

levothyroxine	<b>Tablet:</b> 25 micrograms; 50 micrograms; 100 micrograms (sodium salt).
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#### *Complementary List*

<i>Lugol's solution</i>	<b>Oral liquid:</b> about 130 mg total iodine/ml.
<i>potassium iodide</i>	<b>Tablet:</b> 60 mg.
<i>propylthiouracil</i>	<b>Tablet:</b> 50 mg.

## 19. IMMUNOLOGICALS

### 19.1 Diagnostic agents

All tuberculins should comply with the WHO requirements for tuberculins.

tuberculin, purified protein derivative (PPD)	<b>Injection.</b>
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### 19.2 Sera and immunoglobulins

All plasma fractions should comply with the WHO requirements

anti-tetanus immunoglobulin (human)	<b>Injection:</b> 500 IU in vial.
anti-rabies immunoglobulin (human)	<b>Injection:</b> 150 IU/ml in vial.
anti-venom immunoglobulin*	<b>Injection.</b>

\* Exact type to be defined locally.



**19. IMMUNOLOGICALS** (*continued*)

diphtheria antitoxin                      **Injection:** 10 000 IU; 20 000 IU 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](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.

WHO noted the need for vaccines used in children to be polyvalent.

BCG vaccine

cholera vaccine

diphtheria vaccine

*Haemophilus influenzae* type b vaccine

hepatitis A vaccine

hepatitis B vaccine

influenza vaccine

Japanese encephalitis vaccine

measles vaccine

meningococcal meningitis vaccine

mumps vaccine

pertussis vaccine

pneumococcal vaccine

poliomyelitis vaccine

rabies vaccine

rotavirus vaccine

rubella vaccine

tetanus vaccine

typhoid vaccine

## 19. IMMUNOLOGICALS (continued)

varicella vaccine

yellow fever vaccine

## 20. MUSCLE RELAXANTS (PERIPHERALLY-ACTING) AND CHOLINESTERASE INHIBITORS

neostigmine **Injection:** 500 micrograms in 1-ml ampoule; 2.5 mg (metilsulfate) in 1-ml ampoule.

**Tablet:** 15 mg (bromide).

suxamethonium **Injection:** 50 mg (chloride)/ml in 2-ml ampoule.

**Powder for injection:** (chloride), in vial.

vecuronium **Powder for injection:** 10 mg (bromide) in vial.

### Complementary List

*pyridostigmine* **Injection:** 1 mg in 1-ml ampoule.

**Tablet:** 60 mg (bromide).

## 21. OPHTHALMOLOGICAL PREPARATIONS

### 21.1 Anti-infective agents

aciclovir **Ointment:** 3% W/W.

azithromycin **Solution (eye drops):** 1.5%

gentamicin **Solution (eye drops):** 0.3% (sulfate).

ofloxacin **Solution (eye drops):** 0.3%.

tetracycline **Eye ointment:** 1% (hydrochloride).

### 21.2 Anti-inflammatory agents

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

### 21.3 Local anaesthetics

tetracaine <sup>[a]</sup> **Solution (eye drops):** 0.5% (hydrochloride).

<sup>[a]</sup> Not in preterm neonates.

### 21.4 Miotics and antiglaucoma medicines

### 21.5 Mydriatics

atropine\* <sup>[a]</sup> **Solution (eye drops):** 0.1%; 0.5%; 1% (sulfate).

\* Or homatropine (hydrobromide) or cyclopentolate (hydrochloride).

<sup>[a]</sup> >3 months.

**21. OPHTHALMOLOGICAL PREPARATIONS** *(continued)***Complementary List**

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

**22. OXYTOCICS AND ANTIOXYTOCICS**~~22.1 Oxytocics~~~~22.2 Antioxytocics (tocolytics)~~**23. PERITONEAL DIALYSIS SOLUTION****Complementary List**

*intraperitoneal dialysis solution (of appropriate composition)*      **Parenteral solution.**

**24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS****24.1 Medicines used in psychotic disorders****Complementary List**

*chlorpromazine*      **Injection:** 25 mg (hydrochloride)/ml in 2-ml ampoule.  
**Oral liquid:** 25 mg (hydrochloride)/5 ml.  
**Tablet:** 10 mg; 25 mg; 50 mg; 100 mg (hydrochloride).

*haloperidol*      **Injection:** 5 mg in 1-ml ampoule.  
**Oral liquid:** 2 mg/ml.  
**Solid oral dosage form:** 0.5 mg; 2 mg; 5 mg.

**24.2 Medicines used in mood disorders****24.2.1 Medicines used in depressive disorders****Complementary List**

*fluoxetine* <sup>[a]</sup>      **Solid oral dosage form:** 20 mg (as hydrochloride).  
<sup>[a]</sup> >8 years.

**24.2.2 Medicines used in bipolar disorders****24.3 Medicines for anxiety disorders****24.4 Medicines used for obsessive compulsive disorders****24.5 Medicines for disorders due to psychoactive substance use**

## 25. MEDICINES ACTING ON THE RESPIRATORY TRACT

### 25.1 Antiasthmatic medicines

<input type="checkbox"/> budesonide	<b>Inhalation (aerosol):</b> 100 micrograms per dose; 200 micrograms per dose.
epinephrine (adrenaline)	<b>Injection:</b> 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule.
<input type="checkbox"/> salbutamol	<b>Injection:</b> 50 micrograms (as sulfate)/ml in 5-ml ampoule. <b>Metered dose inhaler (aerosol):</b> 100 micrograms (as sulfate) per dose. <b>Respirator solution for use in nebulizers:</b> 5 mg (as sulfate)/ml.

## 26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID-BASE DISTURBANCES

### 26.1 Oral

oral rehydration salts	See section 17.5.1.
potassium chloride	<b>Powder for solution.</b>

### 26.2 Parenteral

glucose	<b>Injectable solution:</b> 5% (isotonic); 10% (hypertonic); 50% (hypertonic).
glucose with sodium chloride	<b>Injectable solution:</b> 5% glucose, 0.9% sodium chloride (equivalent to Na <sup>+</sup> 150 mmol/L and Cl <sup>-</sup> 150 mmol/L); 5% glucose, 0.45% sodium chloride (equivalent to Na <sup>+</sup> 75 mmol/L and Cl <sup>-</sup> 75 mmol/L).
potassium chloride	<b>Solution for dilution:</b> 7.5% (equivalent to K <sup>+</sup> 1 mmol/ml and Cl 1 mmol/ml); 15% (equivalent to K <sup>+</sup> 2 mmol/ml and Cl 2 mmol/ml).
sodium chloride	<b>Injectable solution:</b> 0.9% isotonic (equivalent to Na <sup>+</sup> 154 mmol/L, Cl <sup>-</sup> 154 mmol/L).
sodium hydrogen carbonate	<b>Injectable solution:</b> 1.4% isotonic (equivalent to Na <sup>+</sup> 167 mmol/L, HCO <sub>3</sub> <sup>-</sup> 167 mmol/L). <b>Solution:</b> 8.4% in 10-ml ampoule (equivalent to Na <sup>+</sup> 1000 mmol/L, HCO <sub>3</sub> <sup>-</sup> 1000 mmol/L).
<input type="checkbox"/> sodium lactate, compound solution	<b>Injectable solution.</b>

## 26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID-BASE DISTURBANCES *(continued)*

### 26.3 Miscellaneous

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

## 27. VITAMINS AND MINERALS

ascorbic acid                              **Tablet:** 50 mg.

cholecalciferol\*                         **Oral liquid:** 400 IU/ml.  
**Solid oral dosage form:** 400 IU; 1000 IU.  
\* Ergocalciferol can be used as an alternative.

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.

pyridoxine                                 **Tablet:** 25 mg (hydrochloride).

retinol                                        **Capsule:** 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.

## 28. EAR, NOSE AND THROAT MEDICINES

acetic acid                                 **Topical:** 2%, in alcohol.

budesonide                                **Nasal spray:** 100 micrograms per dose.

ciprofloxacin                              **Topical:** 0.3% drops (as hydrochloride).

xylometazoline **[a]**                         **Nasal spray:** 0.05%.

**[a]** Not in children less than 3 months.

## 29. SPECIFIC MEDICINES FOR NEONATAL CARE

### 29.1 Medicines administered to the neonate

caffeine citrate	<b>Injection:</b> 20 mg/ml (equivalent to 10 mg caffeine base/ml). <b>Oral liquid:</b> 20 mg/ml (equivalent to 10 mg caffeine base/ml).
chlorhexidine	<b>Solution or gel:</b> 7.1% (digluconate) delivering 4% chlorhexidine (for umbilical cord care).

#### *Complementary List*

<input type="checkbox"/> <i>ibuprofen</i>	<b>Solution for injection:</b> 5 mg/ml.
<input type="checkbox"/> <i>prostaglandin E</i>	<b>Solution for injection:</b> <b>Prostaglandin E1:</b> 0.5 mg/ml in alcohol. <b>Prostaglandin E2:</b> 1 mg/ml.
<i>surfactant</i>	<b>Suspension for intratracheal instillation:</b> 25 mg/ml or 80 mg/ml.

## 30. MEDICINES FOR DISEASES OF JOINTS

### 30.1 Medicines used to treat gout

### 30.2 Disease-modifying agents used in rheumatoid disorders (DMARDs)

#### *Complementary List*

<i>hydroxychloroquine</i>	<b>Solid oral dosage form:</b> 200 mg (as sulfate).
<i>methotrexate</i>	<b>Tablet:</b> 2.5 mg (as sodium salt).

