WHO Technical Report Series
958

THE SELECTION AND USE OF ESSENTIAL MEDICINES

Report of the WHO Expert Committee, 2009
(including the 16th WHO Model List of Essential Medicines
and the 2nd WHO Model List of Essential Medicines for Children)

World Health Organization

Geneva

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17th Expert Committee on the Selection and Use of Essential Medicines

WHO Expert Committee on the Selection and Use of Essential Medicines

Geneva, 23-27 March 2009

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United Nations Population Fund (UNFPA)

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Dr Suzanne Hill, Secretary of the Expert Committee (MAR/EMP), WHO, Geneva, Switzerland

Dr Anna Ridge, Technical Officer (MAR/EMP), WHO, Geneva, Switzerland

Dr Rumesa Akmal, Technical Officer (MAR/EMP), WHO, Geneva, Switzerland

Declaration of interests of Members of the 17th Expert Committee on the Selection and Use of Essential Medicines

Members reported the following:

Professor Noël Cranswick reported being an investigator on clinical trials for GlaxoSmithKline, Wyeth, Pfizer, Eli Lilley and UBC (but not for any products being considered at the meeting or related to them) and also reported being involved in a clinical trial for Biota.

Dr Alexander Nii Oto Dodoo reported receiving a research support grant from WHO to study the pharmacovigilance (PV) of LAPDAP and amodiaquine-artesunate. Grant no. A40471.

Mr Andy Gray reported having accepted travel support from AstraZeneca, Fresenius Kabi and Aspen Pharmacare to attend continuing education events as a guest speaker, and receiving research support grants from various donors of antiretroviral medicines used in AIDS Clinical Trials Group (ACTG) and International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) trials and also from Gilead Sciences. He reported being a member of the Scheduling and Naming Expert Committee of the South African Medicines Control Council and being a director of a government funding agency for biotechnology.

Dr Kalle Hoppu reported giving one-time consultation advice on behalf of the Finnish Investigators Network for Pediatric Medicines to Lundbeck A/S, Denmark, and also a written clinical expert opinion for a regulatory submission to Oy Leiras, Finland Ab.

Dr Marcus M. Reidenberg reported being a member of a data safety and monitoring board for Roche; receiving royalties through the National Institutes of Health (NIH), USA, on the use of gossypol for cancer; being a consultant to and holding stock in Ascenta, a privately-held clinical stage biopharmaceutical company, which does not have have any products on the market at this time; and being a consultant for The Medicines Company.

Professor Anita Zaidi reported receiving research funding from Wyeth in the area of pneumococcal surveillance.

Mrs Jehan Mohammed Ali Al-Fannah, Dr Lisa A. Bero, Professor Abdol Majid Cheraghali, Professor Rohini Fernandopulle, Dr Myriam Henkens, Dr Gregory Kearns, Mr Edgard José Narvàez Delgado and Dr Lenita Wannmacher, reported no conflict of interest.

Temporary Advisers reported the following:

Professor Cleotilde Hidalgo How reported acting as a consultant on a national TB programme task force involved in the revision of a training manual.

Professor Gitanjali Batmanabane, Professor Dai Yao Hua and Professor Elizabeta Zisovska reported no conflict of interest.

Contracts were awarded to the following WHO Collaborating Centres, organizations and individuals for work undertaken in preparation for the Expert Committee Meeting on the Selection of Essential Medicines:

WHO Collaborating Centre for Evidence-Based Research Synthesis and Guideline Development in Reproductive Health, NHS Centre for the Evaluation of Effectiveness of Healthcare, Modena, Italy, — Applications for amiodarone, hydrochlorothiazide and lamotrigine.

WHO Collaborating Centre for Pharmaco-economics and Rational Pharmacotherapy, University of Newcastle, New South Wales, Australia — Application for antivirals, antiemetic medicines, cytotoxics (carboplatin, hydroxycarbamide, ifosfamide, mesna) procaine benzylpenicillin and tranexamic acid.

WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation, University of Verona, Verona, Italy — Application for escitalopram, paroxetine and sertraline.

Children's Mercy Hospitals and Clinics, Kansas City, USA, — Application for antituberculosis medicines.

Dr Sean Beggs, General Paediatrician and Paediatric Clinical Pharmacologist, Royal Hobart Hospital, Senior Lecturer, University of Tasmania — Applications for captopril and carvedilol.

Professor Emilio Perucca, Head, Clinical Trial Center, Institute of Neurology IRCCS C. Mondino Foundation and Professor of Medical Pharmacology, Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy — Application for lorazepam and midazolam.

Dr Patti Whyte, Griffith University, Queensland, Australia — Applications for atazanavir, zidovudine + lamivudine + abacavir and liposomal amphotericin B.

1. Introduction

The 17th meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines was held in Geneva from 23rd to 27th March 2009. The meeting was opened on behalf of the Director-General by Dr Hans V. Hogerzeil, Director of the Department of Essential Medicines and Pharmaceutical Policies (EMP). He stated that WHO's medicine programme and the recommendations of its Expert Committee played an important role in the context of supporting access to primary care and championing the use of evidence-based medicine, which have been identified by the Director-General as priority areas for WHO. He noted that this would be the fifth meeting of the Expert Committee operating under the procedures approved in 2002 and that the early posting of most documents on the web site, together with the rounds of review and comments prior to the meeting ensured transparency of the process. Dr Hogerzeil also briefly explained some aspects of the Committee procedures. He stated that the Committee is not a representative one; all members participate in their own personal capacity and are not allowed to take instructions from any government or any other authority.

2. Open session

This session of the meeting was opened by Dr Hans V. Hogerzeil. He discussed the purpose of the open session and highlighted that it was an opportunity for all stakeholders to participate in the discussions and to comment on issues relating to the WHO Model List of Essential Medicines. He pointed out that the open session provided an opportunity for members of the Expert Committee to receive, at first-hand, additional information and opinions on matters under consideration that would be noted and considered by the Committee when formulating final recommendations in subsequent private sessions.

Discussions and opinions put forward during the open session are reflected in the meeting report. The full texts of the applications for changes, additions or deletions with all the evidence and references, as well as the external reviews and comments received are not included in the report but remain available on the WHO web site at: http://www.who.int/selection_medicines/ committees/expert/17/en/index.html.

As part of the open session, participants were briefed about various activities relating to the Model List. This included an update on activities undertaken in regions to disseminate and implement the WHO Model List, including workshops in the South-East Asian, Western Pacific and European Regions. Points highlighted included the need to update the national processes of selection, especially with regards to Committee membership and potential

conflicts of interest; the importance of developing linkages between treatment guidelines and national lists of essential medicines (EMLs) and procurement, and the potential value of sub-regional harmonization of selection processes.

Participants were given a brief update on activities in relation to World Health Assembly (WHA) resolution 60.20, Better Medicines for Children. Activities highlighted were the pre-International Conference of Drug Regulatory Authorities (ICDRA) meeting (September 2008) on regulatory strategies for improving medicines for children, the work on defining optimal dosage forms of medicines for children that was on the agenda for the Expert Committee, and the need to develop strategies that would be effective in improving the use of medicines in children in many different countries and settings.

A number of organizations made statements that were discussed during the open session.

UNITAID

The UNITAID Secretariat advised the Committee of its work towards a patent pool for medicines. Initially, the focus is to be on priority medicines for HIV, concentrating on those products that are needed but have not yet been developed, such as second-line medicines and paediatric formulations; and on those existing products for which the number of suppliers is insufficient to create economies of scale. Once up and running, the pool could be expanded to serve other disease areas of need. In relation to the proposal from UNITAID and WHO about the identification of essential medicines for HIV, the Committee's advice was requested on what might be priority "missing essential" medicines for consideration for inclusion in a patent pool.

Tobacco Free Initiative

A representative from the Tobacco Free Initiative, WHO, outlined the potential benefits of nicotine replacement therapy (NRT) for aiding smoking cessation, as presented in the application for inclusion of this medicine on the WHO Model List of Essential Medicines. It was highlighted that a third of the world's population smoked and that if current patterns do not change, up to 1 billion people could die from smoking tobacco this century. Nicotine replacement therapy is one of the possible ways to support smoking cessation. The Committee was informed that many people, particularly in low-income countries face substantial barriers to obtaining NRT, which could be removed if NRT was classed as an essential medicine.

International Union Against Cancer

A representative from the International Union Against Cancer (UICC) spoke in support of the application to include NRT on the WHO Model List of Essential Medicines, highlighting that each year, tobacco-related diseases claim nearly 6 million lives and that this figure will increase to 10 million per year within a few decades. It was suggested that a major advancement in combating the harmful effects of tobacco has come from the realization that tobacco addiction is not merely a personal bad habit, but a medical problem that can be addressed through medical interventions. It was stated that the likelihood of successful smoking cessation approximately doubles when NRTs are used. The UICC strongly endorsed the addition of NRTs to the WHO Model List of Essential Medicines.

World Self-Medication Industry

A representative from the World Self-Medication Industry (WSMI) also spoke in support of the inclusion of NRT on the WHO Model List of Essential Medicines. The Committee was informed that WSMI is a federation of over 50 member associations representing manufacturers and distributors of non-prescription medicines on all continents. It was reported that, based on evidence, NRT has been switched from requiring a prescription to being a non-prescription medicine in many countries and has been made available in a variety of forms: chewing gum, patches, inhalers, lozenges and tablets. The WSMI representative stated that inclusion of NRT on the Model List would help to encourage countries which currently do not have NRT as widely available as needed by smokers, to increase its availability through all possible channels and in a variety of forms.

Médecins Sans Frontières

The Committee was informed about the Médecins Sans Frontières (MSF) Campaign for Access to Essential Medicines. MSF discussed the importance of the EML as a tool to help rationalize the use of essential medicines. However, it was pointed out to the Committee that its presentation is currently cumbersome, with the inclusion of many footnotes and a confusing mixture of information on the medicines in terms of dosage forms with treatment guidance. It was recommended that a clear distinction be made between the EML and treatment guidelines or therapeutic protocols, and that a supplementary column should be added to the right-hand side of the list for the inclusion of all footnotes regarding restricted use and protocols.

MSF indicated its support for the inclusion of:

— nifurtimox, for use in combination with eflornithine for the treatment of stage 2 human African trypanosomiasis;

— a dispersible formulation of artemether + lumefantrine because of its easier administration to children;
— misoprostol tablets for the management of the third stage of labour, post-partum haemorrhage and for completing an incomplete abortion as a useful alternative to oxytocin injection.

MSF welcomed the combined UNITAID and WHO initiative for the development of a patent pool to improve the availability of priority essential medicines for HIV.

Drugs for Neglected Diseases initiative

A representative of the Drugs for Neglected Diseases initiative (DNDi) made a statement about the proposal for inclusion of nifurtimox + eflornithine combination therapy to the Model List. The Committee was informed that stage 2 human African trypanosomiasis, caused by *Trypanosoma brucei gambiense*, is a fatal disease which threatens millions of people in sub-Saharan Africa. Given that:

— 70% of patients are still receiving treatment with melarsoprol, which is toxic and increasingly ineffective
— the use of eflornithine as monotherapy presents difficulties, and
— there is a potential for developing resistance to eflornithine when used in monotherapy, the addition of nifurtimox would significantly reduce the number of injections of eflornithine required and decrease the cost of the treatment of human African trypanosomiasis. It was also highlighted that clinical trials in this area are very complicated and that the next possible new treatment for this disease will not be available for at least 6–7 years.

UNICEF

A representative from the United Nations Children's Fund (UNICEF) made a statement to the Committee regarding the importance of the Model List of Essential Medicines and medicines selection in supply chain management. The Committee was told that UNICEF uses the list for guidance and is particularly pleased that in recent years there has been a focus on medicines for children. The Committee was informed that UNICEF plays a "market shaping" role for a few strategic products that are listed on the Model List and requested by programmes. This role includes aggregating needs and influencing industry to improve availability, pricing, quality and innovation of essential products. The representative stated that UNICEF was committed to working with WHO and manufacturers for the development of relevant new products, including medicines for children. The organization welcomed UNITAID's initiative to develop a patent pool for priority medicines.

3. Proposal for revision of listing of pharmaceutical products

The Committee reviewed the proposals by WHO's medicines quality assurance programme, Quality and Safety: Medicines (QSM) regarding the listing of pharmaceutical products in the EMLs. The Committee noted that many inconsistencies have arisen over time in relation to pharmaceutical products currently available around the world and that these inconsistencies often reflect local or regional differences or long-established practices. It agreed that it was necessary to clarify the Committee's policy for specifying dosage forms and strengths on the List.

The Committee agreed on three actions.

First, the Committee agreed that the principle of choice of dosage forms is that, where several forms are possible, the most general form of expression would be used. It accepted the proposal from QSM that the section entitled Explanatory Notes in the Model List should be expanded to provide more information and guidance to users with regard to terminology relating to dosage form and medicine strength. Where there is a clinical advantage to using a specific form, for example, dispersible tablet, this form would be specified. The Explanatory Notes should also include a link to the information about assuring quality of medicines on the WHO EMP/QSM web site.

Second, for future listings the Committee agreed on the following principles.

1. The medicines listed in the left-hand column of the Model List will be named as the *active moieties*, using the International Nonproprietary Name (INN), wherever applicable.
2. Entries in the right-hand column of the Model List will provide information on the dosage forms and on the strengths (for example, the weight per tablet) of products, as found to be available in WHO Member States.

In manufacturing a dosage form, the active pharmaceutical ingredient (API), may be the active moiety *per se* or it may consist of the active moiety together with one or more additional chemical groups or radicals, depending on the nature of the molecule. Commonly APIs are salts, esters or hydrates of the active moiety and are named using an appropriate Modified INN (INNM). In cases where the API is *not* the active moiety, the entry in the right-hand column in the Model List will indicate the form of the API used in the dosage form by specifying the name of the salt, ester etc.

The way in which the strengths of dosage forms are expressed in entries in the right-hand column of the Model List reflects the way that the strengths of products are available (and labelled) on the market in WHO Member

States. Where the strength of products available is expressed in terms of the active moiety, the name of the salt, ester, etc. is specified in parentheses and preceded by the word "as". An amount given in the right-hand column of the Model List is thus to be interpreted as an amount of the active moiety listed in the left-hand column.

Example: *the listing for ampicillin would be*:

Left-hand column: ampicillin	Right-hand column: powder for injection 500 mg and 1 g (as sodium salt)

This is to be interpreted as 500 mg and 1g of ampicillin.

Where the strength of products available is expressed in terms of the API, the full name of the API including the salt, ester, etc. is specified in the right-hand column of the Model List.

Example: *the listing for codeine would be,*

Left-hand column: codeine	Right-hand column: tablet: 30 mg codeine phosphate

This is to be interpreted as 30 mg of codeine phosphate.

For a small number of medicines, in particular certain long-established medicines for which different salts are used as APIs, there are significant differences in the way that products available in WHO Member States are labelled with respect to strength. Where necessary, in these and other instances of potential confusion, a warning note will be included. In such cases further guidance may be found in the WHO Model Formulary.

Third, the Committee requested the Secretariat to review the current entries on the List and revise them according to the above principles. This revised list will be provided at the next meeting.

Finally, the Committee reviewed medicines that are currently listed in a range of strengths (e.g. paracetamol 100 mg to 500 mg) and recommended that they be retained as currently listed to accommodate the wide range of strengths now available.

4. Review of other matters

The Expert Committee discussed how to enhance the use of the WHO Model List of Essential Medicines to improve rational use of medicines. The Committee noted the interventions listed in the WHO medicines strategy 2008–2013 and WHA Resolution 60.16. In enhancing the use of the Model List, WHO should make people aware that the List is part of a globally applicable concept designed to ensure the widest possible access to effective medicines of assured quality. The concept includes the *process* of selection of medicines using standard principles of evidence-based medicine, that is,

a formal assessment of comparative effectiveness, safety and cost. While one product of this process is the WHO Model List of Essential Medicines, the same process can be used for selection of lists of medicines for other purposes, such as national reimbursement schemes.

The Committee suggested the following approaches as ways of enhancing the EML process and 'product':

— WHO should work to increase awareness of the Model List among policy-makers and health-care workers.
— Information about the process of selection and products for inclusion on the Model List should be included in the curriculum of health-care students (e.g. doctors, pharmacists and nurses).
— WHO should adhere to an evidence-based approach to change practice and ensure that the evidence base is available to Member States. For example, WHO could work with the Effective Practice and Organization of Care Group in the Cochrane Collaboration to disseminate information on effective interventions to improve prescribing and use of medicines.
— WHO should increase advocacy to health-care providers through engagement with professional organizations as opinion leaders, noting that there are many experts within the regions who are willing to help locally.
— WHO should explore mechanisms for making the evidence used to make decisions on the selection of medicines for the Model List available to the Member States.
— WHO should enhance the implementation strategies for the WHO Model Formulary.

The Committee noted the work of the WHO–UN Programme on Prequalification of Medicines. The Committee agreed in principle that WHO should prequalify manufacturers of medications included in the Model List to guarantee quality. WHO should explore the possibilities of expanding the scope of the Programme, taking into account priority diseases, availability and manufacturer of APIs, and the need to support the national regulatory authorities and mechanisms for ensuring the quality of APIs and final dosage forms.

The Committee discussed how the Advisory Committee on Safety of Medicines (ACSOM) could enhance or improve on the current activities of the Expert Committee on the Selection and Use of Essential Medicines. A member of ACSOM presented a proposal for improving the presentation of evidence on comparative safety in applications for the Model List. Given the varying backgrounds of applicants, which can be WHO departments, pharmaceutical companies, patient advocacy groups and many others, the Expert Committee noted that it would be difficult to satisfy all the

possible requirements suggested in the proposal. The Expert Committee recommended that there should be collaboration between the two committees to improve the content of applications. The issues presented by the ACSOM will be considered in the process of modifying the "Information for Applicants" form.

On the basis of the experience from several meetings since 2002, the Committee then discussed possible modifications to the currently available "Information for Applicants" form. To enhance the quality of applications and ensure appropriate presentation of all relevant clinical evidence, the Committee suggested the following:

— specifying minimum criteria for acceptance of applications for consideration by the Committee;
— a requirement for a consideration of both paediatric and adult data in all applications;
— specification of API dosage forms and strength in detail;
— specification of more detailed information about the regulatory status of medicines proposed for inclusion;
— clarification of the purpose for listing, i.e. whether an application is for an individual medicine or an individual medicine with a square box; and
— submission of evidence of comparative effectiveness and safety in tabular form, using GRADE tables where appropriate.

5. Review of missing essential medicines for HIV

The Committee reviewed a proposal from the UNITAID Secretariat and WHO regarding the identification of missing essential medicines for HIV. The proposal describes the initiative that the UNITAID Board has endorsed recommending the development of a patent pool as one mechanism for encouraging the development of new products to meet public health needs. Comments on the proposal were received from MSF, including a proposed list of missing essential medicines for HIV (see Appendix 1). Expert reviews were prepared by Mr Andy Gray and Dr Myriam Henkens.

The Committee welcomed the proposal for a patent pool as an example of a new initiative to develop desirable new products. For example, the Committee had previously identified the need for the development of fixed-dose combination (FDC) products for HIV, especially where they improve efficacy and adherence. They acknowledged the need for paediatric dosage forms as well. The Committee had also previously identified the need for additional classes of medicines for HIV and acknowledged research into developing new drugs within existing classes of medicines as well as within new classes. In developing the list of essential medicines to date, the Committee noted that a wide selection of FDC products was not available.

The Committee acknowledged receipt of lists of medicines for possible inclusion in a patent pool (see Appendix 1) and noted that these lists would need periodic revision and updating depending on the progress made in clinical research and drug development. Inclusion in a patent pool or any other list of potentially desirable products does not guarantee that these products will be added to the Model List or included in treatment guidelines. The requirements for inclusion in the Model List are based on evidence for comparative effectiveness, safety and cost of specific products.

In its discussion, the Committee also noted the potential value of applying this approach to other major public health problems. These will have to be considered on a case by case basis, assessing the scope and nature of the public health problem and the apparent utility of this approach (identification of priority missing products for a patent pool) for solving it.

6. Review of the report of the Second Subcommittee and of the provisional Second List of Essential Medicines for Children

6.1 General issues

The Expert Committee considered the report of the meeting of the Expert Subcommittee held in October 2008 (see Part Two) and thanked them for the updated list of Essential Medicines for Children (EMLc). The Expert Committee strongly supported the recommendation from the Subcommittee that in order to meet the critical needs of improving paediatric therapeutics throughout the world, WHO should create approaches to generate the new knowledge necessary for translation of discovery into rational therapeutic practices. The Committee endorsed the recommendations of the Subcommittee regarding clinical research and information gaps related to paediatric therapeutics, ranging from product availability to considerations of medicine selection and therapeutic use. Additional research priorities identified by the Committee were: studies of pharmacokinetics in neonates, for example, oral amoxicillin; effects of malnutrition on pharmacokinetics; medicines for resuscitation in neonates; determining proper dosage; and timing of drug administration in relation to food intake when relevant.

6.2 Review of key recommendations from the Subcommittee for the EMLc

The Committee noted the significant progress in the further development of the EMLc made by the Subcommittee and endorsed the addition of two new sections to the List: medicines for ear, nose and throat

disease and medicines specifically for neonatal care. These medicines are relevant for the paediatric population and will be included on the complete EML.

The Committee recognized the high burden of disease occurring in neonates and young infants and accepted the proposal from the Subcommittee for the addition of an annex to the EMLc listing medicines from the EMLc which are felt to be essential in treating a variety of neonatal conditions.

The Committee considered the recommendation of the Subcommittee that the EMLc remains separate from the "complete" WHO Model List of Essential Medicines for the foreseeable future. The "complete" EML will include the EMLc. Publishing two lists would maintain a critical focus on the needs of children and support advocacy for children's health. The Committee recognized, however, the importance of having a combined list that could facilitate procurement. It recommended that when publishing the complete Model List, WHO should identify those medicines that were included in it *only* for use in children with a new symbol [c].

The Committee discussed current inconsistencies between the two lists and agreed that it was important to harmonize them. This approach is reflected in the recommendations for additions and deletions to the Model List that were made at this meeting. The following inconsistencies were noted and resolved as follows:

— The Subcommittee recommended that the current use of sulfadiazine was only for treatment of toxoplasmosis and should therefore be deleted from Section 6.2.2 and added to Section 6.5.4 in both the complete EML and EMLc. This recommendation was accepted by the Committee.
— The Subcommittee had considered an application for inclusion of fludrocortisone in Section 18 and recommended inclusion on the EMLc; the Committee noted that this would be essential for treatment of congenital adrenal hypoplasia and adrenal failure in adults as well as children, and it was therefore added to the complete EML.
— The Subcommittee had recommended addition of cefalexin to the EMLc as an oral cephalosporin palatable for administration to children, so it was added the EMLc. The Committed did not add it to the EML as palatability is less of a consideration in adults.
— The Subcommittee had recommended the addition of liposomal amphotericin B for treatment of visceral leishmaniasis, and the deletion of pentamidine for this indication as it was no longer used for this purpose in children. The Committee reviewed Section 6.5.2, medicines for leishmaniasis, for concordance between the EML and EMLc and, on the advice of the WHO Department of Control of Neglected Tropical Diseases (NTD), made the same changes to the complete EML.

— The Subcommittee had recommended the addition of a number of medicines for use in palliative care in children (Section 8.4). While noting that many of these medicines may also be used in adults, the Committee decided that further review of the specific medicines and dosage forms was needed to identify those most suitable for inclusion in the same section of the complete List for use in adults. The Committee requested that the Secretariat give this review high priority.
— The Subcommittee had moved caffeine citrate, indicated for use in the treatment of neonatal apnoea, from Section 25.2 to Section 29 (medicines specifically for use in neonates). The Committee agreed that this change should be made in the complete EML as well.

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.

6.3 Review of comments on the second EMLc

The Expert Committee reviewed comments that had been submitted to the Secretariat on the draft report of the Subcommittee published on the WHO web site following the meeting of the Subcommittee.

Chlorhexidine solution

Following the inclusion of chlorhexidine solution in the EMLc by the 2nd Subcommittee of the Expert Committee for the Selection and Use of Essential Medicines, in October 2007, comments were received from the Program for Appropriate Technology in Health (PATH) and the United States Agency for International Development (USAID).

The Committee noted that the comments from both organizations expressed satisfaction with the inclusion of chlorhexidine but sought to inform the Committee about developments in the process of making the recommended 4% solution. The Committee noted that both PATH and USAID forecast the availability of the 4% solution in 2010, and that product specifications have been developed by PATH and are available to manufacturers. USAID pledged their support for this process.

The Committee decided to retain the 20% formulation currently specified on the Model List until the 4% formulation becomes widely available. The Committee confirmed its current position of listing available dosage forms only.

Comments on fluoroquinolones in children

At the second Meeting of the Expert Subcommittee in October 2008, the Subcommittee recommended retaining ciprofloxacin in the Core List of the EMLc after concluding that sufficient evidence was available to support the use of ciprofloxacin as a second-line treatment for specific, severe infections in paediatric patients.

The Committee considered comments received from Dr David Fuller and Mr Hal Fisher of the Fluoroquinolone Toxicity Research Forum in response to this decision. The Fluoroquinolone Toxicity Research Forum is an advocacy group against the use of fluoroquinolones. Both submissions contained general references to cases of permanent harm and to clinical trials to support the case against use of fluoroquinolones in children.

In addition to the information provided, the Committee reviewed the results of a literature review undertaken by the Secretariat. The purpose of the search was to identify new information on the safety of fluoroquinolones in children. Five review studies from 2003 to date, and three clinical trials from the same period had been identified.

The main findings were:

— ciprofloxacin is relatively safer than other fluoroquinolones (*1, 2, 4*).
— fluoroquinolones are associated with arthropathy in children, which is reported to be of moderate intensity, but transien*t (1, 2, 3, 4)*.
— for some indications, i.e. shigellosis, and pseudomonas infections, fluoroquinolones are accepted therapies *(1)*.

The Committee acknowledged the increasing prevalence of resistance to fluoroquinolones and the public health impact of a likely increase of paediatric rhino-pharyngeal carriers of resistant pneumococci if use in this population is not restricted*(1)*.

The Committee considered the risk–benefit balance of continuing to include ciprofloxacin on the EMLc. After giving due consideration to safety concerns and the issue of resistance, it noted that retaining ciprofloxacin on the EMLc would allow its use in treating serious infections for which there is no satisfactory alternative treatment or when evidence supports fluoroquinolones as being the best option. The Committee therefore decided to retain ciprofloxacin in the Core List of the EMLc but a formal review of safety of ciprofloxicin and quinolones in children was requested.

Review of entry of budesonide MDI (paediatrics) Section 25.1: Antiasthmatic medicines

Comments on budesonide as listed in the draft 2nd edition of the EMLc were received from Cécile Mace, Asthma Drug Facility Coordinator,

Quality Assurance Pharmacist, International Union Against Tuberculosis and Lung Disease.

The Committee noted that Miss Mace had correctly pointed out the errors in the description of budesonide metered dose inhlaers with reference to strengths and the salt "dipropionate".

The Committee approved the corrected version as below:

25.1 Antiasthmatic medicines

□ budesonide	Inhalation (aerosol): 100 micrograms per dose 200 micrograms per dose.

The Committee noted the confusion arising from this error as to whether budesonide or beclometasone is the corticosteroid included in the EMLc, and confirmed that budesonide was chosen as it is more widely available.

6.4 Conclusion of review of Subcommittee report

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 Committee also recommended that given the number of reviews still required for sections of the EMLc, an Expert Committee meeting focused on these paediatric medicines should be held as soon as feasible.

7. New applications for paediatric medicines

Section 6. Anti-infective medicines

Section 6.2 Antibacterials

Procaine benzylpenicillin (review) – (EMLc)

This application was commissioned after the October 2007 meeting of the WHO Expert Subcommittee on the Selection and Use of Essential Medicines requested a review of the use of procaine benzylpenicillin in neonates. It was prepared by the WHO Collaborating Centre, Discipline of Clinical Pharmacology, Newcastle, Australia. Expert reviews of the application were prepared by Professor Elizabeta Zisovska and Professor Dai Yao Hua.

The Committee noted that 98% of perinatal mortality occurs in regions of the world with a low income per capita and in the less developed and least developed regions. Twenty-seven per cent of perinatal mortality is due to neonatal sepsis *(5, 6)*. Eight-hundred thousand neonatal deaths occur annually from pneumonia in developing countries *(7)*.

The Committee noted papers cited in the application that showed that in resource-poor settings, families may be unable to gain access to care for sick neonates *(8)*, and that a study of a complex intervention including community-based health care with regular visits by a community-based health worker, early referral and administration of i.m. procaine penicillin and gentamicin to treat infections in the community resulted in reduced mortality *(9)*. While an overall reduction of 27% in neonatal mortality was recorded, it was not possible to calculate the relative importance of procaine penicillin from this result.

The Committee noted that current clinical practice guidelines recommend the use of procaine penicillin in neonates exclusively for the treatment of asymptomatic congenital syphilis *(10, 11, 12)*. One prospective randomized contolled trial (RCT) was cited that provides evidence that procaine penicillin is effective in the treatment of asymptomatic congenital syphilis in neonates, although it achieves lower cerebrospinal fluid (CSF) concentrations than intramuscular (i.m.) benzyl penicillin *(13)*. No data on efficacy of procaine penicillin alone for the management of neonatal sepsis were available. Pharmacokinetic studies cited showed that procaine penicillin takes up to 24 hours to peak in CSF and does not achieve comparable concentrations to i.m. benzyl penicillin *(14, 15, 16)*.

The Committee noted the following concerns about use of procaine penicillin in neonates:

— that adverse effects are well described and include abscesses and neurological damage at the site of injection;
— that the translation of the trials of complex interventions into the community may be hindered by a lack of compliance with safe injection practices; and
— that health-care workers participating in the trials in the community were trained and supervised in proper administration.

The Committee is aware of ongoing trials to further evaluate the role of procaine penicillin and of other antibiotics with potentially more favourable adverse effect profiles in the community-based management of neonates with sepsis. The Committee will review the available data at its next meeting.

The Committee therefore considered whether to retain the current age restriction and note on the use of procaine penicillin. Given the potential mortality benefit in neonates with severe sepsis compared to the adverse

effects, on balance the Committee decided to remove the age restriction, but amended the note to indicate restricted use:

> "Procaine penicillin 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."

Section 6.2.4 Antituberculosis medicines (review, EMLc)

At the first meeting of the Subcommittee, a note was inserted in Section 6.2.4 of the EMLc, requesting a review of the evidence for the doses, and therefore strengths, of the first-line medicines for treatment of tuberculosis (TB) in children, particularly the fixed-dose combination (FDC) products. This request has initiated a programme of work by EMP and the Stop TB Department, WHO, which has included the following activities:

— a comprehensive review of the pharmacokinetic literature for isoniazid, rifampicin and pyrazinamide including studies in children (report by Peter Donald);
— a meeting in July 2008, to review this report and make recommendations on further actions needed (http://www.who.int/selection_medicines/committees/subcommittee/2/TB.pdf);
— consideration of the report of the July meeting at the Subcommittee meeting in October 2008, that led to the recommendation for deletion of the existing low dose FDCs (for children) on the grounds of concerns about inefficacy;
— two reports from simulation studies (agenda papers for this meeting) proposing potential new strengths for FDCs; and
— a review of evidence for safety, especially hepatotoxicity, of isoniazid, rifampicin and pyrazinamide (Peter Donald).

Activities currently being undertaken, but not yet complete for the Committee to review are:

— a systematic review of evidence concerning use of, efficacy, safety and pharmacokinetics of the first-line TB medicines in children less than 6 months of age (due end April 2009);
— a systematic review of evidence of efficacy and safety of the first-line TB medicines in the treatment of extrapulmonary TB in children (due June 2009);
— a systematic review of the evidence for efficacy and safety of intermittent treatment regimens of TB in children (due June 2009);
— updating the WHO TB treatment guidelines for children; this process has commenced and is likely to be completed late 2009.

The pharmacokinetic simulations that have been done suggest two FDCs that would produce levels of systemic exposure predictive of efficacy and safety in children weighing between 5 and 30 kg assuming a single daily dose and not fractionating the tablet in more than half (dosing schedule is in the reports):

— **a 3-drug FDC:** isoniazid 150 mg + pyrazinamide 400 mg + rifampicin 250 mg;
— **a 4-drug FDC:** ethambutol 250 mg + isoniazid 150 mg + pyrazinamide 400 mg + rifampicin 250 mg.

The review of the safety of these drugs in children suggests that these doses would be acceptable in terms of toxicity.

The Committee noted that there are currently no FDCs that deliver the "ideal doses" of first-line medicines for TB treatment in children who weigh between 5 and 30 kg. The Committee also noted a need for a two-drug FDC for use in the continuation phase of treatment and recommended that the following combination (for continuation treatment only) would be reasonable based on the analyses presented:

— isoniazid 150 mg + rifampicin 250 mg.

Products developed as FDC products must meet standards for quality and be in a dosage form appropriate for children. The Committee encouraged the Secretariat to work with relevant stakeholders to promote rapid development of the products and looked forward to their becoming available for assessment for inclusion on the EML. The Committee endorsed the decision of the Subcommittee to delete the low-dose FDCs from the EMLc and recommended that they also be deleted from the complete Model List.

Section 6.3 Antifungal medicines

Liposomal amphotericin B (inclusion in the EMLc)

This application for the inclusion of liposomal amphotericin B in the EMLc was commissioned by the WHO Secretariat following a request from the Subcommittee meeting in October 2008 to assess the evidence for efficacy and safety of liposomal amphotericin B for use in the treatment of fungal infections. The Subcommittee had recommended its inclusion for the treatment of visceral leishmaniasis.

Expert review of the application was prepared by Dr Alexander Dodoo.

The application noted that invasive fungal infections are increasing in prevalence globally, and that these infections are associated with high mortality rates (25–95%) in children. Several guidelines quoted in the application recommend the use of liposomal amphotericin B (LAB) as well

as amphotericin B deoxycholate (ABD). The Centers for Disease Control (CDC), the National Institutes of Health, and the Infectious Diseases Society of America *(17)* guidelines for treatment of children with HIV/AIDS recommend the use of liposomal amphotericin B in patients with compromised renal function.

The Committee noted that some evidence submitted in the application supports the relative efficacy of LAB as compared to ABD. Twenty paediatric observational studies supported the efficacy and safety of LAB in children and neonates. LAB may be less nephrotoxic and is less likely to cause fevers and chills during administration than ABD, but is not significantly different from ABD in terms of hepatotoxicity and reports of electrolyte imbalance.

On balance, the Committee recommended that the listing of amphotericin B in both the EML and the EMLc be modified to specify both the deoxycholate and the liposomal form. It would be up to individual countries to select which to use depending upon availability and cost. The Committee noted that the Formulary should include instructions about the lack of interchangeability of the two dosage forms.

Section 6.5 Antiprotozoal medicines

Section 6.5.3 Antimalarial medicines

Artemether + lumefantrine (inclusion in the EMLc)

An application was prepared by I. Meyer for Novartis Pharma to include the dispersible formulation of artemether + lumefantrine 20 mg +120 mg in the EMLc. This formulation of the FDC non-dispersible tablet is already included in the EML and the EMLc. The application seeks approval for the additional dosage form of "dispersible" tablets.

Expert reviews of the application were prepared by Professor Cleotilde How and Professor Dai Yao Hua.

The Committee noted that artemether + lumefantrine 20 mg + 120 mg is included in the WHO Guidelines for curative treatment of uncomplicated malaria *(18)*. It is already included as the dosage formulation of "tablet" in both the EML and the EMLc.

The Committee acknowledged the therapeutic equivalence of the "dispersible" form supported by a multicentred trial (n = 899) conducted in malaria endemic regions of Africa *(19).* The Committee recommended the addition of the "dispersible" formulation of artemether + lumefantrine 20 mg + 120 mg to the EMLc as a child-friendly dosage form, to be used where available for children in the weight range of 5 kg to 30 kg.

Section 7. Antimigraine medicines

Ibuprofen (inclusion in the EMLc)

This application was prepared for the organization, Lifting The Burden: the Global Campaign to Reduce the Burden of Headache Worldwide, by P. Tfelt-Hansen, Glostrup Hospital, Glostrup, Denmark, and T. Steiner, Chairman, Lifting The Burden: the Global Campaign to Reduce the Burden of Headache Worldwide, Imperial College, London, England. The application seeks the addition of ibuprofen tablets 200 mg to the EMLc as an antimigraine medicine to enable convenient delivery of the dose 7.5–10 mg/kg to children aged 6 years and above.

Expert reviews were prepared by Professor Elizabeta Zisovska and Professor Dai Yao Hua.

The Committee noted that migraine presented an important public health concern for adults as well as children and adolescents *(20)*. It results in significant loss of school days and interferes with education *(21)*.

The Committee noted the studies cited in the application that support the efficacy of ibuprofen in the acute treatment of migraine in children compared with placebo and with paracetamol *(22, 23)*. The Committee noted that ibuprofen 200-mg tablets are already included in the Core List of the EMLc for migraine and recommended no further changes.

Section 12. Cardiovascular medicines

Section 12.4 Medicines used in heart failure

Captopril (inclusion in the EMLc)

An application was prepared by Dr Sean Beggs, General Paediatrician and Paediatric Clinical Pharmacologist, Royal Hobart Hospital, Senior Lecturer, University of Tasmania, in response to the Subcommittee's request for a review of the section on medicines used in the treatment of heart failure in children.

Expert reviews of the application were prepared by Dr Gregory Kearns and Professor Elizabeta Zisovska.

The Committee noted that the application was supported by evidence of efficacy and safety of angiotensin-converting enzyme inhibitors (ACE-I) from various adult studies. The causes and types of heart failure in children are significantly different from those in adults and the evidence of efficacy and safety of use of ACE-I in children comes from a few small observational studies. None of the studies done in children directly compare various ACE-I. The question of use of these medicines in the treatment of hypertension was also discussed, noting that the current application did not address this directly.

The Committee considered whether to list enalapril or captopril as an indicative angiotensin-converting enzyme inhibitor, with a square box. There is slightly more evidence for efficacy and safety for enalapril and it is licensed by at least one stringent regulatory authority for use in children. The Committee noted that the European Medicines Agency (EMEA) may have further information available about this topic in the future and suggested that WHO continue to collaborate with the Agency as data become available.

On balance, noting that a flexible oral solid dosage form would be desirable, the Committee recommended the inclusion of enalapril in the EMLc for the treatment of hypertension in children, with the addition of the square box symbol.

Carvedilol (Inclusion in the EMLc)

This application was prepared by Dr Sean Beggs, General Paediatrician and Paediatric Clinical Pharmacologist, Royal Hobart Hospital, Senior Lecturer, University of Tasmania, following a request by the Subcommittee. Expert reviews of the application were prepared by Dr Kalle Hoppu and Dr Gregory Kearns.

The application presented evidence from adult studies *(24, 25, 26)* to support the efficacy and safety of carvedilol in treating heart failure, and summarized studies published to establish the role of carvedilol in heart failure in children. The Committee noted that beta-blockers have major dose-related side-effects that may limit their use in children with severe heart failure *(27)*.

Noting again that the causes and types of heart failure in children are significantly different from those in adults, the Committee decided that at present there was not enough evidence of comparative effectiveness and safety to justify inclusion of carvedilol in the Complementary List of the EMLc.

Section 17. Gastrointestinal medicines

Section 17.2 Antiemetic medicines (Inclusion of ondansetron in the EMLc)

A review of the use of antiemetics in children, particularly for the treatment of postoperative nausea and vomiting (PONV), was prepared by the Discipline of Clinical Pharmacology, University of Newcastle, Australia, following a request by the 2nd Subcommittee. Expert reviews of the submission were prepared by Dr Marcus Reidenberg and Mrs Jehan Al-Fannah.

The Committee noted that data summarized in the submission showed that, of the antiemetics available, those with the greatest evidence of efficacy in

the prevention of PONV were ondansetron and dexamethasone. The use of promethazine in treatment of PONV was not supported by any published data.

The Committee noted the guidelines from the Society for Ambulatory Anesthesia (SAMBA) *(28)* that recommend ondansetron as first-line treatment for prevention of PONV, with the addition of dexamethasone as required. Metoclopramide and promethazine are not currently recommended.

The Committee recognized that all the medicines for the prevention of PONV have age restrictions on use, with the exception of ondansetron which is licensed for use in children older than 1 month by the US Food and Drug Administration (FDA). Droperidol has a black box warning from the FDA due to its association with adverse cardiovascular effects *(28)*. One review of trials in children showed a relative risk of 1.15 to 1.66 for adverse effects with droperidol; the higher risks are associated with higher doses and longer exposure *(29)*.

The Committee recommended the inclusion of ondansetron with a square box symbol and dexamethasone as an antiemetic on both the EML and EMLc. It recommended the retention of metoclopramide as an antiemetic for children. It recommended that promethazine be deleted from the EML and EMLc due to lack of efficacy in PONV. The Committee also noted that H1 blockers are effective for motion sickness, but did not consider this to be a public health priority.

Section 18. Hormones

Section 18.5 Insulins and other antidiabetic agents

Access to essential diabetes medicines for children in the developing world

The Committee was provided with the report of the meeting on Access to Essential Diabetes Medicines for Children in the Developing World. The Committee noted with concern the activities of the Insulin for Life Prevention Centers in relation to collecting unused medicines for redistribution and recommended that the group adhere to WHO Guidelines for Drug Donations regarding use of expired medicines.

The Committee would welcome an application for inclusion of glucagon on the EML.

8. Review of the comments on the Report of the Informal Expert Meeting on Dosage Forms of Medicines for Children

The original terms of reference for the Expert Subcommittee included determining suitability criteria for dosage forms of medicines for

children, and considering the feasibility of manufacturing appropriate formulations for those priority medicines for which no suitable dosage form exists.

At its first meeting in October 2008, the Subcommittee reported that the work addressing suitability criteria for dosage forms was still incomplete. Subsequently, an informal expert consultation on dosage forms of medicines for children was held (December 2008) and the report from that meeting was provided as an agenda paper for the Expert Committee. The literature review used as a background paper for that meeting is available on request; it is being prepared for submission for publication.

The report of the December meeting includes 10 proposed recommendations. Numerous comments have also been received on the report, and these have been posted on the web. Key general issues identified in those comments are:

— lack of detailed discussion of regulatory issues;
— whether there is sufficient consideration of the feasibility of manufacturing preferred dosage forms and the impact on dispensing; and
— whether there is sufficient consideration of commercial and market issues.

The Committee endorsed the report and decided to include it as Appendix 2 to the Committee report in its current form. The Committee recognized the importance of the comments received on the report in stimulating discussion. The Committee requested that the Secretariat continue to develop the report in consultation with stakeholders with the goal of having a revised report for review by this Committee, the Expert Committee on Pharmaceutical Specifications, and other relevant groups within WHO.

The Committee also considered extemporaneous preparations involving polypharmacy. The Committee noted that in 1985, WHO defined rational use of medicines as requiring that "patients receive medications appropriate to their needs". The custom in some places is to treat sick children with a mixture of several medicines ("puyer"), not necessarily all appropriate to their needs. Commonly, adult solid dosage forms are mixed together, ground to a powder, and the powder divided into assumed paediatric doses and then dispensed for administration to the child. Often, some medicines in the mixture are not indicated for the condition being treated. These medicines add to the risk of adverse events without any possibility of conferring additional benefit. The Committee recommended that as this practice is irrational it should not be used.

9. Applications for the 16th WHO Model List of Essential Medicines

Section 4. Antidotes and other substances used in poisonings

Section 4.2 Specific

Pralidoxime (inclusion)

An application for the inclusion of pralidoxime was prepared by the Department of Clinical Pharmacology, School of Medicine and Public Health, Faculty of Health, University of Newcastle, New South Wales, Australia. The application was commissioned by the Secretariat.

Expert reviews of the application were prepared by Professor Noël Cranswick, Professor Elizabeta Zisovska and Professor Cleotilde How. Comments were received from Ms Joanna Tempowski, Scientist, Chemical Safety, Department of Protection of the Human Environment, WHO.

The Committee noted that the application provided a thorough review of the available evidence regarding the efficacy and safety of pralidoxime given to adults for the treatment of organophosphate poisoning. It was noted by all expert reviewers that available evidence does not support the suggestion that pralidoxime treatment alone represents an effective antidote for acute organophosphate poisoning in adults. This opinion was supported by considering five systematic reviews of multiple studies, both controlled and uncontrolled. The Committee noted several challenges concerning the interpretation of existing data from adult studies, such as inconsistency in dose and method of administration of pralidoxime, time of onset of treatment related to the ingestion of or exposure to the organophosphate and concomitant use of other treatments for organophosphate poisoning (e.g., atropine sulfate, early mechanical ventilation). The Committee also noted that there are data from several small paediatric case-series, not cited in reviews included in the application, where continuous intravenous infusion of pralidoxime at doses higher than those reported from many adult studies appeared to be associated with efficacy and safety *(30)*. The Committee was aware of an additional large study that has not yet been reported *(31)*.

The Committee agreed that the majority of evidence from the studies in adults suggests that the efficacy of pralidoxime, as used in these studies, was not demonstrated. The Committee recognized the need for further research to evaluate the impact of dosing regimens for both children and adults, the effect on different organophosphates, and the potential efficacy and safety of different oximes. The Committee also noted that pralidoxime is comparatively expensive. On this basis, the Committee recommended that pralidoxime should not be added to the WHO Model List of Essential Medicines at this time.

Section 5. Anticonvulsants/antiepileptics

Lamotrigine (inclusion)

An application was submitted by Centro per la Valutazione della Efficacia della Assistenza Sanitaria (CeVEAS), NHS Centre for the Evaluation of Effectiveness of Health Care, WHO Collaborating Centre for Evidence-Based Research Synthesis and Guideline Development in Reproductive Health, Modena, Italy, for the addition of lamotrigine as monotherapy for the treatment of new onset partial epilepsy in patients not tolerating carbamazepine and for the treatment of new onset generalized epilepsy in women who are contemplating pregnancy. Listing was proposed as an individual medicine.

Expert reviews of the application were prepared by Professor Gitanjali Batmanabane and Mr Edgard Narváez Delgado. Comments in relation to the application were received from Dr Benedetto Saraceno, Director, Department of Mental Health and Substance Abuse, WHO.

The Committee noted that the application provided a comprehensive and systematic review of all the available evidence for the efficacy and safety of lamotrigine for the treatment of epilepsy in adults. The Committee noted that evidence for its efficacy and safety in children is very limited.

The evidence supporting the use of lamotrigine in new onset partial epilepsy came from one pragmatic RCT of moderate quality *(32)*, one systematic review of four short-term RCTs of moderate quality *(33)* and a further four short-term RCTs with quality ranging from moderate to very low *(34, 35, 36, 37)*. Overall the results were not conclusively in favour of lamotrigine. Carbamazepine was found to be superior to lamotrigine in terms of efficacy outcomes (freedom from seizures in short-term follow-up and time to first seizure in long-term follow up).

The Committee was concerned that the evidence of effectiveness and safety for the use of lamotrigine in pregnant women is currently limited and of a conflicting nature. They noted that data presented in the application from two recent epidemiological studies suggest that the risk of orofacial cleft may be higher among offspring of women treated with lamotrigine during pregnancy *(38, 39)*.

The Committee did not recommend the inclusion of lamotrigine on the Model List based on the lack of evidence of its superior efficacy and safety and cost-effectiveness with respect to comparators, and the availability of suitable alternative first-line antiepileptics which are already on the Model List. The Committee recommended a review of second-line antiepileptics for a future meeting, including a review of topiramate, lamotrigine and gabapentin as a second-line therapy for children and adults.

Addition of lorazepam and midazolam

An application was submitted by Professor Emilio Perucca, Head, Clinical Trial Centre, Institute of Neurology IRCCS C Mondino Foundation and Professor of Medical Pharmacology, Department of Internal Medicine and Therapeutics, University of Pavia, Italy, for the addition of parenteral lorazepam 2 mg/ml; 4 mg/ml, for the intravenous treatment of prolonged convulsive seizures and status epilepticus in children and adults, and the addition of parenteral midazolam (5 mg/ml) for buccal administration for the treatment of repetitive and prolonged convulsive seizures, including status epilepticus where intravenous access is unavailable, in both children and adults. The proposed listing in each case was as an individual medicine and formulation.

Expert reviews of the application were prepared by Mr Edgard Narváez Delgado and Professor Gitanjali Batmanabane. Comments in support of the application were received from Dr Bernadetto Saraceno, Director, Department of Mental Health and Substance Abuse, WHO.

The Committee noted that the application included a comprehensive summary of all the available evidence for the effectiveness and safety of parenteral lorazepam and parenteral midazolam for buccal administration for the treatment of prolonged convulsive seizures and status epilepticus in children and adults.

Lorazepam (inclusion)

The Committee noted that the evidence presented in the application to support the superior effectiveness and safety of lorazepam compared to a range of other drug treatments for status epilepticus in adults and children came from two Cochrane Reviews *(40, 41)* and five randomized comparative trials of parenteral lorazepam *(42, 43, 44, 45, 46)*. Overall, the evidence showed that lorazepam was at least as effective as diazepam and had fewer adverse effects when used for the management of status epilepticus.

The Committee recommended the inclusion of parenteral lorazepam with a square box to replace diazepam on the Model List based on its comparative effectiveness and safety with respect to other medicines for the management of prolonged convulsive seizures and status epilepticus in adults and children. The rectal formulation of diazepam was maintained because it is a commercially available preparation and offers an option for treatment of severe seizures in patients when intravenous access is not available.

Midazolam (inclusion)

The Committee noted that the evidence presented in the application to support the superior effectiveness and safety of buccal midazolam compared to rectal diazepam came from one Cochrane Review *(1)*, three RCTs *(47, 48,*

49) and one quasi-randomized trial *(50)*. The Committee noted that although the evidence for effectiveness came from studies in both high-income and resource-poor countries, the majority of the evidence for efficacy and safety had been generated from its use in accident and emergency departments and not at community level. The Committee also noted that buccal midazolam is not available in many countries and parenteral midazolam is currently not licensed for buccal use in acute seizure disorders. Parenteral midazolam is only licensed for use for sedation and anaesthesia.

The Committee did not recommend the addition of parenteral midazolam to the Model List at this time due to the lack of a substantial body of evidence to show its effectiveness and safety in community settings for treating seizures, and the availability of a suitable alternative already on the Model List.

Section 6. Anti-infective medicines

Section 6.2 Antibacterials

Section 6.2.4 Antituberculosis medicines

Rifabutin (inclusion)

An application was submitted by Dr Reuben Granich, Medical Officer (HIV/TB), Department of HIV/AIDS, WHO, for the inclusion of rifabutin 150 mg capsule for the treatment of tuberculosis in HIV-infected patients treated with a concomitant ritonavir-boosted protease inhibitor. Listing was requested as an individual medicine as part of the therapeutic group of antituberculosis therapy.

Expert reviews of the application were prepared by Professor Dai Yao Hua and Professor Cleotilde Hidalgo How.

The Committee noted that rifamycins are an essential component of modern short-course regimens for treating TB and antiretroviral therapy (ART), in combination with WHO-recommended DOTS, is an essential component of TB control and significantly improves survival in HIV/TB co-infected patients. Ritonavir-boosted protease inhibitor (PI) based ART is recommended by WHO as the preferred second-line therapy for HIV infected individuals or as an alternative option in those who have adverse reactions or contraindications to non-nucleoside reverse transcriptase inhibitors (NNRTIs) used in standard first-line therapy. Under normal circumstances rifampicin is the recommended rifamycin in modern standard TB therapy; however rifampicin interacts with protease inhibitors leading to sub-therapeutic concentrations of protease inhibitors mediated by CYP3A4. In contrast, rifabutin has little effect on PI serum concentrations allowing the concomitant use of rifabutin and ritonavir-boosted PIs.

The evidence presented in the application to demonstrate the comparative effectiveness and safety of rifabutin versus rifampicin for the treatment of TB was based on a Cochrane Review *(51)* (5 RCTs, 924 patients). The review found that there was no difference in terms of efficacy between rifabutin-containing and rifampicin-containing regimens as assessed by sputum culture conversion at two, three, or six months from the start of treatment However, the Committee noted that HIV-positive people were under-represented in the trials included. The only comparative RCT in HIV-positive patients, which was included in the review, found both rifamycins to be safe and effective, and demonstrated more rapid clearance of acid-fast bacilli in the rifabutin-treated arm *(52)*.

The Committee acknowledged that evidence presented in the application from observational cohort studies, which included HIV-infected patients treated with ART, did not point to an inferior performance of rifabutin. The Committee noted that according to a cost-analysis of PI-based ART with rifampicin-based or rifabutin-based TB regimens, undertaken in March and April 2007, the total combined cost of HIV and TB therapies using rifabutin was cheaper than that of treatment with rifampicin.

The Committee recommended that rifabutin be added to the Core Model List based on the public health need, evidence of equivalent efficacy and safety compared to rifampicin for the treatment of TB, and the fact that it has little effect on PI serum concentrations, allowing the concomitant use of rifabutin and ritonavir-boosted PIs in HIV-infected individuals requiring second-line ART and treatment of tuberculosis.

Section 6.4 Antiviral medicines

Section 6.4.2 Antiretrovirals

Atazanavir (inclusion)

An application was prepared by Dr Patti Whyte, on behalf of the WHO Department of HIV/AIDS, for the inclusion of atazanavir (ATV), 100 mg and 300 mg capsules, for the treatment of HIV-1 infection in adults, on the Model List. Expert reviews were prepared by Dr Lennita Wannmacher and Professor Anita Zaidi.

The Committee noted that the application provided a comprehensive review of all the currently available evidence for the use of atazanavir (unboosted and boosted with ritonavir) in the treatment of HIV-1 infection in adults. A working group convened by WHO in 2007 *(53)* to develop guidance for second-line drugs, ranked atazanavir boosted with ritonavir as one of the highest priorities for the protease inhibitor component of second-line treatment.

The Committee noted that the application provided evidence from a large number of RCTs *(54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70)* to support the comparable efficacy of atazanavir, either alone or in combination with ritonavir or other antiretroviral agents versus appropriate comparators for both the first-line and second-line treatment of HIV-1 in adults. Overall, the results indicated that atazanavir unboosted and boosted is an effective PI with a low pill burden. In second-line treatment, boosted ATV appeared to be more efficacious than unboosted ATV. For all the studies which reported lipid outcomes the ATV-treated groups had significantly lower changes in lipid levels than the comparison groups.

The Committee noted that there was limited direct evidence of the efficacy of ATV in populations in resource-poor countries. However, evidence from a meta-analysis of antiretroviral treatment programmes in resource-poor settings *(71)* included in the application demonstrated efficacy rates similar to those reported for developed countries for first-line treatment regimens. The Committee acknowledged that although the meta-analysis did not specifically assess second-line treatment it was still probably reasonable to conclude that the efficacy of ATV is likely to be similar across developed and resource-poor countries.