### 30.3 Juvenile joint diseases

acetylsalicylic acid* (acute or chronic use)	<b>Suppository:</b> 50 mg to 150 mg. <b>Tablet:</b> 100 mg to 500 mg. * For use for rheumatic fever, juvenile arthritis, Kawasaki disease.
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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 18th WHO Model List of Essential Medicines and the 4th WHO Model List of Essential Medicines for Children, sorted by ATC code number.

ATC code	ATC group/medicine or item	Section
<b>A</b>	<b>ALIMENTARY TRACT AND METABOLISM</b>	
<b>A02</b>	<b>Drugs for acid related disorders</b>	
A02B	Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)	
A02BA	<i>H2-receptor antagonists</i>	
A02BA02	ranitidine	17.1
A02BC	<i>Proton pump inhibitors</i>	
A02BC01	omeprazole	17.1
<b>A03</b>	<b>Drugs for functional gastrointestinal disorders</b>	
A03B	Belladonna and derivatives, plain	
A03BA	<i>Belladonna alkaloids, tertiary amines</i>	
A03BA01	atropine	1.3; 4.2
A03BB	<i>Belladonna alkaloids, semisynthetic, quaternary ammonium compounds</i>	
A03BB01	hyoscine butylbromide*	2.3
A03F	Propulsives	
A03FA	<i>Propulsives</i>	
A03FA01	metoclopramide	2.3; 17.2
<b>A04</b>	<b>Antiemetics and antinauseants</b>	
A04A	Antiemetics and antinauseants	
A04AA	<i>Serotonin (5HT3) antagonists</i>	
A04AA01	ondansetron	17.2
A04AD	<i>Other antiemetics</i>	
A04AD01	hyoscine hydrobromide*	2.3

ATC code	ATC group/medicine or item	Section
<b>A06</b>	<b>Laxatives</b>	
A06A	Laxatives	
A06AA	<i>Softeners, emollients</i>	
A06AA02	docusate sodium	2.3
A06AB	<i>Contact laxatives</i>	
A06AB06	senna glycosides*	17.4
A06AD	<i>Osmotically acting laxatives</i>	
A06AD11	lactulose	2.3
<b>A07</b>	<b>Antidiarrheals, intestinal antiinflammatory/antiinfective agents</b>	
A07A	Intestinal antiinfectives	
A07AA	<i>Antibiotics</i>	
A07AA06	paromomycin	6.5.2
A07B	Intestinal adsorbents	
A07BA	<i>Charcoal preparations</i>	
A07BA01	medicinal charcoal*	4.1
A07C	Electrolytes with carbohydrates	
A07CA	<i>Oral rehydration salt formulations*</i>	17.5.1; 26.1
A07DA	<i>Antipropulsives</i>	
A07DA03	loperamide	2.3
A07E	Intestinal antiinflammatory agents	
A07EA	<i>Corticosteroids for local use</i>	
A07EA02	hydrocortisone	17.3
A07EC	<i>Aminosalicylic acid and similar agents</i>	
A07EC01	sulfasalazine	17.3; 30.2
<b>A09</b>	<b>Digestives, incl. enzymes</b>	
A09A	Digestives, incl. enzymes	
A09AA	<i>Enzyme preparations</i>	
A09AA02	multienzymes (lipase, protease, etc.)*	17
<b>A10</b>	<b>Drugs used in diabetes</b>	
A10A	Insulins and analogues	
A10AB	<i>Insulins and analogues for injection, fast-acting</i>	
A10AB	insulin injection (soluble)*	18.5
A10AC	<i>Insulins and analogues for injection, intermediate-acting</i>	
A10AC	insulin, intermediate-acting*	18.5



ATC code	ATC group/medicine or item	Section
A10B	Blood glucose lowering drugs, excl. insulins	
A10BA	<i>Biguanides</i>	
A10BA02	metformin	18.5
A10BB	<i>Sulfonamides, urea derivatives</i>	
A10BB01	glibenclamide	18.5
A10BB09	gliclazide	18.5
<b>A11</b>	<b>Vitamins</b>	
A11C	Vitamin A and D, incl. combinations of the two	
A11CA	<i>Vitamin A, plain</i>	
A11CA01	retinol	27
A11CC	<i>Vitamin D and analogues</i>	
A11CC01	ergocalciferol	27
A11CC05	colecalfiferol*	27
A11D	Vitamin B1, plain and in combination with vitamin B6 and B12	
A11DA	<i>Vitamin B1, plain</i>	
A11DA01	thiamine	27
A11G	Ascorbic acid (vitamin C), incl. combinations	
A11GA	<i>Ascorbic acid (vitamin C), plain</i>	
A11GA01	ascorbic acid	27
A11H	Other plain vitamin preparations	
A11HA	<i>Other plain vitamin preparations</i>	
A11HA01	nicotinamide	27
A11HA02	pyridoxine	27
A11HA04	riboflavin	27
<b>A12</b>	<b>Mineral supplements</b>	
A12A	Calcium	
A12AA	<i>Calcium</i>	
A12AA03	calcium gluconate	4.2; 27
A12C	Other mineral supplements	
A12CB	<i>Zinc</i>	
A12CB01	zinc sulfate	17.5.2
A12CD	<i>Fluoride</i>	
A12CD01	sodium fluoride	27
A12CX	<i>Other mineral products*</i>	27

ATC code	ATC group/medicine or item	Section
<b>B</b>	<b>BLOOD AND BLOOD FORMING ORGANS</b>	
<b>B01</b>	<b>Antithrombotic agents</b>	
B01A	Antithrombotic agents	
B01AA	<i>Vitamin K antagonists</i>	
B01AA03	warfarin	10.2
B01AB	<i>Heparin group</i>	
B01AB01	heparin*	10.2
B01AC	<i>Platelet aggregation inhibitors excl. heparin</i>	
B01AC06	acetylsalicylic acid	7.1; 12.5; 30.3
B01AD	<i>Enzymes</i>	
B01AD01	streptokinase	12.5
<b>B02</b>	<b>Antihemorrhagics</b>	
B02A	Antifibrinolytics	
B02AA	<i>Amino acids</i>	
B02AA02	tranexamic acid	10.2
B02B	Vitamin K and other hemostatics	
B02BA	<i>Vitamin K</i>	
B02BA01	phytomenadione	10.2
B02BD	<i>Blood coagulation factors</i>	
B02BD01	coagulation factor IX, II, VII and X in combination*	11.2.2
B02BD02	coagulation factor VIII*	11.2.2
<b>B03</b>	<b>Antianemic preparations</b>	
B03A	Iron preparations*	10.1
B03AD	<i>Iron in combination with folic acid*</i>	10.1
B03B	Vitamin B12 and folic acid	
B03BA	<i>Vitamin B12 (cyanocobalamin and analogues)</i>	
B03BA03	hydroxocobalamin	10.1
B03BB	<i>Folic acid and derivatives</i>	
B03BB01	folic acid	10.1
<b>B05</b>	<b>Blood substitutes and perfusion solutions</b>	
B05A	Blood and related products	
B05A	platelet concentrates	11.1
B05A	whole blood*	11.1

ATC code	ATC group/medicine or item	Section
<i>B05AA</i>	<i>Blood substitutes and plasma protein fractions</i>	
B05AA05	dextran*	11.3
<i>B05AX</i>	<i>Other blood products</i>	
B05AX01	red blood cells*	11.1
B05AX03	fresh frozen plasma*	11.1
B05B	I.V. solutions	
<i>B05BA</i>	<i>Solutions for parenteral nutrition</i>	
B05BA03	carbohydrates*	26.2
B05BA03	glucose	26.2
<i>B05BB</i>	<i>Solutions affecting the electrolyte balance</i>	
B05BB01	electrolytes*	26.2
B05BB02	electrolytes with carbohydrates*	26.2
B05BB02	glucose with sodium chloride	26.2
<i>B05BC</i>	<i>Solutions producing osmotic diuresis</i>	
B05BC01	mannitol	16
B05D	Peritoneal dialytics	
<i>B05DA</i>	<i>Isotonic solutions*</i>	23
B05X	I.V. solution additives	
<i>B05XA</i>	<i>Electrolyte solutions</i>	
B05XA01	potassium chloride	26.1; 26.2
B05XA02	sodium bicarbonate*	26.2
B05XA03	sodium chloride	26.2
B05XA05	magnesium sulfate	5
<b>C</b>	<b>CARDIOVASCULAR SYSTEM</b>	
<b>C01</b>	<b>Cardiac therapy</b>	
C01A	Cardiac glycosides	
<i>C01AA</i>	<i>Digitalis glycosides</i>	
C01AA01	simvastatin	12.6
C01AA05	digoxin	12.2; 12.4
C01B	Antiarrhythmics, class I and III	
<i>C01BB</i>	<i>Antiarrhythmics, class Ib</i>	
C01BB01	lidocaine	12.2
<i>C01BD</i>	<i>Antiarrhythmics, class III</i>	
C01BD01	amiodarone	12.2