The Committee noted that ATV use is associated with a number of adverse effects, in particular hyperbilirubinaemia of uncertain clinical significance. Overall, the evidence presented in the application indicated that ATV is well-tolerated, with an occurrence of adverse reactions similar or with a lower frequency than with comparator PIs.

The Committee noted that the advantages of ATV are its simplicity of administration (once-daily dosing) and its less undesirable effect on lipid profile compared to other PIs. Once-daily dosing may improve adherence on a long-term basis which was seen as a significant advantage by the Committee, since there is evidence that incomplete adherence to modern highly active antiretroviral therapy (HAART) over time is strongly associated with increased mortality *(72)*.

The Committee recommended the inclusion of atazanavir on the Model List and EMLc based on the evidence of the comparable virologic efficacy of ATV + RTV with lopinavir/ritonavir (LPV/r) and other PIs, an acceptable safety profile including a less undesirable effect on lipid profile than that of other PIs, and the advantage of once-daily dosing.

Protease inhibitors (review)

At its 15th meeting in March 2007, the Expert Committee recommended a review of Section 6.4.2.3, protease inhibitors, to reflect changes in treatment

guidelines, use and availability of these medicines. The WHO Department of HIV/AIDS prepared the review for the Committee.

Expert reviews were provided by Mr Andy Gray and Professor Anita Zaidi.

The Committee, noting that this was not a standard data-driven application, evaluated it taking account of other WHO materials and accessible evidence. The proposals included:

A. To remove all formulations of nelfinavir (NFV) from the Model List.
B. To add the heat-stable FDC formulations of lopinavir/ritonavir (LPV/r 200 mg + 50 mg and 100 mg + 25 mg tablets) to the Model List, while retaining the existing listing of formulations that require refrigeration (133.33 mg + 33.33 mg capsules and 400 mg + 100 mg/5 ml oral liquid) until these have been replaced in most markets.
C. To remove the 200 mg and 333 mg tablet formulations of indinavir (IDV) from the Model List.
D. To remove the 200 mg hard gel capsule formulation of saquinavir (SQV) from the Model List, and to replace this with the 500 mg tablet formulation, but noting that this is to be used particularly for the treatment of tuberculosis co-infected HIV patients where concomitant use of a protease inhibitor with rifampicin is unavoidable.
E. To consider a separate application for the inclusion of atazanavir (ATV).
F. To add the heat-stable formulations of ritonavir (RTV 100 mg and 25 mg tablets) to the Model List, while retaining the existing listing of formulations that require refrigeration (100 mg capsule and 400 mg/5 ml oral liquid) until these have been replaced in most markets.
G. To remove the 40 mg tablet formulation of stavudine (d4T) from the Model List.
H. To add the FDC formulation of zidovudine/lamivudine/abacavir (AZT/3TC/ABC 300 mg + 150 mg + 300 mg) to the Model List.

It was noted that request G deals with the listing of a nucleoside reverse-transcriptase inhibitor (NRTI) and not a protease inhibitor. Items E and H are dealt with separately.

The evidence for the suggested removal of the 40 mg adult dose of d4T was provided in an addendum to the 2006 *WHO Guidelines on antiretroviral therapy for HIV infection in adults and adolescents (73)*. Data from three sources were reviewed *(74, 75, 76)*. The evidence and recommendation were summarized as follows:

> "A systematic review of nine randomized trials and six observational cohort studies strongly suggests that stavudine-containing regimens maintain

clinical and virologic efficacy when stavudine is dosed at 30 mg twice daily, and that this reduced dose is associated with lower rates of toxicity, especially peripheral neuropathy, compared to the 40 mg twice daily dose. Complementary studies have also demonstrated a significant reduction of mitochondrial DNA depletion in patients on the 30 mg twice daily dose. However, there are limited data available about reducing the incidence of lactic acidosis with this strategy. Based on available evidence, the Guidelines Development Group has concluded that the 30 mg formulation of stavudine, dosed twice daily, should be used for all adult and adolescent patients, irrespective of body weight. This recommendation, which was previously considered an option, is now established as the preferred approach when d4T is used as part of an ARV therapeutic regimen."

The Committee considered the review by Mr Gray and recommended:

1. That all formulations of nelfinavir (NFV) be removed from the Model List on the basis of non-availability and reduced need for this medicine as part of a comprehensive antiretroviral treatment (ART) programme.
2. That the heat-stable FDC formulations of lopinavir/ritonavir (LPV/r 200 mg + 50 mg and 100 mg + 25 mg tablets) be added to the Model List, while retaining the existing listing of formulations that require refrigeration (133.33 mg + 33.33 mg capsules and 400 mg + 100 mg/5 ml oral liquid) until these have been replaced in most markets.
3. That the 200 mg and 333 mg tablet formulations of indinavir (IDV) be removed from the Model List on the basis that these formulations are not needed as part of a comprehensive ART programme.
4. That the 200 mg hard gel capsule formulation of saquinavir (SQV) be retained and the 500 mg tablet formulation be added, as this dosage form is required (though not the most desirable option) for the treatment of tuberculosis co-infected HIV patients where concomitant use of a protease inhibitor with rifampicin is unavoidable.
5. That the heat-stable formulations of ritonavir (RTV 100 mg and 25 mg tablets) be added to the Model List, while retaining the existing listing of formulations that require refrigeration (100 mg capsule and 400 mg/5 ml oral liquid) until these have been replaced in most markets.
6. That the 40 mg tablet formulation of stavudine (d4T) be removed from the Model List, on the basis of its safety profile and to ensure consistency with WHO guidelines.

Fixed-dose combinations

Zidovudine + lamivudine + abacavir (AZT/3TC/ABC) (inclusion)

An application was submitted by Dr Patti Whyte on behalf of the WHO Department of HIV/AIDS for the inclusion of the combination tablet zidovudine/lamivudine/abacavir (AZT/3TC/ABC) for the treatment of HIV

infection. Listing was requested as an FDC of the antiretrovirals group, including three nucleoside reverse transcriptase inhibitors.

Expert reviews of the application were prepared by Dr Lennita Wannmacher and Professor Anita Zaidi.

The Committee noted that the quality application provided a comprehensive overview of all the currently available evidence regarding the safety and efficacy of this FDC therapy for the treatment of HIV infection in adults.

The Committee noted that the evidence presented in the application provided conflicting results regarding the efficacy of AZT/3TC/ABC. A systematic review *(77)*, which assessed triple combination therapy in antiretroviral-naive HIV-infected adults, found that triple NRTI regimens including AZT/3TC/ABC were virologically inferior to NNRTI and ritonavir-boosted PI-based regimens. One double-blind RCT *(78)* demonstrated that AZT/3TC/ABC was virologically inferior to regimens including efavirenz, such that the AZT/3TC/ABC arm of the trial was halted. A retrospective database review *(79)* comparing AZT/3TC/ABC and AZT/3TC/EFV concluded that AZT/3TC combined with EFV was superior to AZT/3TC/ABC. All the other trials presented in the application indicated that AZT/3TC/ABC was non-inferior to the comparator regimen.

The Committee noted that although there is some evidence from RCTs *(80, 81)* to show that the FDC AZT/3TC/ABC causes fewer symptoms of lipodystrophy and presented a more favourable lipid profile than other ART regimens, there are some safety concerns with the use of abacavir.

Abacavir has been associated with serious and sometimes fatal hypersensitivity reactions in patients. Across the available trials, suspected hypersensitivity reactions occurred more frequently in the groups treated with AZT/3TC/ABC than in those treated with combination regimens not including abacavir *(81, 82)*. Evidence from a recent large multi-cohort study *(83)* has also shown an excess incidence of myocardial infarction in patients treated with abacavir.

The Committee acknowledged that the fixed-dose triple combination AZT/3TC/ABC is comparatively more expensive than a double combination AZT/3TC plus abacavir. Median prices per patient per year in low-income countries are US$ 852 versus US$ 450, respectively. Under the same conditions, AZT/3TC/ABC is also more expensive than the current preferred triple combination ATZ/3TC/EVZ (US$ 322) for the initial treatment of HIV infection *(84)*.

The Committee did not recommend the addition of this new FDC to the Model List due to a lack of specific evidence of the superior efficacy of the

AZT/3TC/ABC FDC. Where the combination is needed in individual cases, it can be achieved with the medicines already listed.

Section 6.4.3 Other antivirals

Amantadine and rimantadine, oseltamivir, zanamivir (inclusion)

Applications for the inclusion of four antiviral medicines: amantadine, rimantadine, oseltamivir and zanamivir, were commissioned by the Secretariat after discussion with the WHO Department of Global Influenza Preparedness (GIP). This follows collaboration between EMP and GIP since 2006, on preparing treatment guidelines for pandemic influenza, and developing strategies to enhance access to antiviral medicines in the context of developing plans for pandemic preparedness.

Expert reviews were provided by Professor Rohini Fernandopulle and Dr Miriam Henkens.

The applications summarize the public health issues in relation to pandemic influenza. The WHO guidelines for the treatment of human infection with H5N1 disease were published in 2006 and have been reviewed every year since initial publication. There has been no significant change to the recommendations. Oseltamivir or neuraminidase inhibitors remain the first choice of treatment in the context of non-pandemic H5N1 infection. However, during the past year there have been increasing reports of H1N1 resistance to oseltamivir *(85)*. The case for combination treatment as the primary recommendation is therefore likely to be re-examined.

The Committee noted that all four applications provide comprehensive summaries of evidence, based on the GRADE profiles and updated searches that have been used in the guideline development process. The clinical evidence is based primarily on the systematic reviews published by Jefferson et al., 2006 *(86, 87)*.

The Committee considered that for the adamantanes, there is more evidence to support the use of amantadine than rimantadine in the prophylaxis and treatment of seasonal influenza, but only eight case reports of use of amantadine in patients with confirmed H5N1 infection. The benefits of treatment in patients with seasonal influenza are limited to reduction in symptoms; there are no data on influenza-related mortality. For the neuraminidase inhibitors, the Committee noted that there had been four trials of oseltamivir and seven trials of the use of zanamivir in treatment of seasonal influenza that suggest reduction in duration of symptoms. The results in confirmed human cases of H5N1 treated with oseltamivir were summarized in the application. There had been no published report of use of zanamivir.

There had been one small RCT of combined treatment with inhaled zanamivir and rimantadine, compared with rimantadine alone, in hospitalized patients with serious influenza *(88)*. There were no differences in effects between treatment groups. There has been considerable discussion in the literature about the need to develop combination treatments for influenza, given the rapid development of resistance, but as yet there are no other clinical trials that can be used as the basis for a recommendation.

The Committee noted that the costs of amantadine and rimantadine vary but are generally less expensive than the neuraminidase inhibitors. Overall, the evidence to support the effectiveness of any of the four antivirals for treatment of avian influenza remains of very low quality. The effect of these medicines on seasonal influenza is better established, but may be of less importance. When used for treatment of individual cases of H5N1, the cost is low but in the context of seasonal influenza, they have not been accepted as cost-effective. On balance, the potential advantage of the inclusion of any of them on the Model List would be to perhaps increase availability and decrease price. This would be critical in the context of responding to a pandemic, but the pandemic preparedness plans already include stockpiling of antivirals (often donated). It is not clear that addition of the medicines to the Model List would enhance this access programme.

After consideration of these factors, the Committee recommended not including any of the antivirals on the Model List at the present time. However the Committee endorsed the proposal for an emergency meeting mechanism to consider one or more of the antivirals, including for paediatric use, should a pandemic occur.

Section 6.5 Antiprotozoal medicines

Section 6.5.5 Antitrypanosomal medicines

Nifurtimox + eflornithine (inclusion)

An application was prepared by the Drugs for Neglected Diseases initiative (DNDi), for the inclusion of nifurtimox for use in addition to eflornithine as nifurtimox-eflornithine combination therapy (NECT) for treating stage 2 human African trypanosomiasis (HAT).

An expert review of the application was prepared by Mr Andy Gray and comments in its support were received from several organizations and two WHO departments (The Institute of Tropical Medicine, Belgium; Eastern Africa Network for Trypanosomiasis, United Republic of Tanzania; the Department of Pharmaceutical Medicines, Swiss Tropical Institute, Basle, Switzerland; Médecins Sans Frontières; National HAT Control Programme, Ministry of Health Democratic Republic of Congo; Director, WHO Collaborating Centre for African Trypanosomiasis Treatment

Failure and Drug Resistance; Department of Control of Neglected Tropical Diseases, WHO; UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), WHO).

The Committee noted that second-stage HAT is invariably fatal, and that 60 million people are estimated to be at risk in endemic areas (Harhay et al. submitted for publication). Nifurtimox is already recommended in WHO *(89)* and MSF *(90)* guidelines for use in treating HAT as second-line treatment, given as oral monotherapy for 60 days.

The application was based on two small published studies and one unpublished study *(91, 92, 93)*. The Committee accepted that the new regimen was not inferior to eflornithine monotherapy and was less likely to be interrupted as a result of adverse events. The Committee noted that melarsoprol is unacceptably toxic *(94),* and is associated with a high rate of resistance *(95, 96)*. The comparisons of procurement costs suggest that NECT is half as expensive as eflornithine monotherapy. The Committee noted that specific data concerning children were not available.

The Committee noted that trials on this disease are difficult to conduct, because of issues of toxicity and cost and difficulty of administration of existing treatments as well as challenges in follow-up and outcome assessment (requiring lumbar puncture). Recognizing the severity of the disease and the toxicity of existing treatment, the Committee recommended the inclusion of nifurtimox in Section 6.5.5 (for use in the NECT protocol). Postmarketing surveillance is strongly recommended. A review of melarsoprol in the treatment of *Trypanosoma brucei gambiense* is proposed.

Section 7. Antimigraine medicines

Sumatriptan (inclusion)

In 2007, the Expert Committee rejected an application for the inclusion of sumatriptan on the Model List on the basis that the evidence provided did not demonstrate the superior comparative effectiveness, safety and cost-effectiveness of sumatriptan as compared to the currently available medicines for the treatment of acute migraine on the Model List.

A revised application has been submitted on behalf of Lifting The Burden: the Global Campaign to Reduce the Burden of Headache Worldwide by Peer Tfelt-Hansen, Consultant in Neurology, Chairman, International Headache Society Standing Committee on Clinical Trials, Danish Headache Centre, Department of Neurology, University of Copenhagen, Glostrup Hospital, Glostrup, Denmark, for the inclusion of sumatriptan 50 mg in the Model List as a second-line treatment for acute migraine. Listing is requested as an individual medicine, not as a representative of its class. The application also

proposed that paracetamol for the treatment of migraine should be deleted from the Model List.

Expert reviews of the application were prepared by Mrs Jerhan Al-Fannah and Professor Gitanjali Batmanabane. Additional comments were received from Dr Benedetto Saraceno, Director, Department of Mental Health and Substance Abuse, WHO.

The Committee noted that the application did not systematically review and present all the available evidence to support the comparative safety and effectiveness of sumatriptan for the treatment of acute migraine. High-quality clinical evidence does support the superiority of sumatriptan for the acute management of migraine over placebo *(97)*. Evidence from a further six RCTs *(98, 99, 100, 101, 102, 103)* published since the Cochrane Review for sumatriptan was last updated, was reviewed by the Committee. Results from these trials showed that sumatriptan was at best equivalent to comparators; in two instances it was possibly inferior. The Committee noted that all the studies were undertaken in high-income western countries.

The Committee noted that there is currently insufficient evidence to support the use of sumatriptan as a second-line medicine in patients who do not respond to aspirin. The evidence presented in the application for this indication came from two small open-label treatment studies of eletriptan, rather than sumatriptan (113 and 110 patients with migraine; no comparison group) *(104, 105)*.

Given that the comparative efficacy, safety and cost-effectiveness of sumatriptan versus other triptans and aspirin was not established, the Committee recommended that sumatriptan not be added to the Model List. The Committee suggested a review of more data on effects of triptans in patients who do not respond to first-line therapy.

The Committee decided that the deletion of paracetamol from this section would only be considered if a formal application was submitted for review. The application would need to provide a systematic and comprehensive summary of all the available evidence to support the claims of a lack of efficacy and safety of paracetamol for the treatment of acute migraine.

Section 8. Antineoplastic, immunosuppressives and medicines used in palliative care

Section 8.2 Cytotoxic medicines

Carboplatin (inclusion)

An application has been submitted by the WHO Collaborating Centre, University of Newcastle, Australia, for the inclusion of carboplatin for the

treatment of advanced ovarian cancer. The application was commissioned by the Secretariat on the recommendation of the International Network for Cancer Treatment and Research.

An expert review of the application was prepared by Dr Marcus M. Reidenberg.

The Committee noted that the application included supportive evidence for the effectiveness and safety of carboplatin from systematic reviews *(106, 107, 108)* and RCTs *(109, 110, 111)*.

The Committee noted that the most recent meta-analysis came from a Cochrane Review *(108)*, which showed that carboplatin was no more or less effective than cisplatin in any particular subgroup of women with advanced ovarian cancer.

The Committee noted that the toxicity profiles of carboplatin and cisplatin are different, with carboplatin being better tolerated overall than cisplatin. The major dose-limiting adverse effects associated with carboplatin are thrombocytopaenia and leukopaenia; those associated with cisplatin are nephrotoxicity, ototoxicity, neurotoxicity and emesis.

The Committee noted that the evidence presented in the application indicated that carboplatin was more cost-effective than cisplatin.

Overall, the evidence provided in the application supports the public health need, comparable effectiveness and generally more favourable tolerability of carboplatin than cisplatin. The Committee therefore recommended that carboplatin replace cisplatin on the Complementary Model List (with a square box) for the treatment of advanced ovarian cancer.

Hydroxycarbamide (inclusion)

An application was submitted by the WHO Collaborating Centre, University of Newcastle, Australia, for the inclusion of hydroxycarbamide on the Model List. Listing is requested as an individual medicine. The application was commissioned by the Secretariat on the recommendation of the International Network for Cancer Treatment and Research.

The application focused on the use of hydroxycarbamide in the treatment of adults with chronic myeloproliferative disorders: chronic myelogenous leukaemia, essential thrombocythemia and polycythemia vera, and head and neck cancer.

Expert reviews of the application were prepared by Professor Abdol Majid Cheraghali and Professor Noël Cranswick.

The Committee noted that the application presented evidence from meta-analyses *(112, 113)* and clinical trials *(114, 115, 116, 117, 118, 119,*

120, 121, 122, 123, 124, 125, 126, 127) which included relevant RCTs and observational studies, to support the use of hydroxycarbamide in the treatment of adults with chronic myeloproliferative disorders: chronic myelogenous leukaemia, essential thrombocythemia and polycythemia vera, and head and neck cancer.

The Committee noted that although the evidence for the cost-effectiveness of hydroxycarbamide is generally limited, there is some evidence from economic evaluations using hydroxycarbamide as a comparator which suggests it is the treatment of choice if the cost of the newer comparator is prohibitively expensive or if the newer treatment is not tolerated well by the patient.

The Committee recommended the inclusion of hydroxycarbamide on the Complementary Model List, based on its role in multiagent chemotherapy and radiotherapy regimens for advanced squamous cell head and neck cancer, evidence to support its effectiveness and safety as an alternative to interferon-α in the treatment of chronic myelogenous leukaemia, and evidence to support its role in the treatment of high-risk patients with essential thrombocythemia. The Committee recommended the inclusion of a wide range of dosage strengths because the dosage must be calculated for each patient individually and must be based on body weight.

Ifosfamide (inclusion)

An application was submitted for the inclusion of ifosfamide on the Model List by the WHO Collaborating Centre, University of Newcastle, Australia, on the recommendation of the International Network for Cancer Treatment and Research. The application focused on the use of ifosfamide in the treatment of individuals with soft tissue and bone sarcomas, non-Hodgkin's lymphoma, cervical cancer, ovarian cancer, and testicular germ cell tumours.

Expert review of the application was prepared by Professor Noël Cranswick.

The Committee noted that the application provided a comprehensive review of the available evidence for the use of ifosfamide in multiagent chemotherapy regimens for a range of different cancers. Evidence from meta-analyses, *(128, 129,130)* RCTs *(131, 132, 133)* and observational studies *(134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146)* was cited to support the use of ifosfamide as part of a multi-agent chemotherapy regimen for the treatment of individuals with soft tissue and bone sarcomas, non-Hodgkin's lymphoma, cervical cancer, ovarian cancer, and testicular germ cell tumours. However, the Committee noted that overall the evidence from systematic reviews and RCTs was not sufficiently conclusive to support the use of ifosfamide-combination chemotherapy

regimens in the treatment of solid tumours and that although a large number of observational studies demonstrated reasonable response rates, there was no overall benefit in terms of survival.

The Committee noted that ifosfamide is recommended as an integral component of several regimens by the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Where alternatives are stated for the treatment of certain cancer types, these chemotherapy agents are already included on the Model List.

The Committee recommended the inclusion of ifosfamide on the Complementary Model List given the wide range of cancers for which this medicine can be used.

Mesna (inclusion)

An application was submitted by the WHO Collaborating Centre, University of Newcastle, Australia, for the inclusion of mercaptoethane sulphonate (mesna) for the prevention of oxazaphosphorine-induced haemorrhagic cystitis. Proposed formulations for inclusion were: tablets 400 mg; 600 mg and injection 400 mg/4ml; 1g/10 ml. The application was commissioned by the Secretariat on the recommendation of the International Network for Cancer Treatment and Research.

An expert review of the application was prepared by Professor Noël Cranswick.

The Committee noted that mesna was developed as a specific chemoprotective compound against acrolein-induced bladder toxicity, a dose-limiting side-effect of both cyclophosphamide and ifosfamide.

The Committee noted the good quality of the application, which provided a comprehensive review of the available evidence. The application cited nine RCTs, of which five *(147, 148, 149, 150, 151)* showed that mesna was effective in reducing the incidence of haemorrhagic cystitis in patients receiving ifosfamide and/or cyclophosphamide as part of a multiagent chemotherapy regimen. It was noted by the Committee that all these studies were small and of poor quality. The remaining four trials *(152, 153, 154, 155)* did not show mesna prophylaxis to be effective. The three largest RCTs (with between 100 to 200 patients) showed that mesna was not effective in preventing haemorrhagic cystitis or moderate-severe haematuria in patients receiving a cyclophosphamide-based chemotherapy regimen.

The Committee acknowledged that the evidence for the efficacy of mesna in reducing the incidence of urotoxicity associated with ifosfamide and/or cyclophosphamide chemotherapy was not conclusive. Although the current evidence is equivocal, the current standard of care is that mesna is used as

an adjunctive therapy. Recognizing this, the Committee recommended its inclusion on the Complementary Model List.

Section 10. Medicines affecting the blood

Tranexamic acid (inclusion)

An application for inclusion of tranexamic acid was prepared by the WHO Collaborating Centre, University of Newcastle, Australia, following a proposal from the Cochrane Injuries Group (Dr Ian Roberts, London School of Hygiene and Tropical Medicine).

Expert reviews of the application were prepared by Professor Noël Cranswick and Professor Abdol Majid Cheragli.

The Committee noted that cardiac surgery is associated with high risks of massive blood loss *(156)*. Massive blood loss is strongly associated with in-hospital mortality *(156)*. Transfusions with red blood cells are costly (157) and are associated with several adverse events *(158)*. The blood bank costs are also rising due to the increasing number of safety measures required *(159)*.

The Committee acknowledged that tranexamic acid is effective in reducing perioperative blood loss in cardiac surgery in adults but the potential benefit in terms of reducing transfusion was not described. Tranexamic acid was found not to differ significantly from placebo in its effects on myocardial infarction, stroke, deep vein thrombosis, pulmonary embolus, renal failure and dysfunction, or death *(160, 161)*. The Committee also questioned the public health importance of this indication. Additional evidence identified by the Secretariat showed that tranexamic acid may decrease blood loss in orthopaedic surgery and partial hepatectomies. However, the currently available literature on the clinical utility of tranexamic acid in orthopaedic surgery is not clear.

The Committee concluded that there is not enough evidence of effectiveness in indications that are relevant to public health priorities to support the inclusion of tranexamic acid at this time.

Section 12. Cardiovascular medicines

Section 12.2 Antiarrhythmic medicines

Amiodarone (inclusion)

Following a request from the Expert Committee in 2007, an application was prepared by the WHO Collaborating Centre for Evidence-Based Research Synthesis and Guideline Development in Reproductive Health for the inclusion of amiodarone; tablets 100 mg, 200 mg, 400 mg and 50 mg/ml vials and ampoules, for both the acute and chronic treatment of supraventricular and ventricular arrhythmias.

Expert reviews of the application were prepared by Dr Gregory L. Kearns and Professor Abdol Majid Cheraghali.

The Committee noted that the efficacy and safety data presented in the application were derived from RCTs and systematic reviews and generally supported the view that amiodarone is both effective and safe for use in arrhythmic disorders, but did not support the use of amiodarone in the routine treatment of chronic heart failure.

The Committee also noted the role of amiodarone in selected acute care settings. Amiodarone is recommended in both the PALS and ACLS guidelines for cardiac arrest with pulseless ventricular tachycardia or ventricular fibrillation (unresponsive to defibrillation, cardiopulmonary resuscitation and vasopressor administration). It is also recommended in the PALS guidelines for supraventricular tachycardia (unresponsive to vagal manoeuvres and adenosine).

The Committee noted the recommendation that amiodarone treatment should be initiated by a specialist and baseline investigations performed before treatment begins (chest X-ray, pulmonary, thyroid and liver function tests). Thereafter, longitudinal assessment of thyroid and liver function is required and other specialist investigations may be necessary during the course of treatment. Safe use also requires vigilant assessment of concomitant drug–drug interactions with warfarin and digoxin in particular.

Based on the evidence presented in the application the Committee recommended inclusion of amiodarone on the Complementary Model List. In the absence of evidence of effectiveness and safety of the medicine in children, the Committee did not add it to the EMLc, but requested further review of the antiarrythmics as used in children.

Section 12.4 Medicines used in heart failure

Hydrochlorothiazide (new formulations)

The application for hydrochlorothiazide (new formulations) was commissioned by the Secretariat as part of a review of the section on medicines used in heart failure. It was prepared by the NHS Centre for the Evaluation of Effectiveness of Health Care (CeVEAS), Local Health Unit, Modena, Italy. Comments on the application were received from MSF.

An expert review of the application was prepared by Mr Andy Gray.

The Committee noted the one Cochrane Review *(162)* (n = 202) cited showed that thiazides are useful in the relief of symptoms, reduce episodes of de-compensation, and improve exercise tolerance, but do not

affect the outcome of heart failure. It also noted evidence of relative efficacy of thiazides in hypertension when compared to beta-blockers *(163)*.

The Committee noted that although thiazides have various potentially serious side-effects, they are relatively safe at doses below 25 mg/day and that their antihypertensive effect has largely been achieved at this dose *(164)*.

The Committee noted that the application did not present any evidence for the safety or efficacy of thiazides in children and therefore was not able to recommend its addition to the EMLc but requested a further review of paediatric evidence for use of thiazides for hypertension.

The Committee supported the inclusion of the 12.5 mg tablet and the suspension form 50 mg per 5 ml of hydrochlorothiazide to the Model List for the treatment of hypertension.

Quinidine (deletion)

An application was prepared by the Public Health and Pharmacology Department, Weill Medical College of Cornell University, New York, USA, for the deletion of quinidine 200 mg from the Model List.

Expert reviews of the application were prepared by Dr Kalle Hoppu and Dr Lennita Wannmacher.

The Committee noted that a recent Cochrane Review *(165)* and a large multicentre RCT *(166)* were cited in the application to support the lack of superior efficacy of quinidine over other antiarrhythmic medicines and strategies in prolonging the life of cardiac patients.

The Committee recognized that quinidine has many serious adverse effects; it is associated with increased morbidity, risk of QT prolongation and induction of fatal arrhythmias in the adult population. It interacts with a large number of other medicines with potentially fatal consequences, including anti-infectives and antifungals, which are used extensively in developing countries.

The Committee accepted that the evidence presented could also apply to procainamide, another class IA antiarrhythmic agent currently on the Model List.

The Committee recommended the deletion of quinidine and procainamide from the Complementary Model List because of the lack of evidence of superior efficacy or safety when compared to other antiarrhythmic medicines, and the availability of effective and safer alternatives, on the Model List.

Section 17. Gastrointestinal medicines

Section 17.1 Antacids and other antiulcer medicines

Omeprazole (inclusion)

This application was prepared by Universities Allied for Essential Medicines (UAEM), Weill Cornell Medical College — The Rockefeller University — Sloan-Kettering Cancer Institute Chapter. It proposes the addition of omeprazole as a representative of proton pump inhibitors (PPIs) in the Core Model List. Comments in support were received from MSF, which also requested the retention of antacids in the Core Model List.

An expert review of the application was prepared by Professor Abdol Majid Cheraghali.

The Committee noted the public health need for PPIs in the effective treatment of *Helicobacter pylori*, prevention of gastric cancer and various other conditions, and that PPIs are recommended by the American College of Gastroenterology Practice Guidelines for Dyspepsia, and the British National Health Service (NHS) guidelines.

The Committee noted the evidence provided in the application (based on the National Institute for Clinical and Public Health Excellence Guidelines) and the additional Cochrane systematic reviews identified by the Secretariat, of greater efficacy of PPIs than other therapies for gastro-oesophageal reflux, dyspepsia, and upper gastrointestinal tract bleeding in control of symptoms and inflammation. The same reviews established the comparability of the efficacy of other PPIs with that of omeprazole.

The Committee noted that the safety profile of omeprazole is acceptable for short-term use and that there have been case-reports of rare toxic hepatitis and acute interstitial nephritis. In the long term, PPIs interfere with calcium absorption resulting in increased prevalence of hip fractures *(167)*, and also increase susceptibility to gastrointestinal and respiratory infections. The minimum effective dose is recommended for long-term use. The Committee accepted that the cost per dose of omeprazole is similar to that of histamine-2 receptor antagonists, making PPIs more cost-effective.

The Committee recommended the inclusion of omeprazole as a representative PPI in the Core Model List. It recommended a review of antacids and histamine-2 receptor antagonists to assess their continued usefulness relative to PPIs in the Model List and a review of treatment regimens for *H. pylori* infections.

Endar (inclusion)

An application was submitted by Dr Mahesh Mokashi, from Mumbai, India, for the addition of "Endar" oral syrup to the Model List for the treatment of diarrhoea and dysentery in children and adults.

Expert reviews of the application were prepared by Professor Anita Zaidi and Professor Elizabeth Zisovska.

The Committee noted that this application was incomplete, did not contain data on efficacy or safety, or information on the composition of the product. Based on the information given in the application, the preparation "Endar" does not currently fit the criteria that would allow it to be considered as an essential medicine. The Committee therefore rejected the application for inclusion of "Endar" syrup on the Model List.

The Committee discussed whether applications submitted with inadequate evidence should be considered. The Committee directed the Secretariat to ensure that all applications meet the following criteria before being included on the Committee agenda:

— they present scientific evidence on efficacy and safety; and
— the medicine has a product composition defined in a way that is reproducible.

The Secretariat should screen applications in consultation with Committee members and the relevant WHO departments, as necessary.

Oral rehydration salts (inclusion)

An application was submitted by Dr Olivier Fontaine, Medical Officer, Department of Newborn and Child Health and Development, WHO, for the inclusion in the Model List of a 200-ml pack size of oral rehydration salts (ORS) for the home treatment of diarrhoea.

The Committee noted that the efficacy and safety of ORS is well established and that a 1-litre packet has been included on the Model List since its inception in 1977. The ORS formula in the Model List was changed in 2003 to a new reduced osmolarity ORS, which had been shown to reduce the need for unplanned intravenous infusions in the treatment of acute non-cholera diarrhoea in children.

The Committee noted that the rationale for the inclusion of the new 200 ml packet size for ORS is that there is now a need to provide an ORS packet more adapted to the home treatment of diarrhoea, which is mainly diarrhoea without dehydration.

The Committee recommended the inclusion of the 200-ml, 500-ml and 1-L packet sizes of ORS for the home management of diarrhoea, as this should increase the acceptability and availability of ORS for home use in many countries.

Section 22. Oxytocics and antioxytocics

Misoprostol (inclusion)

Applications for the inclusion of misoprostol 100- and 200-microgram tablets were submitted by Gynuity Health Projects and Venture Strategies for Health, for the prevention of postpartum haemorrhage (PPH) and by Gynuity Health Projects, for the treatment of first trimester incomplete abortion.

Misoprostol is currently included on the Model List as:

— a 25 microgram vaginal tablet, for use in induction of labour, on the Complementary List (added in 2005);
— in combination with mifepristone as a 200 microgram tablet, for termination of pregnancy (where legally permitted and culturally acceptable), on the Complementary List (added in 2005).

Expert reviews of the applications were prepared by Dr Marcus Reidenberg and Dr Lennita Wannmacher.

The public health relevance of treatments for both indications (PPH and incomplete abortion) had been accepted previously by the Expert Committee and is documented in the applications. It is further supported in the many letters received by the Secretariat in support of the proposals from organizations and individuals. In brief, PPH remains the major cause of maternal death (25% of mortality, WHO World Health Report 2005), and the risk of death from PPH is much higher in developing than in developed countries. In addition, atonic uterus is the main cause of PPH *(168)*. The Committee also noted one letter against the proposals, on the grounds of the potential for use of misoprostol as an abortifacient.

Prevention of postpartum haemorrhage

The Committee noted the systematic review of seven trials *(169)* comparing 600 micrograms misoprostol with other uterotonics. In the context of active management of labour by a skilled birth attendant, in comparison with oxytocin, misoprostol appears to be less effective and is associated with more adverse effects. The major argument made in the application is that misoprostol should be an option in situations where oxytocin is NOT available. The evidence for this claim is based on three published trials *(170, 171, 172)*. The estimates of efficacy of misoprostol compared with placebo are not consistent across the

trials which took place in settings mostl likely to be similar to those where it is used; there is a significant risk of increased shivering and fever, and an unresolved concern about increased mortality. Furthermore, the Committee is aware of a completed, but not yet reported, large trial assessing the effect of misoprostol on maternal blood loss and mortality.

Treatment of incomplete abortion in the first trimester

The application identified 22 relevant studies that directly compare the use of misoprostol with surgery for the treatment of incomplete first trimester abortion. Based on these data, there is no statistically significant difference between surgery and oral misoprostol in terms of uterine clearance up to 14 days after administration. Comparison of adverse effects showed that while misoprostol administration was associated with predictable adverse effects (such as bleeding and pyrexia) due to the pharmacological actions of the medicine, these effects generally did not require further interventions (such as blood transfusion) and were reported as acceptable by the women. The adverse effect profile of misoprostol needs to be compared with the potential risks of surgery in unsafe settings. The application cites one unpublished study to support the proposal that 400 micrograms orally may be equivalent to 600 micrograms orally, but the data are not provided in detail.

The application presents current prices of misoprostol and a brief summary of some published cost-effectiveness data.

With respect to use of misoprostol for the treatment of incomplete abortion, the Committee decided that the evidence showed that misoprostol is as effective as surgery and, in some settings, may be safer as well as cheaper and therefore recommended inclusion of the 200 microgram tablet on the Complementary List with a note indicating the appropriate use, for management of incomplete abortion and miscarriage.

For prevention of PPH, the Committee decided that the data presented in the application did not establish sufficient evidence of comparative effectiveness, safety or cost-effectiveness and therefore the Committee did not include misoprostol for this indication. The Committee will review this decision after the results of the large trial become available.

Section 24. Psychotherapeutic medicines

Section 24.1 Medicines used in psychotic disorders

Clozapine, olanzapine, risperidone, quetiapine, aripiprazole and ziprasidone (inclusion)

An application was prepared by Dr Dale L. Johnson, President of the World Fellowship for Schizophrenia and Allied Disorders, for the inclusion of

clozapine, olanzapine, risperidone, quetiapine, aripiprazole and ziprasidone on the Model List for the treatment of psychotic disorders.

Expert reviews of the application were prepared by Dr Lisa A. Bero and Dr Kalle Hoppu. Comments were received from Dr John McEwen, Member of the WHO Expert Advisory Panel on Drug Evaluation, Dr Jean Rigal, Medical Director, MSF, France, and Dr Benedetto Saraceno, Director of the Department of Mental Health and Substance Abuse, WHO.

The Committee noted that, although the application provided some information on the comparative effectiveness and side-effects of the proposed medications, the information presented was neither comprehensive nor did it provide a systematic review of the evidence. A literature search undertaken by one of the expert reviewers revealed that evidence from many relevant Cochrane Reviews *(173, 174, 175, 176, 177, 178)* and a drug class review on atypical antipsychotic drugs by the Drug Effectiveness Review Project *(179),* had not been included. It was also noted that the application did not provide a comprehensive review of the comparative benefit–risk profiles for the individual medicines.

Regarding clozapine, the Committee noted that it has an important role in the treatment of schizophrenia in people unresponsive to, or intolerant of, other antipsychotics. However, the application presented only a limited number of clinical studies to support the efficacy of clozapine and did not present comprehensive information regarding its unique safety issues. Noting the comments on safety from Dr John McEwen, the Committee requested that a specific review of clozapine be commissioned before it is considered for inclusion in the Model List.

Based on the evidence presented in this application, the Committee decided not to include an atypical antipsychotic on the List at this meeting. The Committee agreed that there was a need to review the section on antipsychotics. It requested that as soon as possible the Department of Essential Medicines and Pharmaceutical Policies commission a formal application containing a comprehensive summary of the evidence on the comparative effectiveness and adverse effects of these medicines, for review at the next meeting.

Section 24.2 Medicines used in mood disorders

Section 24.2.1 Medicines used in depressive disorders

Fluoxetine, paroxetine and sertraline (inclusion)

An application was submitted by Dr Dale L. Johnson, President, World Fellowship for Schizophrenia and Allied Disorders, for the addition of fluoxetine, paroxetine and sertraline to the Model List for the treatment of depressive disorders.

An expert review of the application was prepared by Dr Lisa A. Bero. Comments in relation to this application were received from Dr Jean Rigal, Medical Director, MSF, France, and Dr Benedetto Saraceno, Director, Department of Mental Health and Substance Abuse, WHO.

The Committee noted that the application did not contain a comprehensive review of all the available literature regarding these selective-serotonin reuptake inhibitors (SSRIs). Neither evidence from relevant Cochrane Reviews *(180)* nor from a recent drug class review for second-generation antidepressants by the Drug Effectiveness Review Project *(181)* was cited in the application.

Fluoxetine is already on the Model List for this indication.

The Committee decided that the evidence provided was not sufficient to recommend the addition of paroxetine and sertraline or addition of a square box to fluoxetine.

Section 24.3 Medicines used in generalized anxiety and sleep disorders

The Committee was asked to consider the separation of medicines used in generalized anxiety disorder and sleep disorder into different sections. The Committee noted that although anxiety and sleep problems may simultaneously be present in the same individual there are specific epidemiological and clinical differences between the two conditions, and in recent years these two conditions have been progressively treated with different pharmacological and non-pharmacological interventions. At present there are no medicines for listing under sleep disorders, therefore the Committee recommended that sleep disorders should be deleted from the heading of Section 24.3. A new sub-section specifically for sleep disorders on the Model List was not justified at the time of the meeting.

Addition of a selective-serotonin reuptake inhibitor (escitalopram, paroxetine and sertraline)

An application was submitted by Dr Corrado Barbui and Dr Andrea Cipriani, Department of Medicine and Public Health, Section of Psychiatry and Clinical Psychology, University of Verona, Italy, for the inclusion of an SSRI on the Model List for the treatment of adults with generalized anxiety disorder. The proposed medicines for inclusion were paroxetine 20 mg, sertraline 50 mg and escitalopram 5 mg. Listing was requested as an individual medicine. The application was commissioned by the Department of Essential Medicines and Pharmaceutical Policies, WHO.

Expert reviews of the application were prepared by Dr Lisa A. Bero and Dr Kalle Hoppu. Comments in relation to the application were received

from Dr Jean Rigal, Medical Director, MSF, France, and Dr Benedetto Saraceno, Director, Department of Mental Health and Substance Abuse, WHO.

Evidence from RCTs supported the use of escitalopram, paroxetine and sertraline compared to placebo, benzodiazepines and older antidepressants for the treatment of generalized anxiety disorder (GAD). However, the Committee noted that there was limited information regarding the public health burden of this condition in low-income and middle-income countries and that all of the evidence for efficacy and safety had come from clinical trials undertaken in health-care settings in high-income countries. The Committee noted that there was not a substantial body of evidence to establish the superior efficacy and safety of one SSRI over another for the treatment of GAD.

The Committee noted that no formal cost-effectiveness analyses have been conducted so far in individuals with GAD.

Overall the Committee decided that the evidence provided in the application did not support the public health need or comparative effectiveness, safety and cost-effectiveness for the addition of escitalopram, paroxetine or sertraline to the Model List at this time.

Section 24.5 Medicines used in substance dependence programmes

Nicotine replacement therapy (inclusion)

An application was submitted by Dr Douglas Bettcher, Director of the Tobacco Free Initiative, for the inclusion of nicotine replacement therapy (NRT) on the Model List. Listing is requested as an example of a therapeutic group under the heading "nicotine (systemic) for smoking cessation". All available dosage forms were specified in the application.

Expert reviews were prepared by Mr Edgard José Narvàez Delgado and Mrs Jehan Mohammed Ali Al-Fannah.

The largest and most recent systematic review included in the application was a Cochrane Review, which included 111 randomized and quasi-randomized controlled studies of the effectiveness of NRT among 43 040 men and women, and demonstrated that all forms of NRT were effective as part of a strategy to promote smoking cessation in individuals *(182).* However, there were no data showing that availability of NRT reduces smoking rates in a population.

The Committee noted that the risk–benefit profile of NRT was well defined and noted that the potential benefits of smoking cessation outweighed the risks of NRT.

The application provided a review of the cost-effectiveness of NRT in a wide variety of countries and settings, and in various smoking cessation programmes. However, no data were presented regarding comparable cost-effectiveness between the different types and formulations of NRT.

The Committee considered the addition of NRT in the context of the Framework Convention on Tobacco Control. The Committee recommended that nicotine patches and gum be added to the Model List because of the public health need, high-quality evidence of effectiveness, and acceptable safety and cost effectiveness. Other forms were not recommended for inclusion at this time due to the availability of less evidence of comparative safety, effectiveness and cost in diverse populations.

Section 25. Medicines acting on the respiratory tract

Section 25.1 Antiasthmatics and medicines for chronic obstructive pulmonary disease

Beclometasone (new formulation)

An application was received from Professor Nadia Ait Khaled of the International Union against Tuberculosis and Lung Disease for the inclusion of beclometasone 100 micrograms for the treatment of asthma and chronic obstructive pulmonary disease.

Expert reviews of the application were prepared by Mrs Jehan Mohammed Ali Al-Fannah and Professor Rohini Fernandopulle. Comments in support of the application were received from Dr Jean Rigal, MSF International.

The Committee noted that beclometasone dipropionate has been in use for almost 30 years as an inhaled asthma medication and is already listed in the Model List in the 50 microgram and 250 microgram dosage forms. Its efficacy and safety have long been established. The modification is requested because the move from chlorofluorocarbon (CFC) to hydrofluoroalkane (HFA) formulations necessitates a change in strength.

The Committee recommended the addition of the 100 microgram beclometasone dosage form to the Model List and the deletion of the 250 microgram strength.

Cromoglicic acid (reinstatement)

An email was received from Mr Alan Edwards of the David Hide Asthma and Allergy Research Centre, Isle of Wight, England. No formal application was prepared for consideration by the Committee.

Expert reviews of the information provided were prepared by Dr Myriam Henkens and Dr Gregory Kearns.

The Committee noted that the information provided to support the re-instatement of cromoglicic acid did not include any new studies demonstrating its superior efficacy and safety compared to placebo or comparators for the treatment of asthma.

The Committee noted that the Cochrane Review of inhaled sodium cromoglycate in children was updated in 2008 in response to criticism of the methods and conclusions in the original review *(183)*. However, the main findings remained the same: there is still insufficient evidence to be certain about the efficacy of cromoglicic acid over placebo for the treatment of chronic asthma in children.

Evidence from a new Cochrane Review comparing inhaled corticosteroids with sodium cromoglycate in children and adults with asthma, published in 2006 *(184),* was provided to the Committee by the Secretariat. This review included 17 trials involving 1279 children and eight trials involving 321 adults with asthma. The review found that inhaled corticosteroids were superior to sodium cromoglycate on measures of lung function and asthma control for both adults and children with chronic asthma. No differences in adverse effects between inhaled corticosteroids and sodium cromoglycate were found.

The Committee did not recommend the reinstatement of cromoglicic acid in the Core List at this time and commented that until there was substantial new evidence in support of its superior safety and efficacy for the treatment of asthma, the reinstatement of cromoglicic acid in the WHO Model List of Essential Medicines is not recommended.

10. Summary of recommendations

Additions, changes and deletions to the Model List

1. **The Committee made the following changes to the Sections:**
   Section 6.2.2: Sulfadiazine was deleted from this section as it is only indicated for the treatment of toxoplasmosis.
   Section 6.3 and Section 6.5.2: The listing of liposomal amphotericin B was modified to specify both the deoxycholate and the liposomal form.
   Section 6.5.4: Sulfadiazine was added to this section because it is only used for the treatment of toxoplasmosis.
   Section 18: Fludrocortisone was added to provide concordance with the EMLc since it was noted by the Committee that it would be essential for the treatment of congenital adrenal hypoplasia and adrenal failure in adults.
   Section 24.3: The term "sleep disorders" was deleted from the heading of the section on the basis that there are specific epidemiological and clinical differences between generalized anxiety disorders and sleep

disorders. The creation of a new subsection for sleep disorders was not deemed appropriate at this time as there were no specific medicines for listing.

2. **The Committee recommended the following additions to the Model List:**

Section 5: Parenteral diazepam with a square box was replaced by parenteral lorazepam, 2 mg/ml and 4mg/ml in 1-ml ampoule, with a square box. The rectal solution or gel formulation of diazepam was retained on the Model List.

Section 6.2.4: Addition of rifabutin capsule 150 mg with the note: for use in patients with HIV receiving protease inhibitors. Rifabutin was not added to the EMLc at this meeting because there was a lack of evidence of its efficacy and safety in children.

Section 6.3: Addition of the liposomal formulation of amphotericin B.

Section 6.4.2.3: Addition of atazanavir 100 mg; 150 mg and 300 mg solid oral dosage forms.

Section 6.4.2.3: Addition of heat-stable, fixed-dose combination formulations of lopinavir/ritonavir 100 mg + 25 mg and 200 mg + 50 mg tablets.

Section 6.4.2.3: Addition of heat-stable ritonavir 100 mg and 25 mg tablets.

Section 6.4.2.3: Addition of saquinavir 500 mg tablet.

Section 6.5.5: Addition of nifurtimox 120 mg tablet with the note: only to be used in combination with eflornithine for the treatment of *Typanosoma brucei gambiense* infection.

Section 8.2: Addition of carboplatin as the representative platinum compound, 50 mg/5 ml, 150 mg/15 ml, 450 mg/45 ml and 600 mg/60 ml injection.

Section 8.2: Addition of hydroxycarbamide 200 mg, 250 mg, 300 mg, 400 mg and 500 mg capsules and 1 g tablet.

Section 8.2: Addition of ifosfamide 1-g and 2-g vials of powder for injection.

Section 8.2: Addition of mesna 100 mg/ml injection and 400 mg and 600 mg tablets.

Section 12.2: Addition of amiodarone 50 mg/ml injection and 100 mg, 200 mg and 400 mg tablets to the Complementary List.

Section 12.3: Addition of hydrochlorothiazide 12.5 mg tablet and 50 mg/5 ml oral liquid.

Section 17: Addition of omeprazole as a representative proton pump inhibitor, 10 mg, 20 mg and 40 mg oral solid dosage form and 20 mg and 40 mg sachets of powder for oral suspension.

Section 17.2: Addition of ondansetron with a square box, 2 mg/ml injection, 4 mg/5 ml oral liquid and 4 mg, 8 mg and 24 mg solid oral dosage form.

Section 17.2: Addition of dexamethasone 4 mg/ml injection, 0.5 mg/5 ml and 2 mg/5 ml oral liquid and 0.5 mg, 0.75 mg, 1.5 mg, 4 mg oral solid dosage form.

Section 17.5.1: Addition of 200 ml and 500 ml and 1 L packet sizes for oral rehydration therapy.

Section 22.1: Addition of misoprostol 200 microgram tablet to the Complementary List with the note that it is for the management of incomplete abortion and miscarriage.

Section 24.5: Addition of nicotine replacement therapy chewing gum 2 mg and 4 mg and transdermal patches 5 mg to 30 mg/16 hours and 7 mg to 21 mg/24 hours.

Section 25.1: Addition of beclometasone 100 micrograms per dose inhalation formulation (aerosol, CFC-free form).

3. **The Committee recommended that the following medicines should be deleted from the Model List:**

Section 6.2.4: Deletion of the 60 mg + 30 mg combination of rifampicin + isoniazid and the 60 mg + 30 mg + 150 mg combination of rifampicin + isoniazid + pyrazinamide on the basis that these combinations provide an inefficacious dose for children.

Section 6.4.2: Deletion of the 200 mg and 333 mg tablet formulations of indinavir on the basis that these formulations are not needed as part of a comprehensive antiretroviral treatment programme.

Section 6.4.2: Deletion of all formulations of nelfinavir on the basis of non-availability and reduced need for this medicine as part of a comprehensive antiretroviral treatment programme.

Section 6.4.2: Deletion of the 40 mg tablet formulation of stavudine on the basis of its safety profile and to ensure consistency with WHO guidelines.

Section 6.5.2: Deletion of pentamidine powder for injection 200 mg and 300 mg on the basis that it is no longer recommended for the treatment of visceral leishmaniasis in adults and to provide concordance between the Model List and EMLc.

Section 8.2: Deletion of cisplatin powder for injection 10 mg and 50 mg in vial as carboplatin is superior.

Section 12.2: Deletion of quinidine 200 mg tablet and procainamide 100 mg/ml injection due to their inferior efficacy and safety compared with other antiarrhythmic medicines.

Section 17.2: Deletion of promethazine on the grounds of its lack of efficacy in postoperative nausea and vomiting.

4. **The Committee considered proposals for the following medicines but rejected their inclusion in the Model List:**

Section 4.2: Pralidoxime injection — rejected on the grounds that the currently available evidence from studies in adults did not sufficiently demonstrate its efficacy and safety.

Section 5: Lamotrigine tablets and chewable dispersible tablets — rejected on the grounds of insufficient evidence of superior safety, efficacy and cost-effectiveness compared to comparators and the availability of suitable alternative antiepileptics which are already on the Model List.

Midazolam oral liquid — rejected on the grounds of insufficient evidence to show its effectiveness and safety in community settings for treatment of seizures and the availability of a suitable alternative already on the Model List.

Section 6.4.2.1: Zidovudine + lamivudine + abacavir fixed-dose combination tablet — rejected on the grounds of a lack of specific evidence of the superior efficacy of this fixed-dose combination and where the combination is required in individual cases, it can be achieved with the medicines already listed.

Section 6.4.3: Amantadine and rimantadine tablets, capsules and oral liquid formulations, oseltamivir capsules and oral suspension, zanamivir powder for oral inhalation — rejected on the grounds that the evidence to support the effectiveness of any of the four antivirals for treatment of avian flu is of a very low quality.

Section 7: Sumatriptan 50 mg tablet — rejected on the grounds that the comparative efficacy, safety and cost-effectiveness of sumatriptan versus other triptans and aspirin was not established.

Section 10: Tranexamic acid intravenous infusion — rejected on the grounds that there is not enough evidence of its effectiveness in indications that are relevant to public health priorities at this time.

Section 17: Endar syrup — the application was rejected on the grounds that it was incomplete. It did not include any scientific evidence for the efficacy and safety of the proposed product and did not define the product composition in a way that was reproducible.

Section 22.1: Misoprostol 200 microgram tablet, for the prevention of postpartum haemorrhage — the application was rejected on the grounds that the evidence currently available to the Committee did not establish the comparative effectiveness and safety in the proposed context and setting for use of the product.

Section 24.1: Clozapine, olanzipine, risperidone, quetiapine, aripiprazole and zipasidone — the application was rejected on the grounds that the application did not provide sufficient information regarding the comparative effectiveness and safety of the proposed

medicines. The Committee requested a formal review of this section for consideration at the next meeting.

Section 24.2.1: Paroxetine and sertraline — rejected on the grounds of insufficient evidence of their comparative effectiveness, safety and cost-effectiveness being available at this time.

Section 24.3: Escitalopram 5 mg tablet, paroxetine 20 mg tablet, sertraline 50 mg tablet — rejected on the grounds that the evidence did not support the public health need or comparative effectiveness, safety and cost-effectiveness for their addition at this time.

Section 25: Cromoglicic acid — reinstatement was rejected on the grounds that there was no new supporting evidence to show its superior safety and efficacy for the treatment of asthma at this time.

Additions, changes and deletions to the EMLc

1. **The Committee made the following changes to the Sections:**
   Section 6.2: The age restriction was removed from procaine benzylpenicillin on the basis of potential mortality benefits in neonates with severe sepsis. However, the note was amended to indicate restricted use: 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.
   Section 6.3 and Section 6.5.2: The listing of liposomal amphotericin B was modified to specify both the deoxycholate and the liposomal form.

2. **The Committee recommended the following additions to the EMLc:**
   Section 6.3: and Section 6.5.2: Addition of the liposomal formulation of amphotericin B.
   Section 6.5.3.1: Addition of artemether + lumefantrine 20 mg + 120 mg dispersible tablet.
   Section 12.4: Addition of enalapril as the indicative angiotensin-converting enzyme inhibitor, 2.5 mg and 5 mg tablets.
   Section 17.2: Addition of ondansetron with a square box, 2 mg/ml injection, 4 mg/5 ml oral liquid and 4 mg and 8 mg solid oral dosage form.

3. **The Committee recommended that the following listings for medicines be amended to correct dosage strength and form:**
   Section 25.1: Strength of budesonide was corrected to 100 micrograms per dose and 200 micrograms per dose inhalation (aerosol).

4. **The Committee considered proposals for the following medicines but rejected their inclusion in the Model List for Children:**
   Section 12.4: Carvedilol tablets — rejected on the grounds that there was not enough evidence of comparative effectiveness and safety to justify inclusion in the Complementary List of the EMLc.