ATC code	ATC group/medicine or item	Section
C01C	Cardiac stimulants excl. cardiac glycosides	
<i>C01CA</i>	<i>Adrenergic and dopaminergic agents</i>	
C01CA04	dopamine	12.4
C01CA24	epinephrine (adrenaline)	3; 12.2; 25.1
C01D	Vasodilators used in cardiac diseases	
<i>C01DA</i>	<i>Organic nitrates</i>	
C01DA02	glyceryl trinitrate	12.1
C01DA08	isosorbide dinitrate	12.1
<b>C02</b>	<b>Antihypertensives</b>	
C02A	Antiadrenergic agents, centrally acting	
<i>C02AB</i>	<i>Methyldopa</i>	
C02AB01	methyldopa (levorotatory)*	12.3
C02D	Arteriolar smooth muscle, agents acting on	
<i>C02DB</i>	<i>Hydrazinophthalazine derivatives</i>	
C02DB02	hydrazaline	12.3
<i>C02DD</i>	<i>Nitroferricyanide derivatives</i>	
C02DD01	nitroprusside*	12.3
<b>C03</b>	<b>Diuretics</b>	
C03A	Low-ceiling diuretics, thiazides	
<i>C03AA</i>	<i>Thiazides, plain</i>	
C03AA03	hydrochlorothiazide	12.3; 12.4; 16
C03C	High-ceiling diuretics	
<i>C03CA</i>	<i>Sulfonamides, plain</i>	
C03CA01	furosemide	12.4; 16
C03D	Potassium-sparing agents	
<i>C03DA</i>	<i>Aldosterone antagonists</i>	
C03DA01	spironolactone	16; 12.4
<i>C03DB</i>	<i>Other potassium-sparing agents</i>	
C03DB01	amiloride	16
<b>C07</b>	<b>Beta blocking agents</b>	
C07A	Beta blocking agents	
<i>C07AA</i>	<i>Beta blocking agents, non-selective</i>	
C07AA05	propranolol	7.2

ATC code	ATC group/medicine or item	Section
C07AB	<i>Beta blocking agents, selective</i>	
C07AB07	bisoprolol	12.1; 12.2; 12.3; 12.4
<b>C08</b>	<b>Calcium channel blockers</b>	
C08C	Selective calcium channel blockers with mainly vascular effects	
C08CA	<i>Dihydropyridine derivatives</i>	
C08CA01	amlodipine	12.3
C08CA05	nifedipine	22.2
C08D	Selective calcium channel blockers with direct cardiac effects	
C08DA	<i>Phenylalkylamine derivatives</i>	
C08DA01	verapamil	12.1; 12.2
<b>C09</b>	<b>Agents acting on the renin-angiotensin system</b>	
C09A	ACE inhibitors, plain	
C09AA	ACE inhibitors, plain	
C09AA02	enalapril	12.3; 12.4
<b>D</b>	<b>DERMATOLOGICALS</b>	
<b>D01</b>	<b>Antifungals for dermatological use</b>	
D01A	Antifungals for topical use	
D01AA	<i>Antibiotics</i>	
D01AA01	nystatin	6.3
D01AC	<i>Imidazole and triazole derivatives</i>	
D01AC02	miconazole	13.1
D01AE	<i>Other antifungals for topical use</i>	
D01AE12	salicylic acid	13.4
D01AE13	selenium sulfide	13.1
D01B	Antifungals for systemic use	
D01BA	<i>Antifungals for systemic use</i>	
D01BA01	griseofulvin	6.3
D01BA02	terbinafine	13.1
<b>D02</b>	<b>Emollients and protectives</b>	
D02A	Emollients and protectives	
D02AB	<i>Zinc products*</i>	13.3
D02AB	<i>Calamine lotion</i>	13.3

ATC code	ATC group/medicine or item	Section
D02AE	<i>Carbamide products</i>	
D02AE01	carbamide*	13.5
<b>D05</b>	<b>Antipsoriatics</b>	
D05A	Antipsoriatics for topical use	
<b>D06</b>	<b>Antibiotics and chemotherapeutics for dermatological use</b>	
D06A	Antibiotics for topical use	
D06AX	Other antibiotics for topical use	
D06AX09	mupirocin	13.2
D06B	Chemotherapeutics for topical use	
D06BA	<i>Sulfonamides</i>	
D06BA01	silver sulfadiazine	13.2
D06BB	Antivirals	
D06BB04	podophyllotoxin*	13.5
<b>D07</b>	<b>Corticosteroids, dermatological preparations</b>	
D07A	Corticosteroids, plain	
D07AA	<i>Corticosteroids, weak (group I)</i>	
D07AA02	hydrocortisone	13.3
D07AC	<i>Corticosteroids, potent (group III)</i>	
D07AC01	betamethasone	13.3
<b>D08</b>	<b>Antiseptics and disinfectants</b>	
D08A	Antiseptics and disinfectants	
D08AC	<i>Biguanides and amidines</i>	
D08AC02	chlorhexidine	15.1; 29.1
D08AE	<i>Phenol and derivatives</i>	
D08AE05	chloroxylenol	15.2
D08AG	<i>Iodine products</i>	
D08AG02	povidone-iodine*	15.1
D08AX	<i>Other antiseptics and disinfectants*</i>	15
D08AX06	potassium permanganate	13.2
D08AX08	ethanol	15.1
<b>D10</b>	<b>Anti-acne preparations</b>	
D10A	Anti-acne preparations for topical use	
D10AE	<i>Peroxides</i>	
D10AE01	benzoyl peroxide	13.4

ATC code	ATC group/medicine or item	Section
<b>G</b>	<b>GENITO URINARY SYSTEM AND SEX HORMONES</b>	
<b>G01</b>	<b>Gynecological antiinfectives and antiseptics</b>	
G01A	Antiinfectives and antiseptics, excl. combinations with corticosteroids	
<i>G01AF</i>	<i>Imidazole derivatives</i>	
G01AF02	clotrimazole	6.3
<b>G02</b>	<b>Other gynecologicals</b>	
G02A	Oxytocics	
<i>G02AB</i>	<i>Ergot alkaloids</i>	
G02AB03	ergometrine	22.1
<i>G02AD</i>	<i>Prostaglandins</i>	
G02AD06	misoprostol	22.1
G02B	Contraceptives for topical use	
<i>G02BA</i>	<i>Intrauterine contraceptives</i>	
G02BA02	plastic IUD with copper*	18.3.3
G02BA03	plastic IUD with progesteron*	18.3.5
<i>G02BB</i>	<i>Intravaginal contraceptives*</i>	18.3.4
<b>G03</b>	<b>Sex hormones and modulators of the genital system</b>	
G03A	Hormonal contraceptives for systemic use	
G03AA	Progestogens and estrogens, fixed combinations	
G03AA05	norethisterone and estrogen*	18.3.1
G03AA08	medroxyprogesterone and estrogen*	18.3.2
<i>G03AB</i>	<i>Progestogens and estrogens, sequential preparations</i>	
G03AB03	levonorgestrel and estrogen*	18.3.1
<i>G03AC</i>	<i>Progestogens</i>	
G03AC01	norethisterone*	18.3.2
G03AC03	levonorgestrel	18.3.1
G03AC06	medroxyprogesterone*	18.3.2; 18.7
G03B	Androgens	
<i>G03BA</i>	<i>3-oxoandrosten (4) derivatives</i>	
G03BA03	testosterone	18.2
G03G	Gonadotropins and other ovulation stimulants	
<i>G03GB</i>	<i>Ovulation stimulants, synthetic</i>	
G03GB02	clomifene	18.6

ATC code	ATC group/medicine or item	Section
G03X	Other sex hormones and modulators of the genital system	
G03XB	Antiprogesterons	
G03XB01	mifepristone	22.1
<b>H</b>	<b>SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS</b>	
<b>H01</b>	<b>Pituitary, hypothalamic hormones and analogues</b>	
H01B	Posterior pituitary lobe hormones	
<i>H01BB</i>	<i>Oxytocin and analogues</i>	
H01BB02	oxytocin	22.1
<b>H02</b>	<b>Corticosteroids for systemic use</b>	
H02A	Corticosteroids for systemic use, plain	
<i>H02AA</i>	<i>Mineralocorticoids</i>	
H02AA02	fludrocortisone	18.1
<i>H02AB</i>	<i>Glucocorticoids</i>	
H02AB02	dexamethasone	2.3; 3; 8.3; 17.2; 29.2
H02AB04	methylprednisolone	8.3
H02AB06	prednisolone	3; 8.3
H02AB09	hydrocortisone	3; 8.3
<b>H03</b>	<b>Thyroid therapy</b>	
H03A	Thyroid preparations	
<i>H03AA</i>	<i>Thyroid hormones</i>	
H03AA01	levothyroxine sodium*	18.8
H03B	Antithyroid preparations	
<i>H03BA</i>	<i>Thiouracils</i>	
H03BA02	propylthiouracil	18.8
H03C	Iodine therapy	
<i>H03CA</i>	<i>Iodine therapy*</i>	18.8
<b>H04</b>	<b>Pancreatic hormones</b>	
H04A	Glycogenolytic hormones	
<i>H04AA</i>	<i>Glycogenolytic hormones</i>	
H04AA01	glucagon	18.5



ATC code	ATC group/medicine or item	Section
<b>J</b>	<b>ANTIINFECTIVES FOR SYSTEMIC USE</b>	
<b>J01</b>	<b>Antibacterials for systemic use</b>	
J01A	Tetracyclines	
<i>J01AA</i>	<i>Tetracyclines</i>	
J01AA02	doxycycline	6.2.2; 6.5.3.1; 6.5.3.2
J01B	Amphenicols	
<i>J01BA</i>	<i>Amphenicols</i>	
J01BA01	chloramphenicol	6.2.2
J01C	Beta-lactam antibacterials, penicillins	
<i>J01CA</i>	<i>Penicillins with extended spectrum</i>	
J01CA01	ampicillin	6.2.1
J01CA04	amoxicillin	6.2.1
<i>J01CE</i>	<i>Beta-lactamase sensitive penicillins</i>	
J01CE01	benzylpenicillin	6.2.1
J01CE02	phenoxymethylpenicillin	6.2.1
J01CE08	benzathine benzylpenicillin	6.2.1
J01CE09	procaine benzylpenicillin	6.2.1
<i>J01CF</i>	<i>Beta-lactamase resistant penicillins</i>	
J01CF02	cloxacillin	6.2.1
<i>J01CR</i>	<i>Combinations of penicillins, incl. beta-lactamase inhibitors</i>	
J01CR02	amoxicillin and enzyme inhibitor*	6.2.1
J01D	Other beta-lactam antibacterials	
<i>J01DB</i>	<i>First-generation cephalosporins</i>	
J01DB01	cefalexin	6.2.1
J01DB04	cefazolin	6.2.1
<i>J01DD</i>	<i>Third-generation cephalosporins</i>	
J01DD01	cefotaxime	6.2.1
J01DD02	ceftazidime	6.2.1
J01DD04	ceftriaxone	6.2.1
J01DD08	cefixime	6.2.1
<i>J01DH</i>	<i>Carbapenems</i>	
J01DH5	imipenem and enzyme inhibitor*	6.2.1
J01E	Sulfonamides and trimethoprim	
<i>J01EA</i>	<i>Trimethoprim and derivatives</i>	
J01EA01	trimethoprim	6.2.2