Appendix 1

Proposed lists of priority essential medicines for HIV

1. UNITAID Secretariat/WHO proposal

Table A.1

Proposed lists of priority essential medicines for HIV

Adults: missing essential medicines – medicine/form	**Rationale from current treatment guidelines or Model List**
Stand-alone thermostable formulations of ritonavir or in combination with other protease inhibitors (PIs) e.g. atazanavir/ritonavir (ATV/r) indinavir/ritonavir (IDV/r) saquinavir/ritonavir (SQV/r) fosamprenavir/ritonavir (FPV/r)	Thermostability critical for use in resource-limited settings PIs "boosted"; with ritonavir are recommended for use in second-line treatment regimens
Triple drug first-line combinations: Tenofovir (TDF)-based triple combinations plus efavirenz (EFV) or nevirapine (NVP) plus lamivudine (3TC) or emtricitabine (FTC) e.g. TDF/FTC/NVP TDF/3TC/NVP TDF/FTC/EFV TDF/3TC/EFV Zidovudine (AZT)-based triple combinations plus lamivudine or emtricitabine plus abacavir (ABC) or tenofovir e.g. AZT/3TC/ABC AZT/FTC/ABC AZT/3TC/TDF AZT/FTC/TDF	These are all recommended combination regimens for first-line ART; all are on the Model List as individual components, 2 drugs as fixed-dose combinations (FDCs) also exist but with limited availability
Alternative dual combinations based on lamivudine or emtricitabine plus tenofovir TDF/FTC TDF/3TC	Possible combinations based on current Model List; limited availability at present
Possible valuable second-line triple combinations based on lamivudine or emtricitabine plus tenofovir and a once-daily boosted PI (e.g. ATV/r, LPVr) LPVr/TDF 3TC LPVr/TDF/FTC ATV/r/TDF/FTC ATV/r/TDF /3TC	Components are all on the Model List and/or in treatment guidelines; second-line regimens need further evaluation ideally as once-daily FDCs.
Possible valuable second-line dual and triple combinations Alternative dual combinations based on lamivudine or emtricitabine plus didanosine enteric coated (ddI) ddI/3TC ddI/FTC Triple combinations based on lamivudine or emtricitabine plus didanosine enteric-coated and a once-daily boosted PI (e.g. ATV/r, LPVr) LPVr/ddI/3TC LPVr/ddI/FTC ATV/r/ddI/FTC ATV/r/ddI/3TC	

NOTE: The WHO adult treatment guidelines will be revised in 2009. The revision will consider the potential use of newer products. Consult the WHO web site for more details.

Table A.2
Priority paediatric products

Priority	Product	Recommended ideal dosing strengths
Recommended priority antiretroviral products for infant MTCT prevention		
Urgent	zidovudine	12 mg sachet granules
	nevirapine	6 mg sachet granules
Recommended priority antiretroviral products required for treatment		
Urgent	zidovudine/lamivudine/nevirapine	60/30/50 mg tablet
	zidovudine/lamivudine	60/30 mg tablet
	stavudine/lamivudine	6/30 mg tablet
	stavudine/lamivudine/nevirapine	6/30/50 mg tablet
	abacavir/zidovudine/nevirapine	60/60/50 mg tablet
	nevirapine	50 mg tablet
	lopinavir/ritonavir	100/25 mg tablet
	abacavir	60-mg tablet
High	efavirenz	100 mg tablet
	abacavir/lamivudine	60/30 mg tablet
	zidovudine	60 mg tablet
	zidovudine/lamivudine/abacavir	60/30/60 mg tablet
	stavudine	6 mg tablet
Important	lamivudine	30 mg tablet
	efavirenz/emtricitabine	100/35 mg tablet
	emtricitabine	35 mg tablet
	ritonavir	25 mg tablet
	fosamprenavir	Not examined
	atazanavir	Not examined

2. MSF proposals for additional missing essential medicines for adults for the UNITAID patent pool initiative as at 23-03-2009

Table A.3

Proposals by MSF for additional medicines for adults for the UNITAID patent pool initiative

Drug	Reasons for inclusion
Single drugs	
Darunavir (DVR) Protease inhibitor	More effective and less resistance development than LPV/R. Indicated in international guidelines for treatment experienced patients. Need ritonavir boosting.
Raltegravir (RAL) Integrase inhibitor	A new class. Indicated for treatment experienced, multi class resistant patients. Can be used in treatment naïve patients but not in international guidelines for this indication. Very well tolerated. An important advancement in HIV-1 treatment option.
Maraviroc CCR5 receptor inhibitor	A new class. Indicated for treatment experienced/multi-resistant patients with only CCR5 tropism. HIV-1 subtype C virus seems to carry majority of CCR5 receptors. Use of maraviroc in African subtypes limited.
Etravirine Non-nucleoside reverse transcriptase inhibitor (NNRTI)	Active against mutant NNRTI resistant HIV strains.
Rilpivirine NNRTI	Undergoing Phase III study. Not yet commercialized but promising drug as it is potent, and can be used once daily (with low dose (25 mg.)
Elvitegravir Integrase inhibitor	Undergoing Phase II-III with a booster GS-9350. Potential for being co-formulated.
Booster	
Ritonavir (r) heat-stable	The only booster commercially available with other PIs
GS-9350 CYP 3A inhibitor	Non ARV booster. Entering phase II-III studies. Developed for combination with elvitegravir, and potentially with elvitegravir, TDF and FTC.
SPI-452 CYP 3A inhibitor	Non ARV booster. Only preclinical study done.
Fixed-dose combinations **1. Heat-stable boosted PI (combined with ritonavir)**	
Atazanavir/ritonavir	Validated for first-line and treatment-experienced patients. Advantage of FDC is once daily dosing.

Drug	Reasons for inclusion
Fosamprenavir/ritonavir	Alternative PI for treatment-naïve or experienced patients. Can be used once or twice daily.
Darunavir/ritonavir	Potent PI with main indication for salvage or second-line regimens. Can be used once or twice daily.
2. Heat-stable PI plus NRTIS for second-line	
LPV/r /TDF/3TC	Component of second-line regimens in current WHO guidelines and expert meeting on second lines (2008). LPV/r can be given once daily in PI naïve patients.
ATV/r/TDF/3TC	
LPV/r/ABC + ddI	All didanosine (ddI)-containing combinations are suggested.
LPV/r/3TC + ddI	All didanosine (ddI)-containing combinations are suggested.
ATV/r/3TC + ddI	Co-blisters are needed at the moment as can only be manufactured in buffered tablets or with enteric coating.
ATV/r /3TC /ABC	
3. FDC for first-line combinations	
TDF/ 3TC + NVP (co-blister)	Currently recommended first-line. Interesting combination but NVP is usually given twice daily at least in the first 3–6 months.
TDF/3TC/EFV	Exists in co-formulation and is widely used as first-line internationally. More sources needed (only orginator's available now).

Table A.4

MSF proposal for additional children's essential medicines for the UNITAID patent pool initiative as at 23-03-2009

Drug	Reason for inclusion
Darunavir	Potent protease inhibitor(PI)
Ritonavir heat-stable	For boostingwith other PIs.
Atazanavir	Alternative PI
Fosamprenavir	Alternative PI

Table A.5

MSF proposal for urgent studies in children

Drug	Reason for urgent need for studies in children
Etravirine	Not yet tested in children
Raltegravir	Not yet tested in children
Tenofovir	Accelerate testing
Efavirenz	Accelerate testing in children below 3 years old
Darunavir	Accelerate testing in children below 6 years old

Appendix 2

Report of the Informal Expert Meeting on Dosage Forms of Medicines for Children

WHO Headquarters, Geneva, Switzerland, 15–16 December 2008[1]

Executive summary

In December 2008, a group of paediatricians, pharmacists, clinical pharmacologists and representatives of the European Medicines Agency (EMEA), the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), Medicines for Malaria Venture (MMV), National Institutes of Health (NIH), the United Nations Children's Fund (UNICEF), and the Bill and Melinda Gates Foundation, attended a meeting hosted by WHO to discuss the preferred dosage form of medicines for children. The participants considered the terms of reference in relation to dosage forms of medicines for children provided to the Expert Subcommittee on the Selection and Use of Essential Medicines by the Executive Board in May 2007. A review of published information on different dosage forms of medicines for children was provided to the meeting participants, together with a review of end-user needs. The influence of sociocultural issues on the acceptability of dosage forms of medicines used for children was also considered in the discussion.

As a result of this consultation, the group identified the dosage forms of medicines most suitable for children, paying particular attention to conditions prevailing in developing countries, and flagged future areas of research required in this area. This report summarizes the existing evidence, provides an overview of the outcomes of the meeting and details the suggested recommendations. It will be reviewed by the Expert Committee on the Selection and Use of Essential Medicines at its next meeting in March 2009, in the context of the report from the Subcommittee on Essential Medicines for Children.

Declaration of interests

Expert participants in the Informal Expert Meeting on Dosage Forms for Children reported the following relevant interests (in accordance with WHO procedures, for the period of the last three years):

[1] This publication contains the Report of the Informal Expert Meeting on Dosage Forms of Medicines for Children and does not necessarily represent the decisions or policies of the World Health Organization.

— Professor Jorg Breitkreutz reported receiving research support from DSM, Austria, Medice Germany, Gen-Plus Germany and Bayer Schering Germany, and holding shares in Ethicare GmbH, Germany.
— Dr Kalle Hoppu reported receiving lecture fees from Leiras Ltd, Finland, Oy Swedish Orphan Ab Finland, Norit Pharmaceuticals, the Netherlands and one-time consultation fees from Lundbeck A7S, Denmark.
— Dr Stuart MacLeod reported receiving one-time consulting fees from Eli Lilly, and that the Research Unit of which is he is Executive Director receives grants from several pharmaceutical and biotechnology companies, but that he is not a principal investigator on any of these projects.
— Professor Tony Nunn reported that his research unit receives grants from the UK National Institute for Health Research.
— Dr Stephen Spielberg reported being the Principal Investigator of the Institute for Pediatric Innovation (IPI).

Professor Rohini Fernandopulle, Dr George Giacoia, Professor Henning Kristensen, Dr Jane Robertson and Professor Peter York reported no conflict of interest. Dr Herrad-Odilia Krenkel and Dr Klaus Rose are employees of commercial organizations.

Introduction

The global mortality rate in children aged under five years remains a significant and inequitable problem, particularly within the disease groups of malaria, HIV, tuberculosis, pneumonia, diarrhoea and neonatal infections. Medicines for children has long been a neglected area. The lack of: appropriate paediatric dosage forms; research in the paediatric area; details of the dose (and age-related dose) of paediatric medicines (an important prerequisite in the design of any paediatric medicine) results in children being frequently prescribed medicines that are off-label, unlicensed, or that have been manipulated prior to administration. As a direct consequence, children and their caregivers routinely lack access to safe, effective and appropriate treatment, an effect which significantly contributes to the high mortality and morbidity rates within this age group.

At its meeting in September 2008, the Expert Subcommittee on the Selection and Use of Essential Medicines for Children noted that further work still needed to be completed to fully address two of the Subcommittee's terms of reference:

— to determine suitability criteria for dosage forms of medicines for children, with particular attention to conditions prevailing in developing countries;

— to review the feasibility of manufacturing appropriate formulations for those priority medicines for which no dosage form for children currently exists, specifically considering requirements for use in resource-limited settings, and availability of data on efficacy and safety in the appropriate age groups.

The aim of this meeting on dosage forms of medicines for children was, therefore, to bring together paediatricians, pharmacists, clinical pharmacologists and formulation experts to review the existing evidence in the field on appropriate paediatric formulations, and to identify future lines of research needed to improve the development of preferred dosage forms for children.

Meeting background

Meeting objectives

1. To review the published evidence on what dosage forms of medicines have been developed and administered to children.
2. To determine which existing or novel dosage forms and delivery methods are appropriate for children, considering the feasibility of manufacture.
3. To recommend a preferred dosage form(s) of medicine for children, spanning different geographical and cultural settings.
4. To identify research required to define the preferred dosage form of medicines for children.

Preparatory work

1. A comprehensive review of the published literature, describing current technologies and dosage forms of medicines for children was carried out by Professor Peter York and Dr Amir Amani prior to the meeting.
2. A survey of end-user needs for preferred paediatric dosage forms was carried out by Dr Atieno Ojoo, and a draft document reporting the findings was prepared by Dr Atieno Ojoo and Dr Kalle Hoppu.
3. A literature review on sociocultural issues that influence the acceptability of paediatric dosage forms was carried out by Dr Sienna Craig, Dr Lisa Adams and Dr Stephen Spielberg.

These reviews served as the basis for the meeting participants to propose recommendations for the Expert Committee to consider. All literature reviews, background documents and meeting presentations are available upon request.

Summary of meeting discussion

The meeting was opened by Dr Hans Hogerzeil, Director, Department of Essential Medicines and Pharmaceutical Policies. Dr Hogerzeil highlighted

the discrepancy between the availability of suitable medicines for children and those available for adults, and emphasized the significant reduction of childhood mortality and morbidity that could be achieved through improvement in the global access to suitable medicines for children.

Professor Peter York presented his review of the currently available dosage forms of medicines for children, and innovations in drug delivery design for children. He outlined the requirements for paediatric medicines, commented on the suitability of available dosage forms for paediatric medicines, and identified recent innovations in dosage form designs and technologies.

Mr David Ubben provided an overview of the work of the Medicines for Malaria Venture, and commented specifically on the progress made and challenges posed in the development of three new paediatric antimalarial combinations.

Dr Atienno Ojoo presented a survey of the end-user requirements for preferred paediatric formulations. She emphasized the importance of taking into account specific end-user's needs, including those of children, parents or caregivers, nurses, pharmacists, prescribing physicians and other health-care workers.

Dr Stephen Spielberg provided an overview of the important sociocultural issues to consider in improving paediatric dosage forms. He suggested that aspects such as acceptability, palatability, tolerance and compliance may vary widely between different cultural settings, and could be significantly influenced by sociocultural issues.

Professor Rohini Fernandopulle presented a survey of caregivers in Sri Lanka, outlining some of the problems faced when using currently available dosage forms of anticonvulsants to treat epilepsy in children.

Summary of evidence

Currently available and innovative paediatric dosage forms — Peter York and Amir Amani

Eight hundred (English language) citations were retrieved, containing references to current activity and innovations in drug delivery system design for children. The identified routes of administration were the oral (liquid and solid dosage forms), topical, parenteral, inhalational and nasal, rectal and ocular routes. No clear trends were identified, and most clinical papers did not report full details of new dosage forms used in studies. There was general acceptance of the benefits of solid dosage forms over liquid dosage forms in terms of stability, dosing and administration issues. Few reports attempted to bridge the gap between "top down" and "bottom up" approaches, and/or included discussion of the manufacturing and regulatory

aspects of paediatric dosage forms. The need for a multidisciplinary and "holistic" approach to paediatric medicines was highlighted and the potential of a "platform" solid dosage form (e.g. granules or pellets) as a preliminary form which would provide flexibility for further processing into a range of alternative paediatric drug delivery systems was presented.

The meeting noted that despite several studies reporting small children as being unable to swallow granules or mini-tablets, there was a lack of evidence for a specific age at which solid dosage forms are clearly acceptable from the clinical and safety perspectives, and further research was needed on this topic.

The meeting agreed that a restricted focus on "innovative" medicines would be counterproductive to the development of paediatric dosage forms, and that it was important to consider the modification of standard technologies in the development of preferred paediatric dosage forms.

The meeting suggested that focusing on the development of suitable dosage forms for use in treating diseases of high burden in childhood (i.e. diarrhoea, pneumonia, neonatal sepsis, prematurity, HIV, tuberculosis and malaria), would achieve the highest impact on reducing childhood morbidity and mortality. An additional consideration was the potential differences in dosage forms for treatment required for acute versus chronic diseases. It was noted that precision of dosing appeared to be less important in the treatment of many public health priority diseases, where the majority of medicines currently used have a wide therapeutic index and the main risk may be underdosing, with resultant inefficacy, rather than excessive dosing with the associated risks of toxicity.

It was also emphasized that, for children of different age groups, dose combinations would require varying percentages of drug composition depending on each drug's absorption, distribution, metabolization and excretion characteristics.

The meeting acknowledged that treatment failure as a measure of outcome was important, and that cost was relevant in the development of preferred paediatric dosage forms.

Desirable attributes of a paediatric dosage form

Several requirements were identified as being key in the identification of a preferred paediatric dosage form. These included:

— minimal frequency of administration;
— minimal impact on lifestyle;
— minimum, non-toxic excipients;
— convenient, easy, reliable administration;

— palatable;
— requiring minimal manipulation by health professionals or carers prior to use (i.e. flexibility and adaptability of the medicine to account for developmental and size differences, with the ability to reliably divide the unit dose);
— transportable and low bulk or weight;
— easily produced, stable in a variety of climates;
— affordable;
— commercially viable.

End-user needs — Atieno Ojoo and Kalle Hoppu Rohini Fernandopulle

An e-mail survey of 38 respondents from 27 countries (including high-income, low-income and middle-income countries) was carried out in order to determine end-user specifications for preferred paediatric dosage forms. Responses were found to be similar across all geographical regions, and in all high-, low- and middle-income countries. The survey identified problems with supply, health workers, quality and storage, as well as specific end-user issues such as palatability, lack of information, caregiver fatigue, pill burden and off-label medicine use. Other general issues included restricted access to clean water and lack of training of dispensing staff; these are particular problems for resource-poor countries.

The findings from a survey of caregivers in Sri Lanka were also presented, outlining some of the problems faced when using currently available dosage forms of anticonvulsants to treat epilepsy in children.

On the basis of these findings, it was suggested that interventions should be targeted at the levels of research and development, policy-makers, manufacturers and procurement and logistics.

Sociocultural aspects — Sienna Craig and Stephen Spielberg

A draft literature review (Sienna Craig et al.) on the sociocultural aspects of paediatric dosage forms highlighted the importance of cultural setting in suitability of dosage forms. Cultural differences were noted in the understanding and expectations of treatment, duration of treatment, palatability, and acceptability of medicines.

Although the meeting acknowledged that cultural setting was important, it was noted that there was insufficient evidence to demonstrate a true variation in cultural acceptability. The possibility of producing a product that would be acceptable across multiple cultures through a platform technology that could be "reformatted" to meet cultural norms, was therefore considered. Platform technologies are technologies that can be used to facilitate a broad

range of application-based activities. i.e. one formulation technology can be used for several active compounds.

Proposed recommendations

1. In general, the dosage forms of medicines that are likely to prove most "suitable" particularly for developing countries are *flexible solid dosage forms*, such as tablets that are oro-dispersible and/or that can be used for preparation of oral liquids (for example suspension or solution). These dosage forms could be used for many of the medicines necessary to treat the diseases that are the major causes of mortality and morbidity in children aged under 5 years (lower respiratory tract infection, malaria, and diarrhoeal diseases).

   Provided the product can be dispersed in breast milk from the mother, it could potentially be used in very young children (0–6 months). This type of product is feasible to manufacture in facilities that have conventional tableting facilities, but requires excipients that ensure stability and palatability. Examples of existing dispersible tablet products suggest that they can be more affordable than standard liquid dosage forms.

   It is necessary to identify appropriate product strengths and ratios of actives (based on physiological development expressed as age or weight bands and with simple dosing regimens) for each medicine, as well ensuring package sizes that allow optimal use under the conditions of public health programmes.

   This type of product may not be suitable for medicines requiring precise dose titration, such as some anticonvulsants, or molecules that are included in Biopharmaceutics Classification System (BCS) classes 2 and 4. Drug substances classified as BCS Class 2, are those with high permeability and low solubility, drug substances classified as BCS Class 4 have low permeability and low solubility.[1]
2. For severe disease conditions (e.g. neonatal sepsis), injections are the best existing option, but developments should include modified vial sizes or strengths to ensure suitability for all age groups (especially neonates) and packaging options that allow easy use. There is a need for the development of injections and infusions that minimize risk of

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1. When an API shows a dose: solubility ratio of 250 ml or lower at 37 °C over a pH range of 1.2–6.8, it can be classified as "highly soluble". When an API is absorbed to an extent of 85% or more, it is considered to be "highly permeable".

References

Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. Geneva, World Health Organization, 2006 (WHO Technical Report Series 937) Annex 7.

Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms. Geneva, World Health Organization, 2006 (WHO Technical Report Series 937) Annex 8 (http://www.who.int/medicines/areas/quality_safety/quality_assurance/regulatory_standards/en/index.html).

electrolyte overload. New developments in injection technology should be assessed, especially those that can be used in community or primary care settings.

3. For oral medicines requiring precise dose measurement or titration, the most "suitable" dosage form should be based on use of a solid platform technology (multi-particulate solid, including those that could be dispersed to form a liquid dose), rather than oral liquids. This can allow production of "tailored" doses and strengths as well as preparation as a range of dosage forms such as tablets or capsules. Examples of current forms are mini-tablets and spherical granules (pellets). In terms of feasibility for the manufacturer, these dosage forms can be manufactured from standard excipients including those that are pre-mixed and suitable for a range of actives, and they have potential flexibility for constructing appropriate fixed-dose combinations (FDCs).
4. Techniques for "difficult molecules" (defined using BCS classes) need to be developed or evaluated including manipulation (e.g. spray drying, micronization) prior to use with some platform that may produce suitable dosage forms for children.
5. As an alternative to injections in severely ill children or children unable to swallow, the use of rectal preparations for indications of severe malaria, pain and infection may be appropriate. Rectal preparations of analgesics exist but would need to be assessed for suitability for hot climates. There may be potential value in the development of some antibiotics as rectal preparations but not all would be suitable for this approach because of erratic bioavailability and/or cultural barriers.
6. Patch or transdermal drug delivery technology may be of use for medicines requiring constant plasma concentrations, but needs to be evaluated further. On the one hand, the technology is likely to remain comparatively expensive, and may not be appropriate for all climates, but there may be unpublished data available to facilitate their assessment and a full evaluation is warranted. It is important that patches are not cut, as this may alter release characteristics.
7. Inhalational administration of substances is necessary for treatment of asthma and chronic lung disease, and has been evaluated for delivery of other molecules. There is a need for development of affordable and standardized devices for administration, although it is recognized that the technology may be complex.
8. Medicines for the treatment of respiratory distress in neonates are available, but in the case of surfactants are expensive and difficult to deliver. New approaches to delivering this product are needed.
9. Other less invasive methods of delivering medicines to children have been developed (e.g. buccal and nasal) but at present the technologies are either not generally affordable or are unavailable. Further study is warranted.

10. Researchers should ensure that full details on any new dosage forms used in paediatric clinical studies are included in publications. A centralized accessible database containing details of published work on paediatric medicines and of where high-quality medicines in appropriate dosage forms are available, should be established.

Research needs

The following research needs were identified:

1. What particle sizes can be comfortably and safely ingested by children at different ages and developmental stages? (This aspect should be looked at from the perspective of both acute and chronic diseases.)
2. To optimize the acceptability of dosage forms, what standards should be set for "granularity" (i.e. the size of the components of the medicine) and "texture" or "mouth feel" (i.e. the "'feeling" of a liquid, semi-solid or suspension in the mouth), taste and smell, at different ages and developmental stages:
   - for the products commonly used for priority diseases?
   - for other products (by BCS class)?
3. What are appropriate standards for palatability testing (where needed) in children, and how should it be done?
4. What evidence exists to define optimal frequency of dosing (and pill burden) in terms of impact on adherence and clinical outcomes? (Consider treatment in diseases requiring both chronic and acute care.)
5. What are the true component costs of different dosage forms of medicines for children?
6. What might be effective strategies for implementing programmes that introduce dispersible tablets or other new forms? For example, experiences with zinc, cotrimoxazole — including the importance of policy advocacy.
7. What can be done to standardize and disseminate information on methods for the manipulation of authorized dosage forms (extemporaneous preparation versus manipulation prior to administration) in children?
8. What is the best method of providing information for health workers and carers, related to the optimal administration of medicines to children (e.g. pictograms or auditory messages).
9. What can be done to develop a micro-coating that is absorbable, dissolvable, and immune to degradation by chewing, and environmental or delivery-vehicle temperature changes?

Next steps and outstanding issues

The recommendations from this technical meeting were to be published on the Expert Committee meeting web site, reviewed by representatives

from industry, academia and end-users in the public and private sector, and discussed at the next meeting of the Expert Committee in March 2009. The literature reviews would be further developed and submitted for publication. Additional information will be sought from other potential resources such as the food industry and the over-the-counter medicine industry, which may be able to provide relevant input on aspects of the development of paediatric dosage forms, such as palatability and patient preference.

Promotion of the need for the preferred dosage forms is required. Pharmaceutical companies interested in the manufacture of these dosage forms need to be identified. Health-care workers and carers of children need to expect "preferred dosage forms".

In order to address the urgent and outstanding research needs identified above, strengthening the quality and quantity of paediatric clinical trials research is essential. A Clinical Trial Registry Platform has been created in order to improve the profile, quality and monitoring of paediatric clinical trials. In addition to this, the panel emphasized the need for continued advocacy in the area of children's medicines, particularly with the creation of market demand through prescribers and patients.

It is acknowledged that the recommendations currently being put forward are not fixed, and that depending on the degree and speed of further technological development, they will probably require revision in future years.

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Annex 1
The 16th WHO Model List of Essential Medicines

Explanatory Notes

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

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

The square box symbol (□) is primarily intended to indicate similar clinical performance within a pharmacological class. The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. Not all square boxes are applicable to medicine selection for children — see the second EMLc for details.

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

The [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.

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 web site: http://www.who.int/medicines/areas/quality_assurance/en/index.html.

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 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/en/index.html.

1. ANAESTHETICS

1.1 General anaesthetics and oxygen

□ halothane	Inhalation.
ketamine	Injection: 50 mg (as hydrochloride)/ml in 10-ml vial.
nitrous oxide	Inhalation.
oxygen	Inhalation (medicinal gas).
□ thiopental	Powder for injection: 0.5 g; 1 g (sodium salt) in ampoule.

1.2 Local anaesthetics

□ bupivacaine	Injection: 0.25%; 0.5% (hydrochloride) in vial. Injection for spinal anaesthesia: 0.5% (hydrochloride) in 4-ml ampoule to be mixed with 7.5% glucose solution.
□ lidocaine	Injection: 1%; 2% (hydrochloride) in vial. Injection for spinal anaesthesia: 5% (hydrochloride) in 2-ml ampoule to be mixed with 7.5% glucose solution. Topical forms: 2% to 4% (hydrochloride).
lidocaine + epinephrine (adrenaline)	Dental cartridge: 2% (hydrochloride) + epinephrine 1:80 000. Injection: 1%; 2% (hydrochloride) + epinephrine 1:200 000 in vial.
Complementary List	
ephedrine	Injection: *30 mg (hydrochloride)/ml in 1-ml ampoule.* *(For use in spinal anaesthesia during delivery, to prevent hypotension).*

1.3 Preoperative medication and sedation for short-term procedures

atropine	Injection: 1 mg (sulfate) in 1-ml ampoule.
□ diazepam	Injection: 5 mg/ml in 2-ml ampoule. Tablet: 5 mg.
morphine	Injection: 10 mg (sulfate or hydrochloride) in 1-ml ampoule.
promethazine	Oral liquid: 5 mg (hydrochloride)/5 ml.

2. ANALGESICS, ANTIPYRETICS, NON-STEROIDAL ANTI-INFLAMMATORY MEDICINES (NSAIMs), MEDICINES USED TO TREAT GOUT AND DISEASE MODIFYING AGENTS IN RHEUMATOID DISORDERS (DMARDs)

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

acetylsalicylic acid	Suppository: 50 mg to 150 mg. Tablet: 100 mg to 500 mg.
ibuprofen[a]	Tablet: 200 mg; 400 mg. [a]>3 months.
paracetamol*	Oral liquid: 125 mg/5 ml. Suppository: 100 mg. Tablet: 100 mg to 500 mg. * Not recommended for anti-inflammatory use due to lack of proven benefit to that effect.
Complementary List [c]	
*acetylsalicylic acid**	Suppository: *50 mg to 150 mg.* Tablet: *100 mg to 500 mg.* * *For use for rheumatic fever, juvenile arthritis, Kawasaki disease.*

2.2 Opioid analgesics

codeine	Tablet: 15 mg (phosphate) [c]; 30 mg (phosphate).
morphine	Injection: 10 mg (morphine hydrochloride or morphine sulfate) in 1-ml ampoule. Oral liquid: 10 mg (morphine hydrochloride or morphine sulfate)/5 ml. Tablet: 10 mg (morphine sulfate). Tablet (prolonged release): 10 mg; 30 mg; 60 mg (morphine sulfate).