ATC code	ATC group/medicine or item	Section
<i>J01EC</i>	<i>Intermediate-acting sulfonamides</i>	
J01EC02	sulfadiazine	6.5.4
<i>J01EE</i>	<i>Combinations of sulfonamides and trimethoprim, incl. derivatives</i>	
J01EE01	sulfamethoxazole + trimethoprim	6.2.2; 6.5.4
J01F	Macrolides, lincosamides and streptogramins	
<i>J01FA</i>	<i>Macrolides</i>	
J01FA01	erythromycin	6.2.2
J01FA09	clarithromycin	6.2.2
J01FA10	azithromycin	6.2.2; 21.1
<i>J01FF</i>	<i>Lincosamides</i>	
J01FF01	clindamycin	6.2.2
J01G	Aminoglycoside antibacterials	
<i>J01GA</i>	<i>Streptomycins</i>	
J01GA01	streptomycin	6.2.4
<i>J01GB</i>	<i>Other aminoglycosides</i>	
J01GB03	gentamicin	6.2.2
J01GB04	kanamycin	6.2.4
J01GB06	amikacin	6.2.4
J01M	Quinolone antibacterials	
<i>J01MA</i>	<i>Fluoroquinolones</i>	
J01MA01	ofloxacin	6.2.4; 21.1
J01MA12	levofloxacin	6.2.4
J01MA02	ciprofloxacin	6.2.2
J01X	Other antibacterials	
<i>J01XA</i>	<i>Glycopeptide antibacterials</i>	
J01XA01	vancomycin	6.2.2
<i>J01XD</i>	<i>Imidazole derivatives</i>	
J01XD01	metronidazole	6.2.2; 6.5.1
<i>J01XE</i>	<i>Nitrofurantoin derivatives</i>	
J01XE01	nitrofurantoin	6.2.2
<i>J01XX</i>	<i>Other antibacterials</i>	
J01XX04	spectinomycin	6.2.2
<b>J02</b>	<b>Antimycotics for systemic use</b>	
J02A	Antimycotics for systemic use	

ATC code	ATC group/medicine or item	Section
<i>J02AA</i>	<i>Antibiotics</i>	
J02AA01	amphotericin B	6.3; 6.5.2
<i>J02AC</i>	<i>Triazole derivatives</i>	
J02AC01	fluconazole	6.3
<i>J02AX</i>	<i>Other antimycotics for systemic use</i>	
J02AX01	flucytosine	6.3
<b>J04</b>	<b>Antimycobacterials</b>	
J04A	Drugs for treatment of tuberculosis	
<i>J04AA</i>	<i>Aminosalicylic acid and derivatives</i>	
J04AA01	p-aminosalicylic acid*	6.2.4
<i>J04AB</i>	<i>Antibiotics</i>	
J04AB01	cycloserine	6.2.4
J04AB02	rifampicin	6.2.3; 6.2.4
J04AB04	rifabutin	6.2.4
J04AB30	capreomycin	6.2.4
<i>J04AC</i>	<i>Hydrazides</i>	
J04AC01	isoniazid	6.2.4
<i>J04AD</i>	<i>Thiocarbamide derivatives</i>	
J04AD03	ethionamide	6.2.4
J04AD01	protionamide	6.2.4
<i>J04AK</i>	<i>Other drugs for treatment of tuberculosis</i>	
J04AK01	pyrazinamide	6.2.4
J04AK02	ethambutol	6.2.4
<i>J04AM</i>	<i>Combinations of drugs for treatment of tuberculosis*</i>	
J04AM02	rifampicin and isoniazid*	6.2.4
J04AM03	ethambutol and isoniazid*	6.2.4
J04AM05	rifampicin, pyrazinamide and isoniazid*	6.2.4
J04AM06	rifampicin, pyrazinamide, ethambutol and isoniazid*	6.2.4
J04B	Drugs for treatment of lepra	
<i>J04BA</i>	<i>Drugs for treatment of lepra</i>	
J04BA01	clofazimine	6.2.3
J04BA02	dapsone	6.2.3
<b>J05</b>	<b>Antivirals for systemic use</b>	
J05A	Direct acting antivirals	

ATC code	ATC group/medicine or item	Section
<i>J05AB</i>	<i>Nucleosides and nucleotides excl. reverse transcriptase inhibitors</i>	
J05AB01	aciclovir	6.4.1
J05AB04	ribavirin	6.4.3
<i>J05AE</i>	<i>Protease inhibitors</i>	
J05AE01	saquinavir (SQV)	6.4.2.3
J05AE02	indinavir (IDV)	6.4.2.3
J05AE03	ritonavir (r)	6.4.2.3
J05AE08	atazanavir	6.4.2.3
J05AE30	lopinavir + ritonavir (LPV/r)*	6.4.2.3
<i>J05AF</i>	<i>Nucleoside and nucleotide reverse transcriptase inhibitors</i>	
J05AF01	zidovudine (ZDV or AZT)	6.4.2.1
J05AF02	didanosine (ddl)	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 disoproxil fumarate	6.4.2.1
J05AF09	emtricitabine	6.4.2.1
<i>J05AG</i>	<i>Non-nucleoside reverse transcriptase inhibitors</i>	
J05AG01	nevirapine (NVP)	6.4.2.2
J05AG03	efavirenz (EFV or EFZ)	6.4.2.2
<i>J05AH</i>	<i>Neuraminidase inhibitors</i>	
J05AH02	oseltamivir	6.4.3
<i>J05AR</i>	<i>Antivirals for treatment of HIV infections, combinations</i>	
J05AR01	lamivudine + zidovudine (ZDV or AZT)	6.4.2
J05AR03	emtricitabine + tenofovir	6.4.2
J05AR05	lamivudine + nevirapine + zidovudine	6.4.2
J05AR06	efavirenz + emtricitabine + tenofovir	6.4.2
J05AR07	lamivudine + nevirapine + stavudine	6.4.2
<b>J06</b>	<b>Immune sera and immunoglobulins</b>	
J06A	Immune sera	
<i>J06AA</i>	<i>Immune sera</i>	
J06AA01	diphtheria antitoxin	19.2
J06AA03	snake venom antiserum*	19.2
J06B	Immunoglobulins	
<i>J06BA</i>	<i>Immunoglobulins, normal human</i>	
J06BA01	immunoglobulins, normal human, for extravascular admin*	11.2.1
J06BA02	immunoglobulins, normal human, for intravascular admin*	11.2.1

ATC code	ATC group/medicine or item	Section
<i>J06BB</i>	<i>Specific immunoglobulins</i>	
J06BB01	anti-D immunoglobulin (human)	19.2
J06BB02	antitetanus immunoglobulin (human)	19.2
J06BB05	rabies immunoglobulin	19.2
<b>J07</b>	<b>Vaccines</b>	
J07A	Bacterial vaccines	
<i>J07AE</i>	<i>Cholera vaccines</i>	19.3
<i>J07AF</i>	<i>Diphtheria vaccines</i>	
J07AF01	diphtheria toxoid*	19.3
<i>J07AH</i>	<i>Meningococcal vaccines*</i>	19.3
<i>J07AJ</i>	<i>Pertussis vaccines</i>	
J07AJ01	pertussis vaccine	19.3
<i>J07AL</i>	<i>Pneumococcal vaccines</i>	
J07AL01	pneumococcus, purified polysaccharides antigen*	19.3
<i>J07AM</i>	<i>Tetanus vaccines</i>	
J07AM01	tetanus toxoid*	19.3
<i>J07AN</i>	<i>Tuberculosis vaccines</i>	
J07AN01	tuberculosis, live attenuated*	19.3
<i>J07AP</i>	<i>Typhoid vaccines</i>	
J07AP	typhoid vaccine	19.3
J07B	Viral vaccines	
<i>J07BA</i>	<i>Encephalitis vaccines</i>	
J07BA02	encephalitis, Japanese, inactivated, whole virus	19.3
<i>J07BB</i>	<i>Influenza vaccines</i>	
J07BB	influenza vaccine	19.3
<i>J07BC</i>	<i>Hepatitis vaccines</i>	
J07BC01	hepatitis B vaccine	19.3
J07BC02	hepatitis A vaccine	19.3
<i>J07BD</i>	<i>Measles vaccine*</i>	
J07BD01	measles vaccine, live attenuated*	19.3
<i>J07BE</i>	<i>Mumps vaccines</i>	
J07BE01	mumps vaccine, live attenuated*	19.3
<i>J07BF</i>	<i>Poliomyelitis vaccine</i>	19.3
<i>J07BG</i>	<i>Rabies vaccine</i>	19.3