2.3 Medicines used to treat gout

allopurinol	Tablet: 100 mg.

2.4 Disease modifying agents used in rheumatoid disorders (DMARDs)

chloroquine	Tablet: 100 mg; 150 mg (as phosphate or sulfate).
Complementary List	
azathioprine	Tablet: *50 mg.*
methotrexate	Tablet: *2.5 mg (as sodium salt).*
penicillamine	Solid oral dosage form: *250 mg.*
sulfasalazine	Tablet: *500 mg.*

3. ANTIALLERGICS AND MEDICINES USED IN ANAPHYLAXIS

☐ chlorphenamine[a]	Injection: 10 mg (hydrogen maleate) in 1-ml ampoule. Oral liquid: 2 mg/5 ml [c]. Tablet: 4 mg (hydrogen maleate). [a]>1 year.
dexamethasone	Injection: 4 mg dexamethasone phosphate (as disodium salt) in 1-ml ampoule.
epinephrine (adrenaline)	Injection: 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule.
hydrocortisone	Powder for injection: 100 mg (as sodium succinate) in vial.
☐ prednisolone	Oral liquid: 5 mg/ml [c]. Tablet: 5 mg; 25 mg.

4. ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS

4.1 Non-specific

charcoal, activated	Powder.

4.2 Specific

acetylcysteine	Injection: 200 mg/ml in 10-ml ampoule. Oral liquid: 10% [c]; 20% [c].
atropine	Injection: 1 mg (sulfate) in 1-ml ampoule.
calcium gluconate	Injection: 100 mg/ml in 10-ml ampoule.
deferoxamine	Powder for injection: 500 mg (mesilate) in vial.
dimercaprol	Injection in oil: 50 mg/ml in 2-ml ampoule.
DL-methionine*	Tablet: 250 mg. * Will be reviewed for possible deletion.
methylthioninium chloride (methylene blue)	Injection: 10 mg/ml in 10-ml ampoule.
naloxone	Injection: 400 micrograms (hydrochloride) in 1-ml ampoule.
penicillamine	Solid oral dosage form: 250 mg.
potassium ferric hexacyano-ferrate(II) - $2H_20$ (Prussian blue)	Powder for oral administration.
sodium calcium edetate	Injection: 200 mg/ml in 5-ml ampoule.
sodium nitrite	Injection: 30 mg/ml in 10-ml ampoule.
sodium thiosulfate	Injection: 250 mg/ml in 50-ml ampoule.

5. ANTICONVULSANTS/ANTIEPILEPTICS

carbamazepine	Oral liquid: 100 mg/5 ml. Tablet (chewable): 100 mg; 200 mg. Tablet (scored): 100 mg; 200 mg.
diazepam	Gel or rectal solution: 5 mg/ml in 0.5 ml; 2-ml and 4-ml tubes.
□ lorazepam	Parenteral formulation: 2 mg/ml in 1-ml ampoule; 4 mg/ml in 1-ml ampoule.
magnesium sulfate*	Injection: 500 mg/ml in 2-ml ampoule; 500 mg/ml in 10-ml ampoule. * For use in eclampsia and severe pre-eclampsia and not for other convulsant disorders.
phenobarbital	Injection: 200 mg/ml (phenobarbital sodium). Oral liquid: 15 mg/5 ml (phenobarbital). Tablet: 15 mg to 100 mg (phenobarbital).
phenytoin	Capsule: 25 mg; 50 mg; 100 mg (sodium salt). Injection: 50 mg/ml in 5-ml vial (sodium salt). Oral liquid: 25 mg to 30 mg/5 ml.* Tablet: 25 mg; 50 mg; 100 mg (sodium salt). Tablet (chewable): 50 mg. * The presence of both 25 mg/5 ml and 30 mg/5 ml strengths on the same market would cause confusion in prescribing and dispensing and should be avoided.
valproic acid (sodium valproate)	Oral liquid: 200 mg/5 ml. Tablet (crushable): 100 mg. Tablet (enteric-coated): 200 mg; 500 mg (sodium valproate).
Complementary List	
ethosuximide	Capsule: *250 mg.* Oral liquid: *250 mg/5 ml.*

6. ANTI-INFECTIVE MEDICINES

6.1 Anthelminthics

6.1.1 *Intestinal anthelminthics*

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

pyrantel	Oral liquid: 50 mg (as embonate)/ml. Tablet (chewable): 250 mg (as embonate).
6.1.2 *Antifilarials*	
ivermectin	Tablet (scored): 3 mg; 6 mg.
Complementary List	
diethylcarbamazine	Tablet: *50 mg; 100 mg (dihydrogen citrate).*
*suramin sodium**	Powder for injection: *1 g in vial.* ** Will be reviewed for possible deletion.*
6.1.3 *Antischistosomals and antitrematode 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 (anhydrous)/5 ml; 250 mg (anhydrous)/5 ml [c]. Solid oral dosage form: 250 mg; 500 mg (anhydrous).
amoxicillin + clavulanic acid	Oral liquid: 125 mg amoxicillin + 31.25 mg clavulanic acid/5 ml AND 250 mg amoxicillin + 62.5 mg clavulanic acid/5 ml [c]. Tablet: 500 mg + 125 mg.
ampicillin	Powder for injection: 500 mg; 1 g (as sodium salt) in vial.
benzathine benzylpenicillin	Powder for injection: 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	Powder for injection: 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial.
cefalexin [c]	Powder for reconstitution with water: 125 mg/5 ml; 250 mg/5 ml. Solid oral dosage form: 250 mg.

☐ cefazolin* [a]	Powder for injection: 1 g (as sodium salt) in vial. * For surgical prophylaxis. [a] >1 month.
cefixime*	Capsule: 400 mg. * Only listed for single-dose treatment of uncomplicated ano-genital gonorrhoea.
ceftriaxone* [a]	Powder for injection: 250 mg; 1 g (as sodium salt) in vial. * Do not administer with calcium and avoid in infants with hyperbilirubinemia. [a] >41 weeks corrected gestational age.
☐ cloxacillin	Capsule: 500 mg; 1 g (as sodium salt). Powder for injection: 500 mg (as sodium salt) in vial. Powder for oral liquid: 125 mg (as sodium salt)/5 ml.
phenoxymethylpenicillin	Powder for oral liquid: 250 mg (as potassium salt)/5 ml. Tablet: 250 mg (as potassium salt).
procaine benzylpenicillin*	Powder for injection: 1 g (=1 million IU); 3 g (=3 million IU) in vial. * 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]	Powder for injection: *250 mg per vial.* * *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. 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 [c]. Solution for IV infusion: 2 mg/ml [c]. Tablet: 250 mg (as hydrochloride).
doxycycline [a]	Oral liquid: 25 mg/5 ml [c]; 50 mg/5 ml [c]. Solid oral dosage form: 50 mg [c]; 100 mg (hydrochloride). [a] Use in children <8 years only for life-threatening infections when no alternative exists.
☐ erythromycin	Powder for injection: 500 mg (as lactobionate) in vial. Powder for oral liquid: 125 mg/5 ml (as stearate or ethyl succinate). Solid oral dosage form: 250 mg (as stearate or ethyl succinate).
☐ gentamicin	Injection: 10 mg; 40 mg (as sulfate)/ml in 2-ml vial.
☐ metronidazole	Injection: 500 mg in 100-ml vial. Oral liquid: 200 mg (as benzoate)/5 ml. Suppository: 500 mg; 1 g. Tablet: 200 mg to 500 mg.
nitrofurantoin	Oral liquid: 25 mg/5 ml [c]. Tablet: 100 mg.
spectinomycin	Powder for injection: 2 g (as hydrochloride) in vial.
sulfamethoxazole + trimethoprim	Injection: 80 mg + 16 mg/ml in 5-ml ampoule; 80 mg + 16 mg/ml in 10-ml ampoule. Oral liquid: 200 mg + 40 mg/5 ml. Tablet: 100 mg + 20 mg; 400 mg + 80 mg.
trimethoprim [a]	Oral liquid: 50 mg/5 ml [c]. Tablet: 100 mg; 200 mg. [a] >6 months.
Complementary List	
clindamycin	Capsule: *150 mg.* Injection: *150 mg (as phosphate)/ml.* Oral liquid: *75 mg/5 ml* [c].
vancomycin	Powder for injection: *250 mg (as hydrochloride) in vial.*

6.2.3 *Antileprosy medicines*

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

clofazimine	Capsule: 50 mg; 100 mg.
dapsone	Tablet: 25 mg; 50 mg; 100 mg.
rifampicin	Solid oral dosage form: 150 mg; 300 mg.

6.2.4 *Antituberculosis medicines*

ethambutol	Oral liquid: 25 mg/ml [c]. Tablet: 100 mg to 400 mg (hydrochloride).
ethambutol + isoniazid	Tablet: 400 mg + 150 mg.
ethambutol + isoniazid + pyrazinamide + rifampicin	Tablet: 275 mg + 75 mg + 400 mg + 150 mg.
ethambutol + isoniazid + rifampicin	Tablet: 275 mg + 75 mg + 150 mg.
isoniazid	Oral liquid: 50 mg/5 ml [c]. Tablet: 100 mg to 300 mg. Tablet (scored): 50 mg.
isoniazid + pyrazinamide + rifampicin	Tablet: 75 mg + 400 mg + 150 mg. 150 mg + 500 mg + 150 mg **(For intermittent use three times weekly)**.
isoniazid + rifampicin	Tablet: 75 mg + 150 mg; 150 mg + 300 mg. 60 mg + 60 mg **(For intermittent use three times weekly)**. 150 mg + 150 mg **(For intermittent use three times weekly)**.
pyrazinamide	Oral liquid: 30 mg/ml [c]. Tablet: 400 mg. Tablet (dispersible): 150 mg. Tablet (scored): 150 mg.
rifabutin	Capsule: 150 mg.* * For use only in patients with HIV receiving protease inhibitors.
rifampicin	Oral liquid: 20 mg/ml [c]. Solid oral dosage form: 150 mg; 300 mg.
streptomycin	Powder for injection: 1 g (as sulfate) in vial.

Complementary List

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

amikacin	Powder for injection: *100 mg; 500 mg; 1 g in vial.*
capreomycin	Powder for injection: *1 g in vial.*
cycloserine	Solid oral dosage form: *250 mg.*
ethionamide	Tablet: *125 mg; 250 mg.*
kanamycin	Powder for injection: *1 g in vial.*
*ofloxacin**	Tablet: *200 mg; 400 mg.* ** Levofloxacin may be an alternative based on availability and programme considerations.*
p-aminosalicylic acid	Granules: *4 g in sachet.* Tablet: *500 mg.*

6.3 Antifungal medicines

clotrimazole	Vaginal cream: 1%; 10%. Vaginal tablet: 100 mg; 500 mg.
□ fluconazole	Capsule: 50 mg. Injection: 2 mg/ml in vial. Oral liquid: 50 mg/5 ml.
griseofulvin	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.

Complementary List

amphotericin B	Powder for injection: *50 mg in vial.* *As deoxycholate or liposomal.*
flucytosine	Capsule: *250 mg.* Infusion: *2.5 g in 250 ml.*
potassium iodide	Saturated solution.

6.4 Antiviral medicines

6.4.1 *Antiherpes medicines*

□ aciclovir	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). The Committee emphasizes the importance of using these products in accordance with global and national guidelines. The Committee recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.
Scored tablets can be used in children and therefore can be considered for inclusion in the listing of tablets, provided adequate quality products are available.

6.4.2.1 *Nucleoside/Nucleotide reverse transcriptase inhibitor*s

abacavir (ABC)	Oral liquid: 100 mg (as sulfate)/5 ml. Tablet: 300 mg (as sulfate).
didanosine (ddI)	Buffered powder for oral liquid: 100 mg; 167 mg; 250 mg packets. Capsule (unbuffered enteric-coated): 125 mg; 200 mg; 250 mg; 400 mg. Tablet (buffered chewable, dispersible): 25 mg; 50 mg; 100 mg; 150 mg; 200 mg.
emtricitabine (FTC)* [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.
stavudine (d4T)	Capsule: 15 mg; 20 mg; 30 mg. Powder for oral liquid: 5 mg/5 ml.
tenofovir disoproxil fumarate (TDF)	Tablet: 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil).
zidovudine (ZDV or AZT)	Capsule: 100 mg; 250 mg. Oral liquid: 50 mg/5 ml. Solution for IV infusion injection: 10 mg/ml in 20-ml vial. Tablet: 300 mg.

6.4.2.2 *Non-nucleoside reverse transcriptase inhibitors*

efavirenz (EFV or EFZ) [a]	Capsule: 50 mg; 100 mg; 200 mg. Oral liquid: 150 mg/5 ml. Tablet: 600 mg. [a] >3 years or >10 kg weight.
nevirapine (NVP)	Oral liquid: 50 mg/5 ml. Tablet: 200 mg.

6.4.2.3 Protease inhibitors

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

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

FIXED-DOSE COMBINATIONS

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

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 only.

6.5 Antiprotozoal medicines

6.5.1 *Antiamoebic and antigiardiasis medicines*

diloxanide [a]	Tablet: 500 mg (furoate). [a] >25 kg.
□ metronidazole	Injection: 500 mg in 100-ml vial. Oral liquid: 200 mg (as benzoate)/5 ml. Tablet: 200 mg to 500 mg.

6.5.2 *Antileishmaniasis medicines*

amphotericin B	Powder for injection: 50 mg in vial. As deoxycholate or liposomal.
paromomycin	Solution for intramuscular injection: 750 mg of paromomycin base present as the sulfate.
sodium stibogluconate or meglumine antimoniate	Injection: 100 mg/ml, 1 vial = 30 ml or 30%, equivalent to approximately 8.1% antimony 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. The Committee recognizes that not all of these FDCs exist and encourages their development and rigorous testing. The Committee also encourages development and testing of rectal dosage formulations.

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

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

6.5.3.2 For prophylaxis

chloroquine*	Oral liquid: 50 mg (as phosphate or sulfate)/5 ml. Tablet: 150 mg (as phosphate or sulfate). * For use only in central American regions, for use for *P.vivax*.
doxycycline [a]	Solid oral dosage form: 100 mg (as hydrochloride). [a] >8 years.
mefloquine [a]	Tablet: 250 mg (as hydrochloride). [a] >5 kg or >3 months.
proguanil*	Tablet: 100 mg (as hydrochloride). * For use only in combination with chloroquine.

6.5.4 *Antipneumocystosis and antitoxoplasmosis medicines*

pyrimethamine	Tablet: 25 mg.
sulfadiazine	Tablet: 500 mg.
sulfamethoxazole + trimethoprim	Injection: 80 mg + 16 mg/ml in 5-ml ampoule; 80 mg + 16 mg/ml in 10-ml ampoule. Oral liquid: 200 mg + 40 mg/5 ml [c]. Tablet: 100 mg + 20 mg; 400 mg + 80 mg [c].

6. ANTI-INFECTIVE MEDICINES *(continued)*

Complementary List

pentamidine	Tablet: *200 mg; 300 mg.*

6.5.5 *Antitrypanosomal medicines*

6.5.5.1 African trypanosomiasis

Medicines for the treatment of 1st stage African trypanosomiasis

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

Medicines for the treatment of 2nd stage African trypanosomiasis

eflornithine*	Injection: 200 mg (hydrochloride)/ml in 100-ml bottle. * To be used for the treatment of *Trypanosoma brucei gambiense* infection.
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.

6.5.5.2 American trypanosomiasis

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

7. ANTIMIGRAINE MEDICINES

7.1 For treatment of acute attack

acetylsalicylic acid	Tablet: 300 mg to 500 mg.
ibuprofen ©	Tablet: 200 mg; 400 mg.
paracetamol	Oral liquid: 125 mg/5 ml ©. Tablet: 300 mg to 500 mg.

7.2 For prophylaxis

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

8. ANTINEOPLASTIC, IMMUNOSUPPRESSIVES AND MEDICINES USED IN PALLIATIVE CARE

8.1 Immunosuppressive medicines

Complementary List

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

8.2 Cytotoxic medicines

Complementary List

allopurinol [cj]	Tablet: *100 mg to 300 mg.*
asparaginase	Powder for injection: *10 000 IU in vial.*
bleomycin	Powder for injection: *15 mg (as sulfate) in vial.*
calcium folinate	Injection: *3 mg/ml in 10-ml ampoule.* Tablet: *15 mg.*
☐ *carboplatin*	Injection: *50 mg/5 ml; 150 mg/15 ml; 450 mg/45 ml; 600 mg/60 ml.*
chlorambucil	Tablet: *2 mg.*
cyclophosphamide	Powder for injection: *500 mg in vial.* Tablet: *25 mg.*
cytarabine	Powder for injection: *100 mg in vial.*
dacarbazine	Powder for injection: *100 mg in vial.*
dactinomycin	Powder for injection: *500 micrograms in vial.*
daunorubicin	Powder for injection: *50 mg (as hydrochloride) in vial.*
doxorubicin	Powder for injection: *10 mg; 50 mg (hydrochloride) in vial.*
etoposide	Capsule: *100 mg.* Injection: *20 mg/ml in 5-ml ampoule.*
fluorouracil	Injection: *50 mg/ml in 5-ml ampoule.*
hydroxycarbamide	Solid oral dosage form: *200 mg; 250 mg; 300 mg; 400 mg; 500 mg; 1 g.*
ifosfamide	Powder for injection: *1 g vial; 2 g vial.*
mercaptopurine	Tablet: *50 mg.*

8. ANTINEOPLASTIC, IMMUNOSUPPRESSIVES AND MEDICINES USED IN PALLIATIVE CARE *(continued)*

mesna	Injection: *100 mg/ml in 4-ml and 10-ml ampoules.* Tablet: *400 mg; 600 mg.*
methotrexate	Powder for injection: *50 mg (as sodium salt) in vial.* Tablet: *2.5 mg (as sodium salt).*
procarbazine	Capsule: *50 mg (as hydrochloride).*
vinblastine	Powder for injection: *10 mg (sulfate) in vial.*
vincristine	Powder for injection: *1 mg; 5 mg (sulfate) in vial.*

8.3 Hormones and antihormones

Complementary List

dexamethasone	Injection: *4 mg dexamethasone phosphate (as disodium salt) in 1-ml ampoule.* Oral liquid*: 2 mg/5 ml* [c].
hydrocortisone	Powder for injection: *100 mg (as sodium succinate) in vial.*
□ *prednisolone*	Oral liquid: *5 mg/ml* [c]. Tablet: *5 mg; 25 mg.*
tamoxifen	Tablet: *10 mg; 20 mg (as citrate).*

8.4 Medicines used in palliative care

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

9. ANTIPARKINSONISM MEDICINES

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

10. MEDICINES AFFECTING THE BLOOD

10.1 Antianaemia medicines

ferrous salt	Oral liquid: equivalent to 25 mg iron (as sulfate)/ml. Tablet: equivalent to 60 mg iron.

10. MEDICINES AFFECTING THE BLOOD *(continued)*

ferrous salt + folic acid	Tablet equivalent to 60 mg iron + 400 micrograms folic acid (Nutritional supplement for use during pregnancy).
folic acid	Tablet: 1 mg; 5 mg.
hydroxocobalamin	Injection: 1 mg in 1-ml ampoule.

10.2 Medicines affecting coagulation

heparin sodium	Injection: 1000 IU/ml; 5000 IU/ml; 20 000 IU/ml in 1-ml ampoule.
phytomenadione	Injection: 1 mg/ml [c]; 10 mg/ml in 5-ml ampoule. Tablet: 10 mg.
protamine sulfate	Injection: 10 mg/ml in 5-ml ampoule.
□ warfarin	Tablet: 1 mg; 2 mg; 5 mg (sodium salt).
Complementary List [c]	
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).*

11. BLOOD PRODUCTS AND PLASMA SUBSTITUTES

11.1 Plasma substitutes

□ dextran 70*	Injectable solution: 6%. * Polygeline, injectable solution, 3.5% is considered as equivalent.

11.2 Plasma fractions for specific use

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

Complementary List

□ *factor VIII concentrate*	Dried.
□ *factor IX complex (coagulation factors II, VII, IX, X) concentrate*	Dried.
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.*

12. CARDIOVASCULAR MEDICINES

12.1 Antianginal medicines

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

12.2 Antiarrhythmic medicines

□ atenolol	Tablet: 50 mg; 100 mg.
digoxin	Injection: 250 micrograms/ml in 2-ml ampoule. Oral liquid: 50 micrograms/ml. Tablet: 62.5 micrograms; 250 micrograms.
epinephrine (adrenaline)	Injection: 100 micrograms/ml (as acid tartrate or hydrochloride) in 10-ml ampoule.
lidocaine	Injection: 20 mg (hydrochloride)/ml in 5-ml ampoule.
verapamil	Injection: 2.5 mg (hydrochloride)/ml in 2-ml ampoule. Tablet: 40 mg; 80 mg (hydrochloride).
Complementary List	
amiodarone	Injection: *50 mg/ml in 3-ml ampoule (hydrochloride).* Tablet (HCl): *100 mg; 200 mg; 400 mg (hydrochloride).*

12.3 Antihypertensive medicines

□ amlodipine	Tablet: 5 mg.
□ atenolol	Tablet: 50 mg; 100 mg.
□ enalapril	Tablet: 2.5 mg; 5 mg.
hydralazine*	Powder for injection: 20 mg (hydrochloride) in ampoule. Tablet: 25 mg; 50 mg (hydrochloride). * Hydralazine is listed for use in the acute management of severe pregnancy-induced hypertension only. Its use in the treatment of essential hypertension is not recommended in view of the availability of more evidence of efficacy and safety of other medicines.
□ hydrochlorothiazide	Oral liquid: 50 mg/5 ml. Solid oral dosage form: 12.5 mg; 25 mg.

12. CARDIOVASCULAR MEDICINES *(continued)*

methyldopa*	Tablet: 250 mg. * Methyldopa is listed for use in the management of pregnancy-induced hypertension only. Its use in the treatment of essential hypertension is not recommended in view of the availability of more evidence of efficacy and safety of other medicines.
Complementary List	
sodium nitroprusside	Powder for infusion: *50 mg in ampoule.*

12.4 Medicines used in heart failure

digoxin	Injection: 250 micrograms/ml in 2-ml ampoule. Oral liquid: 50 micrograms/ml. Tablet: 62.5 micrograms; 250 micrograms.
☐ enalapril	Tablet: 2.5 mg; 5 mg.
☐ furosemide	Injection: 10 mg/ml in 2-ml ampoule. Oral liquid: 20 mg/5 ml [C]. Tablet: 40 mg.
☐ hydrochlorothiazide	Oral liquid: 50 mg/5 ml. Solid oral dosage form: 25 mg.
Complementary List	
dopamine	Injection: *40 mg/ml (hydrochloride) in 5-ml vial.*

12.5 Antithrombotic medicines

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

12.6 Lipid-lowering agents

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

13. DERMATOLOGICAL MEDICINES (topical)

13.1 Antifungal medicines

benzoic acid + salicylic acid	Cream or ointment: 6% + 3%.
☐ miconazole	Cream or ointment: 2% (nitrate).
sodium thiosulfate	Solution: 15%.
Complementary List	
selenium sulfide	Detergent-based suspension: *2%.*

13. DERMATOLOGICAL MEDICINES (topical) *(continued)*

13.2 Anti-infective medicines

☐ methylrosanilinium chloride (gentian violet)	Aqueous solution: 0.5%. Tincture: 0.5%.
neomycin sulfate + ☐ bacitracin	Ointment: 5 mg neomycin sulfate + 250 IU bacitracin zinc/g.
potassium permanganate	Aqueous solution: 1:10 000.
silver sulfadiazine [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	Lotion.
☐ hydrocortisone	Cream or ointment: 1% (acetate).

13.4 Astringent medicines

aluminium diacetate	Solution: 5%.

13.5 Medicines affecting skin differentiation and proliferation

benzoyl peroxide	Cream or lotion: 5%.
coal tar	Solution: 5%.
dithranol	Ointment: 0.1% to 2%.
fluorouracil	Ointment: 5%.
☐ podophyllum resin	Solution: 10% to 25%.
salicylic acid	Solution: 5%.
urea	Cream or ointment: 10%.

13.6 *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. DIAGNOSTIC AGENTS *(continued)*

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.
Complementary List	
barium sulfate [c]	Aqueous suspension.
☐ *meglumine iotroxate*	Solution: *5g to 8 g iodine in 100 ml to 250 ml.*

15. DISINFECTANTS AND ANTISEPTICS

15.1 Antiseptics

☐ chlorhexidine	Solution: 5% (digluconate); 20% (digluconate) (needs to be diluted prior to use for cord care) [c].
☐ ethanol	Solution: 70% (denatured).
☐ polyvidone iodine	Solution: 10%.

15.2 Disinfectants

☐ chlorine base compound	Powder: (0.1% available chlorine) for solution.
☐ chloroxylenol	Solution: 4.8%.
glutaral	Solution: 2%.

16. DIURETICS

amiloride	Tablet: 5 mg (hydrochloride).
☐ furosemide	Injection: 10 mg/ml in 2-ml ampoule. Oral liquid: 20 mg/5 ml [c]. Tablet: 10 mg [c]; 20 mg [c]; 40 mg.
☐ hydrochlorothiazide	Solid oral dosage form: 25 mg.
mannitol	Injectable solution: 10%; 20%.
spironolactone	Tablet: 25 mg.
Complementary List [c]	
☐ *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 tc

□ *pancreatic enzymes*	*Age-appropriate formulations and doses including lipase, protease and amylase.*

17.1 Antacids and other antiulcer medicines

aluminium hydroxide	Oral liquid: 320 mg/5 ml. Tablet: 500 mg.
magnesium hydroxide	Oral liquid: equivalent to 550 mg magnesium oxide/10 ml.
□ 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 in 2-ml ampoule. Oral liquid: 75 mg/5 ml. Tablet: 150 mg (as hydrochloride).

17.2 Antiemetic medicines

dexamethasone	Injection: 4 mg/ml in 1-ml ampoule. 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. 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	glucose: 75 mEq sodium: 75 mEq or mmol/L chloride: 65 mEq or mmol/L potassium: 20 mEq or mmol/L citrate: 10 mmol/L osmolarity: 245 mOsm/L glucose: 13.5 g/L sodium chloride: 2.6 g/L potassium chloride: 1.5 g/L trisodium citrate dihydrate+: 2.9 g/L + trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/L. However, as the stability of this latter formulation is very poor under tropical conditions, it is only recommended when manufactured for immediate use. Powder for dilution in 200 ml; 500 ml; 1 L.

17.5.2 *Medicines for diarrhoea in children*

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

17.5.3 *Antidiarrhoeal (symptomatic) medicines in adults*

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

18. HORMONES, OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES

18.1 Adrenal hormones and synthetic substitutes

fludrocortisone	Tablet: 100 micrograms.
hydrocortisone	Tablet: 5 mg; 10 mg; 20 mg.

18.2 Androgens

Complementary List

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

18.3 Contraceptives

18.3.1 *Oral hormonal contraceptives*

☐ ethinylestradiol + ☐ levonorgestrel	Tablet: 30 micrograms + 150 micrograms.
☐ ethinylestradiol + ☐ norethisterone	Tablet: 35 micrograms + 1 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

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

18.5 Insulins and other antidiabetic agents

glibenclamide	Tablet: 2.5 mg; 5 mg.
insulin injection (soluble)	Injection: 40 IU/ml in 10-ml vial; 100 IU/ml in 10-ml vial.
intermediate-acting insulin	Injection: 40 IU/ml in 10-ml vial; 100 IU/ml in 10-ml vial (as compound insulin zinc suspension or isophane insulin).
metformin	Tablet: 500 mg (hydrochloride).
Complementary List C	
metformin	Tablet: *500 mg (hydrochloride).*

18.6 Ovulation inducers

Complementary List	
clomifene	Tablet: *50 mg (citrate).*

18. HORMONES, OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES *(continued)*

18.7 Progestogens

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

18.8 Thyroid hormones and antithyroid medicines

levothyroxine	Tablet: 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 (Revised 1985). WHO Expert Committee on Biological Standardization. Thirty-sixth report. (WHO Technical Report Series, No. 745, 1987, Annex 1).

tuberculin, purified protein derivative (PPD)	Injection.

19.2 Sera and immunoglobulins

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

anti-D immunoglobulin (human)	Injection: 250 micrograms in single-dose vial.
antitetanus immunoglobulin (human)	Injection: 500 IU in vial.
antivenom immunoglobulin*	Injection. * Exact type to be defined locally.

diphtheria antitoxin	Injection: 10 000 IU; 20 000 IU in vial.
□ rabies immunoglobulin	Injection: 150 IU/ml in vial.

19.3 Vaccines

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

BCG vaccine

cholera vaccine

diphtheria vaccine

hepatitis A vaccine

hepatitis B vaccine

Haemophilus influenzae type b vaccine

influenza vaccine

Japanese encephalitis vaccine

measles vaccine

meningococcal meningitis vaccine

mumps vaccine

pertussis vaccine

pneumococcal vaccine

poliomyelitis vaccine

rabies vaccine

rotavirus vaccine

rubella vaccine

tetanus vaccine

typhoid vaccine

varicella vaccine

yellow fever vaccine

20. MUSCLE RELAXANTS (PERIPHERALLY-ACTING) AND CHOLINESTERASE INHIBITORS

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

21. OPHTHALMOLOGICAL PREPARATIONS

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

21.1 Anti-infective agents

aciclovir	Ointment: 3% W/W.
☐ gentamicin	Solution (eye drops): 0.3% (sulfate).
☐ tetracycline	Eye ointment: 1% (hydrochloride).

21.2 Anti-inflammatory agents

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

21.3 Local anaesthetics

☐ tetracaine [a]	Solution (eye drops): 0.5% (hydrochloride). [a]Not in preterm neonates.

21.4 Miotics and antiglaucoma medicines

acetazolamide	Tablet: 250 mg.
☐ pilocarpine	Solution (eye drops): 2%; 4% (hydrochloride or nitrate).
☐ timolol	Solution (eye drops): 0.25%; 0.5% (as maleate).

21.5 Mydriatics

atropine* [a]	Solution (eye drops): 0.1%; 0.5%; 1% (sulfate). * [c] OR homatropine OR cyclopentolate. [a]>3 months.

21. OPHTHALMOLOGICAL PREPARATIONS *(continued)*

Complementary List

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

22. OXYTOCICS AND ANTIOXYTOCICS

22.1 Oxytocics

☐ ergometrine	Injection: 200 micrograms (hydrogen maleate) in 1-ml ampoule.
oxytocin	Injection: 10 IU in 1-ml ampoule.

Complementary List

misoprostol	Tablet: *200 micrograms.** ** For management of incomplete abortion and miscarriage.* Vaginal tablet: *25 micrograms.*
mifepristone – misoprostol** *Where permitted under national law and where culturally acceptable.*	Tablet *200 mg* – tablet *200 micrograms.* ** Requires close medical supervision.*

22.2 Antioxytocics (tocolytics)

nifedipine	Immediate-release capsule: 10 mg.

23. PERITONEAL DIALYSIS SOLUTION

Complementary List

intraperitoneal dialysis solution (of appropriate composition)	Parenteral solution.

24. PSYCHOTHERAPEUTIC MEDICINES

24.1 Medicines used in psychotic disorders

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

Complementary List [fc]

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*

☐ amitriptyline	Tablet: 25 mg (hydrochloride).
fluoxetine	Solid oral dosage form: 20 mg (present as hydrochloride).

Complementary List [fc]

fluoxetine [a]	Solid oral dosage form: *20 mg (present as hydrochloride).* [a] >8 years.

24.2.2 *Medicines used in bipolar disorders*

carbamazepine	Tablet (scored): 100 mg; 200 mg.
lithium carbonate	Solid oral dosage form: 300 mg.
valproic acid	Tablet (enteric-coated): 200 mg; 500 mg (sodium valproate).

24.3 Medicines used in generalized anxiety

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

24.4 Medicines used for obsessive compulsive disorders and panic attacks

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

24.5 Medicines used in substance dependence programmes

nicotine replacement therapy (NRT)	Chewing gum: 2 mg; 4 mg. Transdermal patch: 5 mg to 30 mg/16 hrs; 7 mg to 21 mg/24 hrs.

Complementary List

☐ *methadone**	Concentrate for oral liquid*: 5 mg/ml; 10 mg/ml (hydrochloride).* Oral liquid: *5 mg/5 ml; 10 mg/5 ml.*

** The square box is added to include buprenorphine. The medicines should only be used within an established support programme.*

25. MEDICINES ACTING ON THE RESPIRATORY TRACT

25.1 Antiasthmatic and medicines for chronic obstructive pulmonary disease

☐ beclometasone	Inhalation (aerosol): 50 micrograms (dipropionate) per dose; 100 micrograms (dipropionate) per dose (as CFC free forms).
☐ budesonide [c]	Inhalation (aerosol): 100 micrograms per dose; 200 micrograms per dose.
epinephrine (adrenaline)	Injection: 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule.
ipratropium bromide	Inhalation (aerosol): 20 micrograms/metered dose.
☐ salbutamol*	Inhalation (aerosol): 100 micrograms (as sulfate) per dose. Injection: 50 micrograms (as sulfate)/ml in 5-ml ampoule. Metered dose inhaler (aerosol): 100 micrograms (as sulfate) per dose. Oral liquid: 2 mg/5 ml. Respirator solution for use in nebulizers: 5 mg (as sulfate)/ml. Tablet: 2 mg; 4 mg (as sulfate). * Oral salbutamol treatment should only be considered when inhaled asthma therapy is not feasible.

26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID-BASE DISTURBANCES

26.1 Oral

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

26.2 Parenteral

glucose	Injectable solution: 5% (isotonic); 10% (hypertonic); 50% (hypertonic).
glucose with sodium chloride	Injectable solution: 4% glucose, 0.18% sodium chloride (equivalent to Na+ 30 mmol/L, Cl- 30 mmol/L). Injectable solution: 5% glucose, 0.9% sodium chloride (equivalent to 150 mmol/L Na+ and 150 mmol/L Cl-); 5% glucose, 0.45% sodium chloride (equivalent to 75 mmol/L Na+ and 75 mmol/L Cl-) [c].
potassium chloride	Solution: 11.2% in 20-ml ampoule (equivalent to K+ 1.5 mmol/ml, Cl- 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].

26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID-BASE DISTURBANCES *(continued)*	
sodium chloride	Injectable solution: 0.9% isotonic (equivalent to Na+ 154 mmol/L, Cl- 154 mmol/L).
sodium hydrogen carbonate	Injectable solution: 1.4% isotonic (equivalent to Na+ 167 mmol/L, HCO3- 167 mmol/L). Solution: 8.4% in 10-ml ampoule (equivalent to Na+ 1000 mmol/L, HCO3-1000 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.
cholecalciferol* [C]	Oral liquid: 400 IU/ml. Solid oral dosage form: 400 IU; 1000 IU. * Ergocalciferol can be used as an alternative.
□ ergocalciferol	Oral liquid: 250 micrograms/ml (10 000 IU/ml). Solid oral dosage form: 1.25 mg (50 000 IU).
iodine	Capsule: 200 mg. Iodized oil: 1 ml (480 mg iodine); 0.5 ml (240 mg iodine) in ampoule (oral or injectable); 0.57 ml (308 mg iodine) in dispenser bottle.
□ nicotinamide	Tablet: 50 mg.
pyridoxine	Tablet: 25 mg (hydrochloride).
retinol	Capsule: 50 000 IU; 100 000 IU; 200 000 IU (as palmitate). Oral oily solution: 100 000 IU (as palmitate)/ml in multidose dispenser. Tablet (sugar-coated): 10 000 IU (as palmitate). Water-miscible injection: 100 000 IU (as palmitate) in 2-ml ampoule.
riboflavin	Tablet: 5 mg.
sodium fluoride	In any appropriate topical formulation.
thiamine	Tablet: 50 mg (hydrochloride).
Complementary List	
calcium gluconate	Injection: *100 mg/ml in 10-ml ampoule.*
28. EAR, NOSE AND THROAT CONDITIONS IN CHILDREN [C]	
acetic acid	Topical: 2%, in alcohol.
□ budesonide	Nasal spray: 100 micrograms per dose.

28. EAR, NOSE AND THROAT CONDITIONS IN CHILDREN [c] *(continued)*

☐ ciprofloxacin	Topical: 0.3% drops.
☐ xylometazoline [a]	Nasal spray: 0.05%. [a]Not in children less than 3 months.

29. SPECIFIC MEDICINES FOR NEONATAL CARE [c]

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

Table 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
chlorphenamine	>1 year
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

Explanation of dosage forms

A. Principal dosage forms used in EML – Oral administration

Term	Definition
Solid oral dosage form	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. The term 'solid oral dosage form' is *never* intended to allow any type of modified-release tablet.
Tablets	Refers to: • uncoated or coated (film-coated or sugar-coated) tablets that are intended to be swallowed whole; • unscored and scored*; • tablets that are intended to be chewed before being swallowed; • tablets that are intended to be dispersed or dissolved in water or another suitable liquid before being swallowed; • tablets that are intended to be crushed before being swallowed. The term 'tablet' without qualification is *never* intended to allow any type of modified-release tablet.
Tablets (qualified)	Refers to a specific type of tablet: **chewable** – tablets that are intended to be chewed before being swallowed; **dispersible** – tablets that are intended to be dispersed in water or another suitable liquid before being swallowed; **soluble** – tablets that are intended to be dissolved in water or another suitable liquid before being swallowed; **crushable** – tablets that are intended to be crushed before being swallowed; **scored** – tablets bearing a break mark or marks where sub-division is intended in order to provide doses of less than one tablet; **sublingual** – tablets that are intended to be placed beneath the tongue. The term 'tablet' is *always* qualified with an additional term (in parentheses) in entries where one of the following types of tablet is intended: **gastro-resistant** (such tablets may sometimes be described as enteric-coated or as delayed-release), **prolonged-release** or another modified-release form.
Capsules	Refers to hard or soft capsules. The term ‹capsule› without qualification is *never* intended to allow any type of modified-release capsule.
Capsules (qualified)	The term ‹capsule› with qualification refers to **gastro-resistant** (such capsules may sometimes be described as enteric-coated or as delayed-release), **prolonged-release** or another modified-release form.

* Scored tablets may be divided for ease of swallowing, provided dose is a whole number of tablets.

Term	Definition
Granules	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 *never* intended to allow any type of modified-release granules.
Oral powder	Preparations that are issued to patient as powder (usually as single-dose) to be taken in or with water or another suitable liquid.
Oral liquid	Liquid preparations intended to be *swallowed* i.e. oral solutions, suspensions, emulsions and oral drops, including those constituted from powders or granules, but *not* those preparations intended for *oromucosal administration* 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 EML – Parenteral administration

Term	Definition
Injection	Refers to solutions, suspensions and emulsions including those constituted from powders or concentrated solutions.
Injection (qualified)	Route of administration is indicated in parentheses where relevant.
Injection (oily)	The term injection is qualified by (oily) in relevant entries.
Intravenous infusion	Refers to solutions and emulsions including those constituted from powders or concentrated solutions.

C. Other dosage forms

Mode of administration	Term to be used
To the eye	Eye drops, eye ointments.
Topical	For liquids: lotions, paints. For semi-solids: cream, ointment.
Rectal	Suppositories, gel or solution.
Vaginal	Pessaries or vaginal tablets.
Inhalation	Powder for inhalation, pressurized inhalation, nebulizer.

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Annex 2
The 2nd WHO Model List of Essential Medicines for Children

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

The format and numbering of the 16th 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.

In the List of Essential Medicines for Children, an additional symbol is used:

R indicates that the Subcommittee has endorsed the medicine as essential but has requested a review of the efficacy and safety to confirm this decision, or to expand use to additional age groups.

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/en/index.html

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 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 at: http://www.who.int/medicines/publications/pharmacopoeia/en/index.html.

1. ANAESTHETICS

1.1 General anaesthetics and oxygen

□ halothane R	Inhalation. R Review for alternative inhalational agents.
ketamine	Injection: 50 mg (as hydrochloride)/ml in 10-ml vial.
nitrous oxide	Inhalation.
oxygen	Inhalation (medicinal gas).
thiopental	Powder for injection: 0.5 g; 1 g (sodium salt) in ampoule.

1.2 Local anaesthetics

□ bupivacaine	Injection: 0.25%; 0.5% (hydrochloride) in vial. Injection for spinal anaesthesia: 0.5% (hydrochloride) in 4-ml ampoule to be mixed with 7.5% glucose solution.
□ lidocaine	Injection: 1%; 2% (hydrochloride) in vial. Injection for spinal anaesthesia: 5% (hydrochloride) in 2-ml ampoule to be mixed with 7.5% glucose solution. Topical forms: 2% to 4% (hydrochloride).
lidocaine + epinephrine (adrenaline)	Dental cartridge: 2% (hydrochloride) + epinephrine 1:80 000. Injection: 1%; 2% (hydrochloride) + epinephrine 1:200 000 in vial.

1.3 Preoperative medication and sedation for short-term procedures R

R Review of appropriate preoperative medication and sedation in children.

atropine	Injection: 1 mg (sulfate) in 1-ml ampoule.
□ diazepam	Injection: 5 mg/ml in 2-ml ampoule. Tablet: 5 mg.
morphine	Injection: 10 mg (sulfate or hydrochloride) in 1-ml ampoule.

2. ANALGESICS, ANTIPYRETICS, NON-STEROIDAL ANTI-INFLAMMATORY MEDICINES (NSAIMs), MEDICINES USED TO TREAT GOUT AND DISEASE MODIFYING AGENTS IN RHEUMATOID DISORDERS (DMARDs)

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

ibuprofen a R	Tablet: 200 mg; 400 mg. a >3 months. R Use in children, focusing on comparative analgesic and antipyretic efficacy and safety.

2. ANALGESICS, ANTIPYRETICS, NON-STEROIDAL ANTI-INFLAMMATORY MEDICINES (NSAIMs), MEDICINES USED TO TREAT GOUT AND DISEASE MODIFYING AGENTS IN RHEUMATOID DISORDERS (DMARDs) *(continued)*

paracetamol*	Oral liquid: 125 mg/5 ml. Suppository: 100 mg. Tablet: 100 mg to 500 mg. * Not recommended for anti-inflammatory use due to lack of proven benefit to that effect.
Complementary List	
*acetylsalicylic acid**	Suppository: *50 mg to 150 mg.* Tablet: *100 mg to 500 mg.* ** For use for rheumatic fever, juvenile arthritis, Kawasaki disease.*

2.2 Opioid analgesics

codeine	Tablet: 15 mg (phosphate).
morphine	Injection: 10 mg (morphine hydrochloride or morphine sulfate) in 1-ml ampoule. Oral liquid: 10 mg (morphine hydrochloride or morphine sulfate)/5 ml. Tablet: 10 mg (morphine sulfate). Tablet (prolonged release): 10 mg; 30 mg; 60 mg (morphine sulfate).

~~2.3 Medicines used to treat gout~~

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

R The Subcommittee noted that there is a need for medicines for the treatment of juvenile arthritis but did not endorse any of the currently listed medicines at this time, requesting a review of this section.

3. ANTIALLERGICS AND MEDICINES USED IN ANAPHYLAXIS

☐ chlorphenamine a R	Injection: 10 mg (hydrogen maleate) in 1-ml ampoule. Oral liquid: 2 mg/5 ml. Tablet: 4 mg (hydrogen maleate). a >1 year. R Review of diphenhydramine to assess comparative efficacy and safety with chlorphenamine as a possible preferable alternative.
dexamethasone	Injection: 4 mg dexamethasone phosphate (as disodium salt) in 1-ml ampoule.
epinephrine (adrenaline)	Injection: 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule.
hydrocortisone	Powder for injection: 100 mg (as sodium succinate) in vial.

3. ANTIALLERGICS AND MEDICINES USED IN ANAPHYLAXIS

□ prednisolone	Oral liquid: 5 mg/ml. Tablet: 5 mg; 25 mg.

4. ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS

4.1 Non-specific

charcoal, activated	Powder.

4.2 Specific

acetylcysteine	Injection: 200 mg/ml in 10-ml ampoule. Oral liquid: 10% and 20%.
atropine	Injection: 1 mg (sulfate) in 1-ml ampoule.
calcium gluconate	Injection: 100 mg/ml in 10-ml ampoule.
deferoxamine R	Powder for injection: 500 mg (mesilate) in vial. R Review use of oral iron and lead chelators in children.
dimercaprol	Injection in oil: 50 mg/ml in 2-ml ampoule.
naloxone	Injection: 400 micrograms (hydrochloride) in 1-ml ampoule.
penicillamine R	Solid oral dosage form: 250 mg. R Comparative effectiveness and safety versus sodium calcium edetate.
sodium calcium edetate R	Injection: 200 mg/ml in 5-ml ampoule. R Comparative effectiveness and safety versus penicillamine.

5. ANTICONVULSANTS/ANTIEPILEPTICS

carbamazepine	Oral liquid: 100 mg/5 ml. Tablet (chewable): 100 mg; 200 mg. Tablet (scored): 100 mg; 200 mg.
diazepam	Gel or rectal solution: 5 mg/ml in 0.5 ml; 2-ml and 4-ml tubes.
□ lorazepam	Parenteral formulation: 2 mg/ml in 1-ml ampoule; 4 mg/ml in 1-ml ampoule.
phenobarbital	Injection: 200 mg/ml (phenobarbital sodium). Oral liquid: 15 mg/5 ml (phenobarbital). Tablet: 15 mg to 100 mg (phenobarbital).

5. ANTICONVULSANTS/ANTIEPILEPTICS *(continued)*

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

6. ANTI-INFECTIVE MEDICINES

6.1 Anthelminthics R

R Review evidence of efficacy and safety of use of anthelminth/antifilarial/antischistosomal and antitrematode medicines in children below the specified age in current licences.

6.1.1 *Intestinal anthelminthics* R

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

6.1.2 *Antifilarials* R

ivermectin	Tablet (scored): 3 mg; 6 mg.
Complementary List	
diethylcarbamazine	Tablet: *50 mg; 100 mg (dihydrogen citrate).*

6.1.3 *Antischistosomals and antitrematode medicines* R

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 (anhydrous)/5 ml; 250 mg (anhydrous)/5 ml. Solid oral dosage form: 250 mg; 500 mg (anhydrous).
amoxicillin + clavulanic acid	Oral liquid: 125 mg amoxicillin + 31.25 mg clavulanic acid/5 ml AND 250 mg amoxicillin + 62.5 mg clavulanic acid/5 ml. Tablet: 500 mg + 125 mg.
ampicillin	Powder for injection: 500 mg; 1 g (as sodium salt) in vial.
benzathine benzylpenicillin	Powder for injection: 900 mg benzylpenicillin (=1.2 million IU) in 5-ml vial; 1.44 g benzylpenicillin (=2.4 million IU) in 5-ml vial.
benzylpenicillin	Powder for injection: 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial.
cefalexin	Powder for reconstitution with water: 125 mg/5 ml; 250 mg/5 ml. Solid oral dosage form: 250 mg.
☐ cefazolin* [a]	Powder for injection: 1 g (as sodium salt) in vial. * For surgical prophylaxis. [a] >1 month.
ceftriaxone* [a]	Powder for injection: 250 mg; 1 g (as sodium salt) in vial. * Do not administer with calcium and avoid in infants with hyperbilirubinemia. [a] >41 weeks corrected gestational age.
☐ cloxacillin	Capsule: 500 mg; 1 g (as sodium salt). Powder for injection: 500 mg (as sodium salt) in vial. Powder for oral liquid: 125 mg (as sodium salt)/5 ml.

phenoxymethylpenicillin	Powder for oral liquid: 250 mg (as potassium salt)/5 ml. Tablet: 250 mg (as potassium salt).
procaine benzylpenicillin*	Powder for injection: 1 g (=1 million IU); 3 g (=3 million IU) in vial. * 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**	Powder for injection: *250 mg per vial.* ** 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. Oral liquid: 200 mg/5 ml. * Only listed 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 R	Oral liquid: 250 mg/5 ml. Solution for IV infusion: 2 mg/ml. Tablet: 250 mg (as hydrochloride).

doxycycline R	Oral liquid: 25 mg/5 ml; 50 mg/5 ml. Solid oral dosage form: 50 mg; 100 mg (hydrochloride). 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 ethyl succinate). Solid oral dosage form: 250 mg (as stearate or ethyl succinate).
□ gentamicin	Injection: 10 mg; 40 mg (as sulfate)/ml in 2-ml vial.
metronidazole	Injection: 500 mg in 100-ml vial. Oral liquid: 200 mg (as benzoate)/5 ml. Tablet: 200 mg to 500 mg.
nitrofurantoin	Oral liquid: 25 mg/5 ml. Tablet: 100 mg.
sulfamethoxazole + trimethoprim	Injection: 80 mg + 16 mg/ml in 5-ml ampoule; 80 mg + 16 mg/ml in 10-ml ampoule. Oral liquid: 200 mg + 40 mg/5 ml. Tablet: 100 mg + 20 mg; 400 mg + 80 mg.
trimethoprim a	Oral liquid: 50 mg/5 ml. Tablet: 100 mg; 200 mg. a >6 months.
Complementary List	
clindamycin	Capsule: *150 mg.* Injection: *150 mg (as phosphate)/ml.* Oral liquid: *75 mg/5 ml.*
vancomycin	Powder for injection: *250 mg (as hydrochloride) in vial.*

6.2.3 *Antileprosy medicines*

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

clofazimine	Capsule: 50 mg; 100 mg.
dapsone	Tablet: 25 mg; 50 mg; 100 mg.
rifampicin	Solid oral dosage form: 150 mg; 300 mg.

6.2.4 *Antituberculosis medicines*

The Subcommittee 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	Oral liquid: 25 mg/ml. Tablet: 100 mg; 400 mg (hydrochloride).
isoniazid	Oral liquid: 50 mg/5 ml. Tablet: 100 mg; 300 mg. Tablet (scored): 50 mg.
pyrazinamide	Oral liquid: 30 mg/ml. Tablet: 400 mg. Tablet (dispersible): 150 mg. Tablet (scored): 150 mg.
rifampicin	Oral liquid: 20 mg/ml. Solid oral dosage form: 150 mg; 300 mg.
streptomycin R	Powder for injection: 1 g (as sulfate) in vial. R Review of safety and efficacy of streptomycin in childhood TB.

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. R

R The Subcommittee requests a review of the medicines for MDR-TB in children.

amikacin	Powder for injection: *100 mg; 500 mg; 1 g in vial.*
capreomycin	Powder for injection: *1 g in vial.*
cycloserine	Solid oral dosage form: *250 mg.*
ethionamide	Tablet: *125 mg; 250 mg.*
kanamycin	Powder for injection: *1 g in vial.*
*ofloxacin**	Tablet: *200 mg; 400 mg.* ** Levofloxacin may be an alternative based on availability and programme considerations.*
p-aminosalicylic acid	Granules: *4 g in sachet.* Tablet: *500 mg.*

6.3 Antifungal medicines

fluconazole	Capsule: 50 mg. Injection: 2 mg/ml in vial. Oral liquid: 50 mg/5 ml.

griseofulvin	Oral liquid: 125 mg/5 ml. Solid oral dosage form: 125 mg; 250 mg.
nystatin	Lozenge: 100 000 IU. Oral liquid: 50 mg/5 ml; 100 000 IU/ml. Tablet: 100 000 IU; 500 000 IU.
Complementary List	
amphotericin B	Powder for injection: *50 mg in vial.* *As deoxycholate or liposomal.*
flucytosine	Capsule: *250 mg.* Infusion: *2.5 g in 250 ml.*
potassium iodide	Saturated solution.

6.4 Antiviral medicines

6.4.1 *Antiherpes medicines*

aciclovir	Oral liquid: 200 mg/5 ml. Powder for injection: 250 mg (as sodium salt) in vial. Tablet: 200 mg.

6.4.2 *Antiretrovirals*

Based on current evidence and experience of use, medicines in the following three classes of antiretrovirals are included as essential medicines for treatment and prevention of HIV (prevention of mother-to-child transmission and post-exposure prophylaxis). The Subcommittee emphasizes the importance of using these products in accordance with global and national guidelines. The Subcommittee 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 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 (ddI)	Buffered powder for oral liquid: 100 mg; 167 mg; 250 mg packets. Capsule (unbuffered enteric-coated): 125 mg; 200 mg; 250 mg; 400 mg. Tablet (buffered chewable, dispersible): 25 mg; 50 mg; 100 mg; 150 mg; 200 mg.
emtricitabine (FTC)* [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.
stavudine (d4T)	Capsule: 15 mg; 20 mg; 30 mg. Powder for oral liquid: 5 mg/5 ml.
zidovudine (ZDV or AZT)	Capsule: 100 mg; 250 mg. Oral liquid: 50 mg/5 ml. Solution for IV infusion injection: 10 mg/ml in 20-ml vial. Tablet: 300 mg.

6.4.2.2 Non-nucleoside reverse transcriptase inhibitors

efavirenz (EFV or EFZ) [a]	Capsule: 50 mg; 100 mg; 200 mg. Oral liquid: 150 mg/5 ml. Tablet: 600 mg. [a]>3 years or >10 kg.
nevirapine (NVP)	Oral liquid: 50 mg/5 ml. Tablet: 200 mg.

6.4.2.3 Protease inhibitors

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

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

FIXED-DOSE COMBINATIONS

lamivudine + nevirapine + stavudine	Tablet: 150 mg + 200 mg + 30 mg. Tablet (dispersible): 30 mg + 50 mg + 6 mg; 60 mg + 100 mg + 12 mg.
lamivudine + nevirapine + zidovudine	Tablet: 30 mg + 50 mg + 60 mg; 150 mg + 200 mg + 300 mg.

lamivudine + zidovudine	Tablet: 30 mg + 60 mg; 150 mg + 300 mg.

6.4.3 *Other antivirals*

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 only.

6.5 Antiprotozoal medicines

6.5.1 *Antiamoebic and antigiardiasis medicines*

diloxanide [a][R]	Tablet: 500 mg (furoate). [a]>25 kg. [R] Review of effectiveness and safety for amoebiasis, with emphasis on comparative efficacy, safety, and age limits compared with oral paromomycin.
□ metronidazole	Injection: 500 mg in 100-ml vial. Oral liquid: 200 mg (as benzoate)/5 ml. Tablet: 200 mg to 500 mg.

6.5.2 *Antileishmaniasis medicines*

amphotericin B	Powder for injection: 50 mg in vial. As deoxycholate or liposomal.
paromomycin	Solution for intramuscular injection: 750 mg of paromomycin base present as the sulfate.
sodium stibogluconate or meglumine antimoniate [R]	Injection: 100 mg/ml, 1 vial = 30 ml or 30%, equivalent to approximately 8.1% antimony in 5-ml ampoule. [R] Review of comparative effectiveness and safety of antimonials for leishmaniasis, and whether they should be kept on the core list or moved to the complementary list.