ATC code	ATC group/medicine or item	Section
J07BH	<i>Rota virus diarrhea vaccines*</i>	19.3
J07BJ	<i>Rubella vaccines</i>	19.3
J07BK	<i>Varicella zoster vaccines*</i>	19.3
J07BL	<i>Yellow fever vaccines</i>	19.3
J07C	Bacterial and viral vaccines, combined	
J07CA	<i>Bacterial and viral vaccines, combined*</i>	19.3
<b>L</b>	<b>ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS</b>	
<b>L01</b>	<b>Antineoplastic agents</b>	
L01A	Alkylating agents	
L01AA	<i>Nitrogen mustard analogues</i>	
L01AA01	cyclophosphamide	8.2
L01AA02	chlorambucil	8.2
L01AA06	ifosfamide	8.2
L01AX	<i>Other alkylating agents</i>	
L01AX04	dacarbazine	8.2
L01B	Antimetabolites	
L01BA	<i>Folic acid analogues</i>	
L01BA01	methotrexate	8.2; 30.2
L01BB	<i>Purine analogues</i>	
L01BB02	mercaptopurine	8.2
L01BB03	tioguanine	8.2
L01BC	<i>Pyrimidine analogues</i>	
L01BC01	cytarabine	8.2
L01BC02	flourouracil	8.2; 13.4
L01C	Plant alkaloids and other natural products	
L01CA	<i>Vinca alkaloids and analogues</i>	
L01CA01	vinblastine	8.2
L01CA02	vincristine	8.2
L01CB	<i>Podophyllotoxin derivatives</i>	
L01CB01	etoposide	8.2
L01CD	<i>Taxanes</i>	
L01CD01	paclitaxel	8.2
L01CD02	docetaxel	8.2

ATC code	ATC group/medicine or item	Section
<b>L01D</b>	<b>Cytotoxic antibiotics and related substances</b>	
<i>L01DA</i>	<i>Actinomycines</i>	
L01DA01	dactinomycin	8.2
<i>L01DB</i>	<i>Anthracyclines and related substances</i>	
L01DB01	doxorubicin	8.2
L01DB02	daunorubicin	8.2
<i>L01DC</i>	<i>Other cytotoxic antibiotics</i>	
L01DC01	bleomycin	8.2
<b>L01X</b>	<b>Other antineoplastic agents</b>	
<i>L01XA</i>	<i>Platinum compounds</i>	
L01XA02	carboplatin	8.2
<i>L01XB</i>	<i>Methylhydrazines</i>	
L01XB01	procarbazine	8.2
<b>L01X</b>	<b>Other antineoplastic agents</b>	
<i>L01XC</i>	<i>Monoclonal antibodies</i>	
L01XC07	bevacizumab	21.6
<i>L01XX</i>	<i>Other antineoplastic agents</i>	
L01XX02	asparaginase	8.2
L01XX05	hydroxycarbamide	8.2; 10.3
L01XX09	mittefosine	6.5.2
<b>L02</b>	<b>Endocrine therapy</b>	
<b>L02B</b>	<b>Hormone antagonists and related agents</b>	
<i>L02BA</i>	<i>Anti-estrogens</i>	
L02BA01	tamoxifen	8.3
<b>L03</b>	<b>Immunostimulants</b>	
<b>L03A</b>	<b>Immunostimulants</b>	
<i>L03AB</i>	<i>Interferons</i>	
L03AB10	peginterferon alfa-2b*	6.4.3
L03AB11	peginterferon alfa-2a*	6.4.3
<b>L04</b>	<b>Immunosuppressants</b>	
<b>L04A</b>	<b>Immunosuppressants</b>	
<i>L04AD</i>	<i>Calcineurin inhibitors</i>	
L04AD01	ciclosporin	8.1

ATC code	ATC group/medicine or item	Section
L04AX	<i>Other immunosuppressants</i>	
L04AX01	azathioprine	8.1; 30.2
<b>M</b>	<b>MUSCULO-SKELETAL SYSTEM</b>	
<b>M01</b>	<b>Antiinflammatory and antirheumatic products</b>	
M01A	Antiinflammatory and antirheumatic products, non-steroids	
M01AE	<i>Propionic acid derivatives</i>	
M01AE01	ibuprofen	2.1; 29
M01C	Specific antirheumatic agents	
M01CC	<i>Penicillamine and similar agents</i>	
M01CC01	penicillamine	4.2; 30.2
<b>M03</b>	<b>Muscle relaxants</b>	
M03A	Muscle relaxants, peripherally acting agents	
M03AA	<i>Curare alkaloids</i>	
M03AA01	alcuronium	20
M03AB	<i>Choline derivatives</i>	
M03AB01	suxamethonium	20
M03AC	<i>Other quaternary ammonium compounds</i>	
M03AC03	vecuronium	20
M03AC04	atracurium	20
<b>M04</b>	<b>Antigout preparations</b>	
M04A	Antigout preparations	
M04AA	<i>Preparations inhibiting uric acid production</i>	
M04AA01	allopurinol	8.2; 30.1
<b>N</b>	<b>NERVOUS SYSTEM</b>	
<b>N01</b>	<b>Anesthetics</b>	
N01A	Anesthetics, general	
N01AB	<i>Halogenated hydrocarbons</i>	
N01AB01	halothane	1.1.1
N01AB06	isoflurane	1.1.1
N01AX	<i>Other general anesthetics</i>	
N01AX03	ketamine	1.1.2
N01AX10	propofol	1.1.2
N01AX13	nitrous oxide	1.1.1



ATC code	ATC group/medicine or item	Section
N01B	Anesthetics, local	
<i>N01BB</i>	<i>Amides</i>	
N01BB01	bupivacaine	1.2
N01BB02	lidocaine	1.2
N01BB52	lidocaine, combinations*	1.2
<b>N02</b>	<b>Analgesics</b>	
N02A	Opioids	
<i>N02AA</i>	<i>Natural opium alkaloids</i>	
N02AA01	morphine	1.3; 2.2
N02AA03	hydromorphone	2.2
N02AA05	oxycodone	2.2
N02B	Other analgesics and antipyretics	
<i>N02BA</i>	<i>Salicylic acid and derivatives</i>	
N02BA01	acetylsalicylic acid	2.1; 7.1
<i>N02BE</i>	<i>Anilides</i>	
N02BE01	paracetamol	2.1; 7.1
<b>N03</b>	<b>Antiepileptics</b>	
N03A	Antiepileptics	
<i>N03AA</i>	<i>Barbiturates and derivatives</i>	
N03AA02	phenobarbital	5
<i>N03AB</i>	<i>Hydantoin derivatives</i>	
N03AB02	phenytoin	5
<i>N03AD</i>	<i>Succinimide derivatives</i>	
N03AD01	ethosuximide	5
<i>N03AF</i>	<i>Carboxamide derivatives</i>	
N03AF01	carbamazepine	5; 24.2.2
<i>N03AG</i>	<i>Fatty acid derivatives</i>	
N03AG01	valproic acid	5; 24.2.2
<b>N04</b>	<b>Anti-parkinson drugs</b>	
N04A	Anticholinergic agents	
<i>N04AA</i>	<i>Tertiary amines</i>	
N04AA02	biperiden	9
N04B	Dopaminergic agents	
<i>N04BA</i>	<i>Dopa and dopa derivatives</i>	
N04BA02	levodopa and decarboxylase inhibitor*	9

ATC code	ATC group/medicine or item	Section
<b>N05</b>	<b>Psycholeptics</b>	
N05A	Antipsychotics	
N05AA	<i>Phenothiazines with aliphatic side-chain</i>	
N05AA01	chlorpromazine	24.1
N05AB	<i>Phenothiazines with piperazine structure</i>	
N05AB02	fluphenazine	24.1
N05AH	<i>Diazepines, oxazepines, thiazepines and oxepines</i>	
N05AH02	clozapine	24.1
N05AD	<i>Butyrophenone derivatives</i>	
N05AD01	haloperidol	2.3; 24.1
N05AN	<i>Lithium</i>	
N05AN01	lithium*	24.2.2
N05AX	<i>Other antipsychotics</i>	
N05AX08	risperidone	24.1
N05B	Anxiolytics	
N05BA	<i>Benzodiazepine derivatives</i>	
N05BA01	diazepam	2.3; 5; 24.3
N05BA06	lorazepam	5
N05C	Hypnotics and sedatives	
N05CD	<i>Benzodiazepine derivatives</i>	
N05CD08	midazolam	1.3
<b>N06</b>	<b>Psychoanaleptics</b>	
N06A	Antidepressants	
N06AA	<i>Non-selective monoamine reuptake inhibitors</i>	
N06AA04	clomipramine	24.4
N06AA09	amitriptyline	2.3; 24.2.1
N06AB	<i>Selective serotonin reuptake inhibitors</i>	
N06AB03	fluoxetine	24.2.1
N06B	Psychostimulants, agents used for ADHD and nootropics	
N06BC	<i>Xanthine derivatives</i>	
N06BC01	caffeine citrate	29
<b>N07</b>	<b>Other nervous system drugs</b>	
N07A	Parasympathomimetics	
N07AA	<i>Anticholinesterases</i>	
N07AA01	neostigmine	20
N07AA02	pyridostigmine	20

ATC code	ATC group/medicine or item	Section
N07B	Drugs used in addictive disorders	
N07BA	<i>Drugs used in nicotine dependence</i>	
N07BA01	nicotine replacement therapy*	24.5
N07BC	<i>Drugs used in opioid dependence</i>	
N07BC02	methadone	24.5
<b>P</b>	<b>ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS</b>	
<b>P01</b>	<b>Antiprotozoals</b>	
P01A	Agents against amoebiasis and other protozoal diseases	
P01AB	Nitroimidazole derivatives	
P01AB01	metronidazole	6.5.1
P01AC	<i>Dichloroacetamide derivatives</i>	
P01AC01	diloxanide	6.5.1
P01B	Antimalarials	
P01BA	<i>Aminoquinolines</i>	
P01BA01	chloroquine	2.4; 6.5.3.1; 6.5.3.2
P01BA02	hydroxychloroquine	30.2
P01BA03	primaquine	6.5.3.1
P01BA06	amodiaquine	6.5.3.1
P01BB	<i>Biguanides</i>	
P01BB01	proguanil	6.5.3.2
P01BC	<i>Methanolquinolines</i>	
P01BC01	quinine	6.5.3.1
P01BC02	mefloquine	6.5.3.1; 6.5.3.2
P01BD	<i>Diaminopyrimidines</i>	
P01BD01	pyrimethamine	6.5.4
P01BD51	pyrimethamine, combinations*	6.5.3.1
P01BE	<i>Artemisinin and derivatives</i>	
P01BE02	artemether	6.5.3.1
P01BE03	artesunate	6.5.3.1
P01BF01	artemether and lumefantrine	6.5.3.1
P01BF02	artesunate and mefloquine	6.5.3.1
P01BF03	artesunate and amodiaquine	6.5.3.1

ATC code	ATC group/medicine or item	Section
P01C	Agents against leishmaniasis and trypanosomiasis	
<i>P01CA</i>	<i>Nitroimidazole derivatives</i>	
P01CA02	benznidazole	6.5.5.2
<i>P01CB</i>	<i>Antimony compounds</i>	
P01CB01	meglumine antimoniate	6.5.2
P01CB02	sodium stibogluconate	6.5.2
<i>P01CC</i>	<i>Nitrofurantoin derivatives</i>	
P01CC01	nifurtimox	6.5.5.1; 6.5.5.2
<i>P01CD</i>	<i>Arsenic compounds</i>	
P01CD01	melarsoprol	6.5.5.1
<i>P01CX</i>	<i>Other agents against leishmaniasis and trypanosomiasis</i>	
P01CX01	pentamidine isethionate*	6.5.4; 6.5.5.1
P01CX02	suramin sodium	6.5.5.1
P01CX03	eflornithine	6.5.5.1
<b>P02</b>	<b>Anthelmintics</b>	
P02B	Antitrematodals	
<i>P02BA</i>	<i>Quinoline derivatives and related substances</i>	
P02BA01	praziquantel	6.1.1; 6.1.3
P02BA02	oxamniquine	6.1.3
<i>P02BX</i>	<i>Other antitrematodal agents</i>	
P02BX04	triclabendazole	6.1.3
P02C	Antinematodal agents	
<i>P02CA</i>	<i>Benzimidazole derivatives</i>	
P02CA01	mebendazole	6.1.1
P02CA03	albendazole	6.1.1; 6.1.2
<i>P02CB</i>	<i>Piperazine and derivatives</i>	
P02CB02	diethylcarbamazine	6.1.2
<i>P02CC</i>	<i>Tetrahydropyrimidine derivatives</i>	
P02CC01	pyrantel	6.1.1
<i>P02CE</i>	<i>Imidazothiazole derivatives</i>	
P02CE01	levamisole	6.1.1
<i>P02CF</i>	<i>Avermectines</i>	
P02CF01	ivermectin	6.1.2

ATC code	ATC group/medicine or item	Section
P02D	Anticestodals	
<i>P02DA</i>	<i>Salicylic acid derivatives</i>	
P02DA01	niclosamide	6.1.1
<b>P03</b>	<b>Ectoparasiticides, incl. scabicides, insecticides and repellents</b>	
P03A	Ectoparasiticides, incl. scabicides	
<i>P03AC</i>	<i>Pyrethrines, incl. synthetic compounds</i>	
P03AC04	permethrin	13.5
<i>P03AX</i>	<i>Other ectoparasiticides, incl. scabicides</i>	
P03AX01	benzyl benzoate	13.6
<b>R</b>	<b>RESPIRATORY SYSTEM</b>	
<b>R01</b>	<b>Nasal preparations</b>	
R01A	Decongestants and other nasal preparations for topical use	
<i>R01AA</i>	<i>Sympathomimetics, plain</i>	
R01AA07	xylometazoline	28
<i>R01AD</i>	<i>Corticosteroids</i>	
R01AD05	budesonide	28
<b>R03</b>	<b>Drugs for obstructive airway diseases</b>	
R03A	Adrenergics, inhalants	
<i>R03AC</i>	<i>Selective beta-2-adrenoreceptor agonists</i>	
R03AC02	salbutamol	25.1
R03B	Other drugs for obstructive airway diseases, inhalants	
<i>R03BA</i>	<i>Glucocorticoids</i>	
R03BA01	beclometasone	25.1
<i>R03BB</i>	<i>Anticholinergics</i>	
R03BB01	ipratropium bromide	25.1
R03C	Adrenergics for systemic use	
<i>R03CA</i>	<i>Alpha- and beta-adrenoreceptor agonists</i>	
R03CA02	ephedrine	1.2
<i>R03CC</i>	<i>Selective beta-2-adrenoreceptor agonists</i>	
R03CC02	salbutamol	25.1
<b>R05</b>	<b>Cough and cold preparations</b>	
R05D	Cough suppressants, excl. combinations with expectorants	
<i>R05DA</i>	<i>Opium alkaloids and derivatives</i>	
R05DA04	codeine	2.2

ATC code	ATC group/medicine or item	Section
<b>R06</b>	<b>Antihistamines for systemic use</b>	
R06A	Antihistamines for systemic use	
<i>R06AE</i>	<i>Piperazine derivatives</i>	
R06AE3	cyclizine	2.3
<i>R06AX</i>	<i>Other antihistamines for systemic use</i>	
R06AX13	loratadine	3
<b>R07</b>	<b>Other respiratory system products</b>	
R07A	Other respiratory system products	
R07AA	<i>Lung surfactants</i>	29
<b>S</b>	<b>SENSORY ORGANS</b>	
<b>S01</b>	<b>Ophthalmologicals</b>	
S01A	Antiinfectives	
<i>S01AA</i>	<i>Antibiotics</i>	
S01AA09	tetracycline	21.1
S01AA11	gentamicin	21.1
<i>S01AD</i>	<i>Antivirals</i>	
S01AD03	aciclovir	21.1
S01B	Antiinflammatory agents	
<i>S01BA</i>	<i>Corticosteroids, plain</i>	
S01BA04	prednisolone	21.2
S01E	Antiglaucoma preparations and miotics	
<i>S01EA</i>	<i>Sympathomimetics in glaucoma therapy</i>	
S01EA01	epinephrine	21.5
<i>S01EB</i>	<i>Parasympathomimetics</i>	
S01EB01	pilocarpine	21.4
<i>S01EC</i>	<i>Carbonic anhydrase inhibitors</i>	
S01EC01	acetazolamide	21.4
<i>S01ED</i>	<i>Beta blocking agents</i>	
S01ED01	timolol	21.4
<i>S01EE</i>	<i>Prostaglandin analogues</i>	
S01EE01	latanoprost	21.4

ATC code	ATC group/medicine or item	Section
S01F	Mydriatics and cycloplegics	
<i>S01FA</i>	<i>Anticholinergics</i>	
S01FA01	atropine	21.5
S01FA06	tropicamide	14.1
S01H	Local anesthetics	
<i>S01HA</i>	<i>Local anesthetics</i>	
S01HA03	tetracaine	21.3
S01J	Diagnostic agents	
<i>S01JA</i>	<i>Colouring agents</i>	
S01JA01	fluorescein	14.1
<b>S02</b>	<b>Otologicals</b>	
S02A	Antiinfectives	
<i>S02AA</i>	<i>Antiinfectives</i>	
S02AA10	acetic acid	28
S02AA15	ciprofloxacin	28
<b>V</b>	<b>VARIOUS</b>	
<b>V03</b>	<b>All other therapeutic products</b>	
V03A	All other therapeutic products	
<i>V03AB</i>	<i>Antidotes</i>	
V03AB03	edetates*	4.2
V03AB06	thiosulfate*	4.2; 13.1
V03AB08	sodium nitrite	4.2
V03AB09	dimercaprol	4.2
V03AB14	protamine*	10.2
V03AB15	naloxone	4.2
V03AB17	methylthioninium chloride (methylene blue)	4.2
V03AB23	acetylcysteine	4.2
V03AB31	potassium ferric hexacyanoferrate (II) · 2H <sub>2</sub> O (Prussian blue)	4.2
V03AB34	fomepizole	4.2
<i>V03AC</i>	<i>Iron chelating agents</i>	
V03AC01	deferoxamine	4.2; 10.3
<i>V03AF</i>	<i>Detoxifying agents for antineoplastic treatment</i>	
V03AF01	mesna	8.2
V03AF03	calcium folinate	8.2

ATC code	ATC group/medicine or item	Section
V03AN	<i>Medical gases</i>	
V03AN01	oxygen	1.1.1
<b>V04</b>	<b>Diagnostic agents</b>	
V04C	Other diagnostic agents	
V04CF	<i>Tuberculosis diagnostics</i>	
V04CF01	tuberculin, purified protein derivative (PPD) - BCG*	19.1
<b>V07</b>	<b>All other non-therapeutic products</b>	
V07A	All other non-therapeutic products	
V07AB	<i>Solvents and diluting agents, incl. irrigating solutions*</i>	26.3
V07AB	<i>Water for Injection</i>	26.3
V07AV	<i>Technical disinfectants*</i>	15.2
<b>V08</b>	<b>Contrast media</b>	
V08A	X-ray contrast media, iodinated	
V08AA	<i>Watersoluble, nephrotropic, high osmolar X-ray contrast media</i>	
V08AA01	diatrizoic acid*	14.2
V08AB	<i>Watersoluble, nephrotropic, low osmolar X-ray contrast media</i>	
V08AB02	iohexol	14.2
V08AC	<i>Watersoluble, hepatotropic X-ray contrast media</i>	
V08AC02	iotroxic acid*	14.2
V08B	X-ray contrast media, non-iodinated	
V08BA	<i>Barium sulfate containing X-ray contrast media</i>	
V08BA01	barium sulfate with suspending agents*	14.2

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



# Annex 4

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

Medicine or item as in EML	ATC code	Section
abacavir (ABC)	J05AF06	6.4.2.1
acetazolamide	S01EC01	21.4
acetic acid	S02AA10	28
acetylcysteine	V03AB23	4.2
acetylsalicylic acid	B01AC06	7.1; 12.5; 30.3
acetylsalicylic acid	N02BA01	2.1; 7.1
aciclovir	J05AB01	6.4.1
aciclovir	S01AD03	21.1
albendazole	P02CA03	6.1.1; 6.1.2
alcuronium	M03AA01	20
allopurinol	M04AA01	8.2; 30.1
amikacin	J01GB06	6.2.4
amiloride	C03DB01	16
amiodarone	C01BD01	12.2
amitriptyline	N06AA09	2.3; 24.2.1
amlodipine	C08CA01	12.3
amodiaquine	P01BA06	6.5.3.1
amoxicillin	J01CA04	6.2.1
amoxicillin and enzyme inhibitor*	J01CR02	6.2.1
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
artemether	P01BE02	6.5.3.1
artemether and lumefantrine	P01BF01	6.5.3.1
artesunate	P01BE03	6.5.3.1
artesunate and amodiaquine	P01BF03	6.5.3.1
artesunate and mefloquine	P01BF02	6.5.3.1
ascorbic acid	A11GA01	27
asparaginase	L01XX02	8.2
atazanavir	J05AE08	6.4.2.3
atracurium	M03AC04	20
atropine	A03BA01	1.3; 4.2

Medicine or item as in EML	ATC code	Section
atropine	S01FA01	21.5
azathioprine	L04AX01	8.1; 30.2
azithromycin	J01FA10	6.2.2; 21.1
bacterial and viral vaccines, combined*	J07CA	19.3
barium sulfate with suspending agents*	V08BA01	14.2
beclometasone	R03BA01	25.1
benzathine benzylpenicillin	J01CE08	6.2.1
benznidazole	P01CA02	6.5.5.2
benzoyl peroxide	D10AE01	13.5
benzyl benzoate	P03AX01	13.6
benzylpenicillin	J01CE01	6.2.1
betamethasone	D07AC01	13.3
bevacizumab	L01XC07	21.6
biperiden	N04AA02	9
bisoprolol	C07AB07	12.1; 12.2; 12.3; 12.4
bleomycin	L01DC01	8.2
budesonide	R01AD05	28
bupivacaine	N01BB01	1.2
caffeine citrate	N06BC01	29
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
carbamide*	D02AE01	13.5
carbohydrates*	B05BA03	26.2
carboplatin	L01XA02	8.2
cefalexin	J01DB01	6.2.1
cefazolin	J01DB04	6.2.1
cefixime	J01DD08	6.2.1
cefotaxime	J01DD01	6.2.1
ceftazidime	J01DD02	6.2.1
ceftriaxone	J01DD04	6.2.1
chlorambucil	L01AA02	8.2
chloramphenicol	J01BA01	6.2.2
chlorhexidine	D08AC02	15.1; 29.1
chloroquine	P01BA01	2.4; 6.5.3.1; 6.5.3.2
chloroxylenol	D08AE05	15.2

Medicine or item as in EML	ATC code	Section
chlorpromazine	N05AA01	24.1
cholera vaccines	J07AE	19.3
ciclosporin	L04AD01	8.1
ciprofloxacin	J01MA02	6.2.2
ciprofloxacin	S02AA15	28
clarithromycin	J01FA09	6.2.2
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
clozapine	N05AH02	24.1
coagulation factor IX, II, VII and X in combination*	B02BD01	11.2.2
coagulation factor VIII*	B02BD02	11.2.2
codeine	R05DA04	2.2
colecalfiferol*	A11CC05	27
Combinations of drugs for treatment of tuberculosis*	J04AM	6.2.4
cyclizine	R06AE3	2.3
cyclophosphamide	L01AA01	8.2
cycloserine	J04AB01	6.2.4
cytarabine	L01BC01	8.2
dacarbazine	L01AX04	8.2
dactinomycin	L01DA01	8.2
dapsone	J04BA02	6.2.3
daunorubicin	L01DB02	8.2
deferoxamine	V03AC01	4.2; 10.3
dexamethasone	H02AB02	2.3; 3; 8.3; 17.2; 29.2
dextran*	B05AA05	11.3
diatrizoic acid*	V08AA01	14.2
diazepam	N05BA01	2.3; 5; 24.3
didanosine (ddl)	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

Medicine or item as in EML	ATC code	Section
diphtheria toxoid*	J07AF01	19.3
docetaxel	L01CD02	8.2
docusate sodium	A06AA02	2.3
dopamine	C01CA04	12.4
doxorubicin	L01DB01	8.2
doxycycline	J01AA02	6.2.2; 6.5.3.1; 6.5.3.2
edetates*	V03AB03	4.2
efavirenz (EFV or EFZ)	J05AG03	6.4.2.2
efavirenz + emtricitabine + tenofovir	J05AR06	6.4.2
eflornithine	P01CX03	6.5.5.1
electrolytes with carbohydrates*	B05BB02	26.2
electrolytes*	B05BB01	26.2
emtricitabine	J05AF09	6.4.2.1
emtricitabine + tenofovir	J05AR03	6.4.2
enalapril	C09AA02	12.3; 12.4
encephalitis, Japanese, inactivated, whole virus	J07BA02	19.3
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
ethambutol and isoniazid*	J04AM03	6.2.4
ethanol	D08AX08	15.1
ethionamide	J04AD03	6.2.4
ethosuximide	N03AD01	5
etoposide	L01CB01	8.2
fluconazole	J02AC01	6.3
flucytosine	J02AX01	6.3
fludrocortisone	H02AA02	18.1
fluorescein	S01JA01	14.1
fluorouracil	L01BC02	8.2; 13.4
fluoxetine	N06AB03	24.2.1
fluphenazine	N05AB02	24.1
folic acid	B03BB01	10.1
fomepizole	V03AB34	4.2

Medicine or item as in EML	ATC code	Section
fresh frozen plasma*	B05AX03	11.1
furosemide	C03CA01	12.4; 16
gentamicin	J01GB03	6.2.2
gentamicin	S01AA11	21.1
glibenclamide	A10BB01	18.5
gliclazide	A10BB09	18.5
glucagon	H04AA01	18.5
glucose*	B05BA03	26.2
glucose with sodium chloride*	B05BB02	26.2
glyceryl trinitrate	C01DA02	12.1
griseofulvin	D01BA01	6.3
haloperidol	N05AD01	2.3; 24.1
halothane	N01AB01	1.1.1
heparin*	B01AB01	10.2
hepatitis A vaccine	J07BC02	19.3
hepatitis B vaccine	J07BC01	19.3
hydrazaline	C02DB02	12.3
hydrochlorothiazide	C03AA03	12.3; 12.4; 16
hydrocortisone	A07EA02	17.3
hydrocortisone	D07AA02	13.3
hydrocortisone	H02AB09	3; 8.3
hydromorphone	N02AA03	2.2
hydroxocobalamin	B03BA03	10.1
hydroxycarbamide	L01XX05	8.2; 10.3
hydroxychloroquine	P01BA02	30.2
hyoscine butylbromide*	A03BB01	2.3
hyoscine hydrobromide*	A04AD01	2.3
ibuprofen	M01AE01	2.1; 29
ifosfamide	L01AA06	8.2
imipenem and enzyme inhibitor*	J01DH5	6.2.1
immunoglobulins, normal human, for extravascular admin*	J06BA01	11.2.1
immunoglobulins, normal human, for intravascular admin*	J06BA02	11.2.1
indinavir (IDV)	J05AE02	6.4.2.3
influenza vaccine	J07BB	19.3
insulin injection (soluble)*	A10AB	18.5

Medicine or item as in EML	ATC code	Section
insulin, intermediate-acting*	A10AC	18.5
Intravaginal contraceptives*	G02BB	18.3.4
Iodine therapy*	H03CA	18.8
iohexol	V08AB02	14.2
iotroxic acid*	V08AC02	14.2
ipratropium bromide	R03BB01	25.1
Iron in combination with folic acid*	B03AD	10.1
Iron preparations*	B03A	10.1
isoflurane	N01AB06	1.1.1
isoniazid	J04AC01	6.2.4
isosorbide dinitrate	C01DA08	12.1
Isotonic solutions*	B05DA	23
ivermectin	P02CF01	6.1.2
kanamycin	J01GB04	6.2.4
ketamine	N01AX03	1.1.2
lactulose	A06AD11	2.3
lamivudine (3TC)	J05AF05	6.4.2.1
lamivudine + nevirapine + stavudine	J05AR07	6.4.2
lamivudine + nevirapine + zidovudine	J05AR05	6.4.2
lamivudine + zidovudine (ZDV or AZT)	J05AR01	6.4.2
latanoprost	S01EE01	21.4
levamisole	P02CE01	6.1.1
levodopa and decarboxylase inhibitor*	N04BA02	9
levofloxacin	J01MA12	6.2.4
levonorgestrel	G03AC03	18.3.1
levonorgestrel and estrogen*	G03AB03	18.3.1
levothyroxine sodium*	H03AA01	18.8
lidocaine	C01BB01	12.2
lidocaine	N01BB02	1.2
lidocaine, combinations*	N01BB52	1.2
lithium*	N05AN01	24.2.2
loperamide	A07DA03	2.3
lopinavir + ritonavir (LPV/r)*	J05AE30	6.4.2.3
loratadine	R06AX13	3
lorazepam	N05BA06	5
Lung surfactants	R07AA	29.1
magnesium sulfate	B05XA05	5
mannitol	B05BC01	16

Medicine or item as in EML	ATC code	Section
measles vaccine, live attenuated*	J07BD01	19.3
mebendazole	P02CA01	6.1.1
medicinal charcoal*	A07BA01	4.1
medroxyprogesterone and estrogen*	G03AA08	18.3.2
medroxyprogesterone*	G03AC06	18.3.2; 18.7
mefloquine	P01BC02	6.5.3.1; 6.5.3.2
meglumine antimoniate	P01CB01	6.5.2
melarsoprol	P01CD01	6.5.5.1
meningococcal vaccines*	J07AH	19.3
mercaptopurine	L01BB02	8.2
mesna	V03AF01	8.2
metformin	A10BA02	18.5
methadone	N07BC02	24.5
methotrexate	L01BA01	8.2; 30.2
methyl dopa (levorotatory)*	C02AB01	12.3
methylprednisolone	Ho2AB04	8.3
methylthioninium chloride (methylene blue)	V03AB17	4.2
metoclopramide	A03FA01	2.3; 17.2
metronidazole	J01XD01	6.2.2; 6.5.1
metronidazole	P01AB01	6.5.1
miconazole	D01AC02	13.1
midazolam	N05CD08	1.3
mifepristone	G03XB01	22.1
miltefosine	L01XX09	6.5.2
misoprostol	G02AD06	22.1
morphine	N02AA01	1.3; 2.2
multienzymes (lipase, protease, etc.)*	A09AA02	17
mumps vaccine, live attenuated*	J07BE01	19.3
mupirocin	D06AX09	13.2
naloxone	V03AB15	4.2
neostigmine	N07AA01	20
nevirapine (NVP)	J05AG01	6.4.2.2
niclosamide	P02DA01	6.1.1
nicotinamide	A11HA01	27
nicotine replacement therapy*	N07BA01	24.5
nifedipine	C08CA05	22.2
nifurtimox	P01CC01	6.5.5.1; 6.5.5.2
nitrofurantoin	J01XE01	6.2.2
nitroprusside*	C02DD01	12.3

Medicine or item as in EML	ATC code	Section
nitrous oxide	N01AX13	1.1.1
norethisterone and estrogen*	G03AA05	18.3.1
norethisterone*	G03AC01	18.3.2
nystatin	D01AA01	6.3
ofloxacin	J01MA01	6.2.4; 21.1
omeprazole	A02BC01	17.1
ondansetron	A04AA01	17.2
oral rehydration salt formulations*	A07CA	17.5.1; 26.1
oseltamivir	J05AH02	6.4.3
other antiseptics and disinfectants*	D08AX	15.2
other mineral products*	A12CX	27
oxamniquine	P02BA02	6.1.3
oxycodone	N02AA05	2.2
oxygen	V03AN01	1.1.1
oxytocin	H01BB02	22.1
paclitaxel	L01CD01	8.2
p-aminosalicylic acid*	J04AA01	6.2.4
paracetamol	N02BE01	2.1; 7.1
paromomycin	A07AA06	6.5.2
peginterferon alfa-2a*	L03AB11	6.4.3
peginterferon alfa-2b*	L03AB10	6.4.3
penicillamine	M01CC01	4.2; 30.2
pentamidine isethionate*	P01CX01	6.5.4; 6.5.5.1
permethrin	P03AC04	13.6
pertussis vaccine	J07AJ01	19.3
phenobarbital	N03AA02	5
phenoxymethylpenicillin	J01CE02	6.2.1
phenytoin	N03AB02	5
phytomenadione	B02BA01	10.2
pilocarpine	S01EB01	21.4
plastic IUD with copper*	G02BA02	18.3.3
plastic IUD with progesteron*	G02BA03	18.3.5
platelet concentrates	B05A	11.1
pneumococcus, purified	J07AL01	19.3
polysaccharides antigen*		
podophyllotoxin*	D06BB04	13.5
poliomyelitis vaccine	J07BF	19.3
potassium chloride	B05XA01	26.1; 26.2



Medicine or item as in EML	ATC code	Section
potassium ferric hexacyanoferrate (II) -2H <sub>2</sub> O (Prussian blue)	V03AB31	4.2
potassium permanganate	D08AX06	13.2
povidone-iodine*	D08AG02	15.1
praziquantel	P02BA01	6.1.1; 6.1.3
prednisolone	H02AB06	3; 8.3
prednisolone	S01BA04	21.2
primaquine	P01BA03	6.5.3.1
procaine benzylpenicillin	J01CE09	6.2.1
procarbazine	L01XB01	8.2
proguanil	P01BB01	6.5.3.2
propofol	N01AX10	1.1.2
propranolol	C07AA05	7.2
propylthiouracil	H03BA02	18.8
protamine*	V03AB14	10.2
protionamide	J04AD01	6.2.4
pyrantel	P02CC01	6.1.1
pyrazinamide	J04AK01	6.2.4
pyridostigmine	N07AA02	20
pyridoxine	A11HA02	27
pyrimethamine	P01BD01	6.5.4
pyrimethamine, combinations*	P01BD51	6.5.3.1
quinine	P01BC01	6.5.3.1
rabies immunoglobulin	J06BB05	19.2
rabies vaccine	J07BG	19.3
ranitidine	A02BA02	17.1
red blood cells*	B05AX01	11.1
retinol	A11CA01	27
ribavirin	J05AB04	6.4.3
riboflavin	A11HA04	27
rifabutin	J04AB04	6.2.4
rifampicin	J04AB02	6.2.3; 6.2.4
rifampicin and isoniazid*	J04AM02	6.2.4
rifampicin, pyrazinamide and isoniazid*	J04AM05	6.2.4
rifampicin, pyrazinamide, ethambutol and isoniazid*	J04AM06	6.2.4
risperidone	N05AX08	24.1
ritonavir (r)	J05AE03	6.4.2.3

Medicine or item as in EML	ATC code	Section
rota virus diarrhea vaccines*	J07BH	19.3
rubella vaccines	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 glycosides*	A06AB06	17.4
silver sulfadiazine	D06BA01	13.2
simvastatin	C01AA01	12.6
snake venom antiserum*	J06AA03	19.2
sodium bicarbonate*	B05XA02	26.2
sodium chloride	B05XA03	26.2
sodium fluoride	A12CD01	27
sodium nitrite	V03AB08	4.2
sodium stibogluconate	P01CB02	6.5.2
Solvents and diluting agents, incl. irrigating solutions*	V07AB	26.3
spectinomycin	J01XX04	6.2.2
spironolactone	C03DA01	16; 12.4
stavudine (d4T)	J05AF04	6.4.2.1
streptokinase	B01AD01	12.5
streptomycin	J01GA01	6.2.4
sulfadiazine	J01EC02	6.5.4
sulfamethoxazole + trimethoprim	J01EE01	6.2.2; 6.5.4
sulfasalazine	A07EC01	17.3; 30.2
suramin sodium	P01CX02	6.5.5.1
suxamethonium	M03AB01	20
tamoxifen	L02BA01	8.3
Technical disinfectants*	V07AV	15.2
tenofovir disoproxil fumarate	J05AF07	6.4.2.1
terbinafine	D01BA02	13.1
testosterone	G03BA03	18.2
tetanus toxoid*	J07AM01	19.3
tetracaine	S01HA03	21.3
tetracycline	S01AA09	21.1
thiamine	A11DA01	27
thiosulfate*	V03AB06	4.2; 13.1

Medicine or item as in EML	ATC code	Section
timolol	S01ED01	21.4
tioguanine	L01BB03	8.2
tranexamic acid	B02AA02	10.2
triclabendazole	P02BX04	6.1.3
trimethoprim	J01EA01	6.2.2
tropicamide	S01FA06	14.1
tuberculin, purified protein derivative (PPD) - BCG*	V04CF01	19.1
tuberculosis, live attenuated*	J07AN01	19.3
typhoid vaccine	J07AP	19.3
valproic acid	N03AG01	5; 24.2.2
vancomycin	J01XA01	6.2.2
varicella zoster vaccines*	J07BK	19.3
vecuronium	M03AC03	20
verapamil	C08DA01	12.1; 12.2
vinblastine	L01CA01	8.2
vincristine	L01CA02	8.2
warfarin	B01AA03	10.2
Water for Injection	V07AB	26.3
whole blood*	B05A	11.1
xylometazoline	R01AA07	28
yellow fever vaccines	J07BL	19.3
zidovudine (ZDV or AZT)	J05AF01	6.4.2.1
Zinc products*	D02AB	13.3
zinc sulfate	A12CB01	17.5.2

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







## SELECTED WHO PUBLICATIONS OF RELATED INTEREST

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### **The selection and use of essential medicines**

Report of the WHO Expert Committee, March 2011

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WHO Technical Report Series, No. 958, 2011, ISBN 9789241209656 (254 pages)

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This report presents the recommendations of the WHO Expert Committee responsible for updating the WHO Model Lists of Essential Medicines. It contains a summary of the Committee's considerations and justifications for additions and changes to the Model Lists, including its recommendations. Annexes to the main report include the revised version of the WHO Model List of Essential Medicines (18th edition) and the WHO Model List of Essential Medicines for Children (4th edition). In addition there is a list of all the items on the Model Lists sorted according to their Anatomical Therapeutic Chemical (ATC) classification codes.