6.5.3 *Antimalarial medicines*

6.5.3.1 For curative treatment

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

amodiaquine*	Tablet: 153 mg or 200 mg (as hydrochloride). * To be used (a) in combination with artesunate 50 mg OR (b) may be used alone for the treatment of *P.vivax, P.ovale* and *P.malariae* infections.
artemether*	Oily injection: 80 mg/ml in 1-ml ampoule. * For use in the management of severe malaria.
artemether + lumefantrine*	Tablet: 20 mg + 120 mg. Tablet (dispersible): 20 mg + 120 mg. * Not recommended in the first trimester of pregnancy or in children below 5 kg.
artesunate*	Injection: ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution. For use in the management of severe malaria. Rectal dosage form: 50 mg; 200 mg capsules (for pre-referral treatment of severe malaria only; patients should be taken to an appropriate health facility for follow-up care). Tablet: 50 mg. * To be used in combination with either amodiaquine, mefloquine or sulfadoxine + pyrimethamine.
chloroquine*	Oral liquid: 50 mg (as phosphate or sulfate)/ 5 ml. Tablet: 100 mg; 150 mg (as phosphate or sulfate). * For use only for the treatment of *P.vivax* infection.
doxycycline*	Capsule: 100 mg (as hydrochloride). Tablet (dispersible): 100 mg (as monohydrate). * For use only in combination with quinine.
mefloquine*	Tablet: 250 mg (as hydrochloride). * To be used in combination with artesunate 50 mg.
primaquine*	Tablet: 7.5 mg; 15 mg (as diphosphate). * Only for use to achieve radical cure of *P.vivax* and *P.ovale* infections, given for 14 days.
quinine*	Injection: 300 mg quinine hydrochloride/ml in 2-ml ampoule. Tablet: 300 mg (quinine sulfate) or 300 mg (quinine bisulfate). * For use only in the management of severe malaria, and should be used in combination with doxycycline.
sulfadoxine + pyrimethamine*	Tablet: 500 mg + 25 mg. * Only in combination with artesunate 50 mg.

6.5.3.2 For prophylaxis

chloroquine*	Oral liquid: 50 mg (as phosphate or sulfate)/ 5 ml. Tablet: 150 mg (as phosphate or sulfate). * For use only for the treatment of *P.vivax* infection.
doxycycline [a]	Solid oral dosage form: 100 mg (as hydrochloride). [a]>8 years.
mefloquine [a]	Tablet: 250 mg (as hydrochloride). [a]>5 kg or >3 months.
proguanil*	Tablet: 100 mg (as hydrochloride). * For use only in combination with chloroquine.

6.5.4 *Antipneumocystosis and antitoxoplasmosis medicines*

pyrimethamine	Tablet: 25 mg.
sulfadiazine	Tablet: 500 mg.
sulfamethoxazole + trimethoprim	Injection: 80 mg + 16 mg/ml in 5-ml ampoule; 80 mg + 16 mg/ml in 10-ml ampoule. Oral liquid: 200 mg + 40 mg/5 ml. Tablet: 100 mg + 20 mg; 400 mg + 80 mg.

6.5.5 *Antitrypanosomal medicines* [R]

[R] The Subcommittee requested a review of evidence for effectiveness and safety for medicines for trypanosomiasis in children.

6.5.5.1 African trypanosomiasis

Medicines for the treatment of 1st stage African trypanosomiasis.

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

Medicines for the treatment of 2nd stage African trypanosomiasis

eflornithine*	Injection: 200 mg (hydrochloride)/ml in 100-ml bottle. * To be used for the treatment of *Trypanosoma brucei gambiense* infection.
melarsoprol	Injection: 3.6% solution in 5-ml ampoule (180 mg of active compound).

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.5.5.2 American trypanosomiasis

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

7. ANTIMIGRAINE MEDICINES

7.1 For treatment of acute attack

ibuprofen	Tablet: 200 mg; 400 mg.
paracetamol	Oral liquid: 125 mg/5 ml. Tablet: 300 mg to 500 mg.

7.2 For prophylaxis

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

8. ANTINEOPLASTIC, IMMUNOSUPPRESSIVES AND MEDICINES USED IN PALLIATIVE CARE R

R The Subcommittee noted that these immunosuppressives and cytotoxics are essential for children but requested that these medicines be reviewed.

8.1 Immunosuppressive medicines

Complementary List

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

8.2 Cytotoxic medicines

Complementary List

allopurinol	Tablet: *100 mg to 300 mg.*
asparaginase	Powder for injection: *10 000 IU in vial.*
bleomycin	Powder for injection: *15 mg (as sulfate) in vial.*
calcium folinate	Injection: *3 mg/ml in 10-ml ampoule.* Tablet: *15 mg.*
□ *carboplatin*	Injection: *50 mg/5 ml; 150 mg/15 ml; 450 mg/45 ml; 600 mg/60 ml.*
chlorambucil	Tablet: *2 mg.*
cyclophosphamide	Powder for injection: *500 mg in vial.* Tablet: *25 mg.*
cytarabine	Powder for injection: *100 mg in vial.*
dacarbazine	Powder for injection: *100 mg in vial.*

8. ANTINEOPLASTIC, IMMUNOSUPPRESSIVES AND MEDICINES USED IN PALLIATIVE CARE R *(continued)*

dactinomycin	Powder for injection: *500 micrograms in vial.*
daunorubicin	Powder for injection: *50 mg (as hydrochloride).*
doxorubicin	Powder for injection: *10 mg; 50 mg (hydrochloride) in vial.*
etoposide	Capsule: *100 mg.* Injection: *20 mg/ml in 5-ml ampoule.*
fluorouracil	Injection: *50 mg/ml in 5-ml ampoule.*
mercaptopurine	Tablet: *50 mg.*
methotrexate	Powder for injection: *50 mg (as sodium salt) in vial.* Tablet: *2.5 mg (as sodium salt).*
procarbazine	Capsule: *50 mg (as hydrochloride).*
vinblastine	Powder for injection: *10 mg (sulfate) in vial.*
vincristine	Powder for injection: *1 mg; 5 mg (sulfate) in vial.*

8.3 Hormones and antihormones

Complementary List

dexamethasone	Injection: *4 mg dexamethasone phosphate (as disodium salt) in 1-ml ampoule.* Oral liquid*: 2 mg/5 ml.*
hydrocortisone	Powder for injection: *100 mg (as sodium succinate) in vial.*
prednisolone	Oral liquid: *5 mg/ml.* Tablet: *5 mg; 25 mg.*

8.4 Medicines used in palliative care

amitriptyline	Tablet: 10 mg; 25 mg.
cyclizine	Injection: 50 mg/ml. Tablet: 50 mg.
dexamethasone	Injection: 4 mg/ml. Tablet: 2 mg.
diazepam	Injection: 5 mg/ml. Oral liquid: 2 mg/5 ml. Rectal solution: 2.5 mg; 5 mg; 10 mg. Tablet: 5 mg; 10 mg.
docusate sodium	Capsule: 100 mg. Oral liquid: 50 mg/5 ml.

8. ANTINEOPLASTIC, IMMUNOSUPPRESSIVES AND MEDICINES USED IN PALLIATIVE CARE R *(continued)*

hyoscine hydrobromide	Injection: 400 micrograms/ml; 600 micrograms/ml. Transdermal patches: 1 mg/72 hours.
ibuprofen* [a]	Oral liquid: 100 mg/5 ml. Tablet: 200 mg; 400 mg; 600 mg. * Specific use for management of bone pain. [a] Not in children less than 3 months.
midazolam	Injection: 1 mg/ml; 5 mg/ml.
morphine	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.
senna	Oral liquid: 7.5 mg/5 ml.

~~9. ANTIPARKINSONISM MEDICINES~~

10. MEDICINES AFFECTING THE BLOOD

10.1 Antianaemia medicines R

R The Subcommittee proposed a review of the evidence for appropriate dose combinations of iron and folic acid for children.

ferrous salt	Oral liquid: equivalent to 25 mg iron (as sulfate)/ml. Tablet: equivalent to 60 mg iron.
folic acid	Tablet: 1 mg; 5 mg.
hydroxocobalamin	Injection: 1 mg in 1-ml ampoule.

10.2 Medicines affecting coagulation

phytomenadione	Injection: 1 mg/ml; 10 mg/ml in 5-ml ampoule. Tablet: 10 mg.
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).*

11. BLOOD PRODUCTS AND PLASMA SUBSTITUTES

11.1 Plasma substitutes R

R The Subcommittee requested a review to determine whether these medicines are essential for children.

11. BLOOD PRODUCTS AND PLASMA SUBSTITUTES *(continued)*

11.2 Plasma fractions for specific use

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

Complementary List

□ *factor VIII concentrate*	Dried.
□ *factor IX complex (coagulation factors, II, VII, IX, X) concentrate*	Dried.
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.*

12. CARDIOVASCULAR MEDICINES

~~12.1 Antianginal medicines~~

12.2 Antiarrhythmic medicines R

R The Subcommittee noted the potential importance of these medicines and requested a review to determine which of these medicines are essential for children.

12.3 Antihypertensive medicines

□ enalapril	Tablet: 2.5 mg; 5 mg.

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 R	Injection: *40 mg (hydrochloride) in 5-ml vial.* R Review of safety and efficacy of dopamine in children.

~~12.5 Antithrombotic medicines~~

12.6 Lipid-lowering agents R

R The Subcommittee noted the potential importance of these medicines in children but requested a review of the section before endorsing any medicine as essential.

13. DERMATOLOGICAL MEDICINES (topical)

13.1 Antifungal medicines

benzoic acid + salicylic acid	Cream or ointment: 6% + 3%.
□ miconazole	Cream or ointment: 2% (nitrate).
Complementary List	
selenium sulfide	Detergent-based suspension: *2%.*

13.2 Anti-infective medicines R

R The Subcommittee requested a review of safety of topical antibiotics including tetracycline ointment in neonates.

□ methylrosanilinium chloride (gentian violet) R	Aqueous solution: 0.5%. Tincture: 0.5%. R Review of safety and toxicity of gentian violet.
neomycin sulfate + □ bacitracin	Ointment: 5 mg neomycin sulfate + 250 IU bacitracin zinc/g.
potassium permanganate	Aqueous solution: 1:10 000.
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	Lotion.
hydrocortisone	Cream or ointment: 1% (acetate).

13.4 Astringent medicines R

R The Subcommittee requested a review to determine whether these medicines are essential for children.

13.5 Medicines affecting skin differentiation and proliferation

benzoyl peroxide	Cream or lotion: 5%.
coal tar	Solution: 5%.
□ podophyllum resin	Solution: 10% to 25%.
salicylic acid	Solution: 5%.
urea	Cream or ointment: 10%.

13.6 Scabicides and pediculicides

□ benzyl benzoate a R	Lotion: 25%. a >2 years. R Review of alternatives to benzyl benzoate for use in younger children (possible role for sulfur-based preparations in younger children).

13. DERMATOLOGICAL MEDICINES (topical) *(continued)*

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 R

R The Subcommittee requested a review of possible alternative contrast agents for use in children.

Complementary List

barium sulfate	Aqueous suspension.

15. DISINFECTANTS AND ANTISEPTICS

15.1 Antiseptics

□ chlorhexidine	Solution: 5% (digluconate); 20% (digluconate) (needs to be diluted prior to use for cord care).
□ ethanol	Solution: 70% (denatured).
□ polyvidone iodine	Solution: 10%.

15.2 Disinfectants

□ chlorine base compound	Powder: (0.1% available chlorine) for solution.
□ chloroxylenol	Solution: 4.8%.
glutaral	Solution: 2%.

16. DIURETICS

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 R	Injectable solution*: 10%; 20%.* R Review of comparative efficacy, safety and place in therapy of mannitol in children.
spironolactone R	Oral liquid: *5 mg/5 ml; 10 mg/5 ml; 25 mg/5 ml.* Tablet: *25 mg.* R Review of comparative efficacy, safety and place in therapy of spironolactone in children.

17. GASTROINTESTINAL MEDICINES

Complementary List

□ *pancreatic enzymes*	*Age-appropriate formulations and doses including lipase, protease and amylase.*

17.1 Antacids and other antiulcer medicines

aluminium hydroxide	Oral liquid: 320 mg/5 ml. Tablet: 500 mg.
magnesium hydroxide	Oral liquid: equivalent to 550 mg magnesium oxide/10 ml.
□ 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 in 2-ml ampoule. Oral liquid: 75 mg/5 ml. Tablet: 150 mg (as hydrochloride).

17.2 Antiemetic medicines

dexamethasone	Injection: 4 mg/ml in 1-ml ampoule. 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. 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. [a] >1 month.

~~17.3 Anti-inflammatory medicines~~

17.4 Laxatives [R]

[R] The Subcommittee noted the potential importance of these medicines in children but requested a review of the section before endorsing any medicine as essential.

17.5 Medicines used in diarrhoea

17.5.1 *Oral rehydration*

17. GASTROINTESTINAL MEDICINES *(continued)*

oral rehydration salts	glucose: 75 mEq sodium: 75 mEq or mmol/L chloride: 65 mEq or mmol/L potassium: 20 mEq or mmol/L citrate: 10 mmol/L osmolarity: 245 mOsm/L glucose: 13.5 g/L sodium chloride: 2.6 g/L potassium chloride: 1.5 g/L trisodium citrate dihydrate+: 2.9 g/L + trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/L. However, as the stability of this latter formulation is very poor under tropical conditions, it is only recommended when manufactured for immediate use. Powder for dilution in 200 ml; 500 ml; 1 L.

17.5.2 *Medicines for diarrhoea in children*

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

~~17.5.3 *Antidiarrhoeal (symptomatic) medicines in adults*~~

18. HORMONES, OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES

18.1 Adrenal hormones and synthetic substitutes

fludrocortisone	Tablet: 100 micrograms.
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*~~

~~**18.4 Estrogens**~~

18.5 Insulins and other antidiabetic agents

insulin injection (soluble)	Injection: 100 IU/ml in 10-ml vial.

18. HORMONES, OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES *(continued)*

intermediate-acting insulin	Injection: 100 IU/ml in 10-ml vial (as compound insulin zinc suspension or isophane insulin).
Complementary List	
metformin	Tablet: *500 mg (hydrochloride).*

~~**18.6 Ovulation inducers**~~

~~**18.7 Progestogens**~~

18.8 Thyroid hormones and antithyroid medicines

levothyroxine	Tablet: 25 micrograms; 50 micrograms; 100 micrograms (sodium salt).
Complementary List	
Lugol›s solution	Oral liquid: *about 130 mg total iodine/ml.*
potassium iodide	Tablet: *60 mg.*
propylthiouracil R	Tablet: *50 mg.* R Review of use of propylthiouracil in children and appropriateness of carbimazole as an alternative.

19. IMMUNOLOGICALS

19.1 Diagnostic agents

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

tuberculin, purified protein derivative (PPD)	Injection.

19.2 Sera and immunoglobulins

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

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

19.3 Vaccines

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

The Subcommittee noted the need for vaccines used in children to be polyvalent.

BCG vaccine

cholera vaccine

diphtheria vaccine

hepatitis A vaccine

hepatitis B vaccine

Haemophilus influenzae type b vaccine

influenza vaccine

Japanese encephalitis vaccine

measles vaccine

meningococcal meningitis vaccine

mumps vaccine

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 R

R The Subcommittee recommended a review of the alternatives available for use in children.

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 R

R The Subcommittee requested a review of newer medicines for potential additions to this list.

21.1 Anti-infective agents

aciclovir	Ointment: 3% W/W.
☐ gentamicin	Solution (eye drops): 0.3% (sulfate).
☐ tetracycline	Eye ointment: 1% (hydrochloride).

21.2 Anti-inflammatory agents

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

21.3 Local anaesthetics

☐ tetracaine a	Solution (eye drops): 0.5% (hydrochloride). a Not in preterm neonates.

~~**21.4 Miotics and antiglaucoma medicines**~~

21.5 Mydriatics

atropine* a	Solution (eye drops): 0.1%; 0.5%; 1% (sulfate). * OR homatropine OR cyclopentolate. a >3 months.
Complementary List	
epinephrine (adrenaline) R	Solution (eye drops): *2% (as hydrochloride).* R Review of anti-infective eye drops, identifying which are most appropriate for use in children.

~~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. PSYCHOTHERAPEUTIC MEDICINES R

R The Subcommittee noted the potential importance of these medicines in children for a variety of disorders and requests a review of the entire section before endorsing any medicine as essential.

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 a	Solid oral dosage form: *20 mg (present as hydrochloride).* a >8 years.

24.2.2 *Medicines used in bipolar disorders* R

24.3 Medicines used in generalized anxiety R

24.4 Medicines used for obsessive compulsive disorders and panic attacks R

24.5 Medicines used in substance dependence programmes R

25. MEDICINES ACTING ON THE RESPIRATORY TRACT

25.1 Antiasthmatic medicines

□ budesonide	Inhalation (aerosol): 100 micrograms per dose; 200 micrograms per dose.
epinephrine (adrenaline)	Injection: 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule.

25. MEDICINES ACTING ON THE RESPIRATORY TRACT *(continued)*

☐ salbutamol*	Injection: 50 micrograms (as sulfate)/ml in 5-ml ampoule. Metered dose inhaler (aerosol): 100 micrograms (as sulfate) per dose. Oral liquid: 2 mg/5 ml. Respirator solution for use in nebulizers: 5 mg (as sulfate)/ml. Tablet: 2 mg; 4 mg (as sulfate). * Oral salbutamol treatment should only be considered when inhaled asthma therapy is not feasible.

26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID-BASE DISTURBANCES

26.1 Oral

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

26.2 Parenteral

glucose	Injectable solution: 5% (isotonic); 10% (hypertonic); 50% (hypertonic).
glucose with sodium chloride	Injectable solution: 5% glucose, 0.9% sodium chloride (equivalent to 150 mmol/L Na+ and 150 mmol/L Cl-); 5% glucose, 0.45% sodium chloride (equivalent to 75 mmol/L Na+ and 75 mmol/L Cl-).
potassium chloride	Solution for dilution: 7.5% (equivalent to K 1 mmol/ml and Cl 1 mmol/ml); 15% (equivalent to K 2 mmol/ml and Cl 2 mmol/ml).
sodium chloride	Injectable solution: 0.9% isotonic (equivalent to Na+ 154 mmol/L, Cl- 154 mmol/L).
sodium hydrogen carbonate	Injectable solution: 1.4% isotonic (equivalent to Na^+ 167 mmol/L, HCO3- 167 mmol/L). Solution: 8.4% in 10-ml ampoule (equivalent to Na^+ 1000 mmol/L, HCO3-1000 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 R

R The Subcommittee noted the need for a review of this section of the list to meet public health needs in children.

ascorbic acid	Tablet: 50 mg.

27. VITAMINS AND MINERALS R *(continued)*

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 CONDITIONS IN CHILDREN R

R Review of role of leukotriene antagonists in the management of childhood allergic rhinitis.

acetic acid	Topical: 2%, in alcohol.
☐ budesonide	Nasal spray: 100 micrograms per dose.
☐ ciprofloxacin	Topical: 0.3% drops.
☐ xylometazoline a	Nasal spray: 0.05%. a Not in children less than 3 months.

29. SPECIFIC MEDICINES FOR NEONATAL CARE

caffeine citrate	Injection: 20 mg/ml (equivalent to 10 mg caffeine base/ml). Oral liquid: 20 mg/ml (equivalent to 10 mg caffeine base/ml).
Complementary List	
☐ *ibuprofen*	Solution for injection: 5 mg/ml.

29. SPECIFIC MEDICINES FOR NEONATAL CARE *(continued)*

☐ *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.*

Table 1
Medicines with age and 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
chlorphenamine	>1 year
diloxanide	>25 kg
doxycycline	>8 years (except for serious infections e.g. cholera)
efavirenz	>3 years or >10 kg
emtrictabine	>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

Explanation of dosage forms

A. Principal dosage forms used in EMLc – Oral administration

Term	Definition
Solid oral dosage form	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. The term 'solid oral dosage form' is *never* intended to allow any type of modified-release tablet.
Tablet	Refers to: • uncoated or coated (film-coated or sugar-coated) tablets that are intended to be swallowed whole; • unscored and scored*; • tablets that are intended to be chewed before being swallowed; • tablets that are intended to be dispersed or dissolved in water or another suitable liquid before being swallowed; • tablets that are intended to be crushed before being swallowed. The term 'tablet' without qualification is *never* intended to allow any type of modified-release tablet.
Tablet (qualified)	Refers to a specific type of tablet: **chewable** – tablets that are intended to be chewed before being swallowed; **dispersible** – tablets that are intended to be dispersed in water or another suitable liquid before being swallowed; **soluble** – tablets that are intended to be dissolved in water or another suitable liquid before being swallowed; **crushable** – tablets that are intended to be crushed before being swallowed; **scored** – tablets bearing a break mark or marks where sub-division is intended in order to provide doses of less than one tablet; **sublingual** – tablets that are intended to be placed beneath the tongue. The term 'tablet' is *always* qualified with an additional term (in parentheses) in entries where one of the following types of tablet is intended: **gastro-resistant** (such tablets may sometimes be described as enteric-coated or as delayed-release), **prolonged-release** or another modified-release form.
Capsule	Refers to hard or soft capsules. The term ‹capsule› without qualification is *never* intended to allow any type of modified-release capsule.
Capsule (qualified)	The term ‹capsule› with qualification refers to **gastro-resistant** (such capsules may sometimes be described as enteric-coated or as delayed-release), **prolonged-release** or another modified-release form.

* Scored tablets may be divided for ease of swallowing, provided dose is a whole number of tablets.

Term	Definition
Granules	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 *never* intended to allow any type of modified-release granules.
Oral powder	Preparations that are issued to patient as powder (usually as single-dose) to be taken in or with water or another suitable liquid.
Oral liquid	Liquid preparations intended to be *swallowed* i.e. oral solutions, suspensions, emulsions and oral drops, including those constituted from powders or granules, but *not* those preparations intended for *oromucosal administration* 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
Injection	Refers to solutions, suspensions and emulsions including those constituted from powders or concentrated solutions.
Injection (qualified)	Route of administration is indicated in parentheses where relevant.
Injection (oily)	The term injection is qualified by (oily) in relevant entries.
Intravenous infusion	Refers to solutions and emulsions including those constituted from powders or concentrated solutions.

C. Other dosage forms

Mode of administration	Term to be used
To the eye	Eye drops, eye ointments.
Topical	For liquids: lotions, paints. For semi-solids: cream, ointment.
Rectal	Suppositories, gel or solution.
Vaginal	Pessaries or vaginal tablets.
Inhalation	Powder for inhalation, pressurized inhalation, nebulizer.

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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 16th WHO Model List of Essential Medicines and the 2nd WHO Model List of Essential Medicines for Children, sorted by ATC code number.

ATC code	ATC group/medicine or item	Section
A	**ALIMENTARY TRACT AND METABOLISM**	
A02	**Drugs for acid related disorders**	
A02A	**Antacids**	
A02AA	*Magnesium compounds*	
A02AA04	magnesium hydroxide	17.1
A02AB	*Aluminium compounds*	
A02AB01	aluminium hydroxide	17.1
A02B	**Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)**	
A02BA	*H_2-receptor antagonists*	
A02BA02	ranitidine	17.1
A02BC	*Proton pump inhibitors*	
A02BC01	omeprazole	17.1
A03	**Drugs for functional gastrointestinal disorders**	
A03B	**Belladonna and derivatives, plain**	
A03BA	*Belladonna alkaloids, tertiary amines*	
A03BA01	atropine	1.3; 4.2
A03F	**Propulsives**	
A03FA	*Propulsives*	
A03FA01	metoclopramide	17.2
A04	**Antiemetics and antinauseants**	
A04A	**Antiemetics and antinauseants**	
A04AA	*Serotonin (5HT3) antagonists*	
A04AA01	ondansetron	17.2
A06	**Laxatives**	
A06A	**Laxatives**	
A06AB	*Contact laxatives*	
A06AB06	senna glycosides*	17.4

ATC code	ATC group/medicine or item	Section
A07	**Antidiarrheals, intestinal antiinflammatory/antiinfective agents**	
A07A	**Intestinal antiinfectives**	
A07AA	*Antibiotics*	
A07AA06	paromomycin	6.5.2
A07B	**Intestinal adsorbents**	
A07BA	*Charcoal preparations*	
A07BA01	medicinal charcoal*	4.1
A07C	**Electrolytes with carbohydrates**	
A07CA	*Oral rehydration salt formulations**	17.5.1; 26.1
A07E	**Intestinal antiinflammatory agents**	
A07EA	*Corticosteroids for local use*	
A07EA02	hydrocortisone	17.3
A07EC	*Aminosalicylic acid and similar agents*	
A07EC01	sulfasalazine	2.4; 17.3
A09	**Digestives, incl. enzymes**	
A09A	**Digestives, incl. enzymes**	
A09AA	*Enzyme preparations*	
A09AA02	multienzymes (lipase, protease, etc.)*	17
A10	**Drugs used in diabetes**	
A10A	**Insulins and analogues**	
A10AB	*Insulins and analogues for injection, fast-acting*	
A10AB	insulin injection (soluble)*	18.5
A10AC	*Insulins and analogues for injection, intermediate-acting*	
A10AC	insulin, intermediate-acting*	18.5
A10B	**Blood glucose lowering drugs, excl. insulins**	
A10BA	*Biguanides*	
A10BA02	metformin	18.5
A10BB	*Sulfonamides, urea derivatives*	
A10BB01	glibenclamide	18.5
A11	**Vitamins**	
A11C	**Vitamin A and D, incl. combinations of the two**	
A11CA	*Vitamin A, plain*	
A11CA01	retinol	27
A11CC	*Vitamin D and analogues*	
A11CC01	ergocalciferol	27
A11CC05	colecalciferol*	27
A11D	**Vitamin B_1, plain and in combination with vitamin B_6 and B_{12}**	
A11DA	*Vitamin B1, plain*	
A11DA01	thiamine	27
A11G	**Ascorbic acid (vitamin C), incl. combinations**	

ATC code	ATC group/medicine or item	Section
A11GA	*Ascorbic acid (vitamin C), plain*	
A11GA01	ascorbic acid	27
A11H	**Other plain vitamin preparations**	
A11HA	*Other plain vitamin preparations*	
A11HA01	nicotinamide	27
A11HA02	pyridoxine	27
A11HA04	riboflavin	27
A12	**Mineral supplements**	
A12A	**Calcium**	
A12AA	*Calcium*	
A12AA03	calcium gluconate	4.2; 27
A12C	**Other mineral supplements**	
A12CB	*Zinc*	
A12CB01	zinc sulfate	17.5.2
A12CD	*Fluoride*	
A12CD01	sodium fluoride	27
A12CX	*Other mineral products**	27
B	**BLOOD AND BLOOD FORMING ORGANS**	
B01	**Antithrombotic agents**	
B01A	**Antithrombotic agents**	
B01AA	*Vitamin K antagonists*	
B01AA03	warfarin	10.2
B01AB	*Heparin group*	
B01AB01	heparin*	10.2
B01AC	*Platelet aggregation inhibitors excl. heparin*	
B01AC06	acetylsalicylic acid	12.5
B01AD	*Enzymes*	
B01AD01	streptokinase	12.5
B02	**Antihemorrhagics**	
B02B	**Vitamin K and other hemostatics**	
B02BA	*Vitamin K*	
B02BA01	phytomenadione	10.2
B02BD	*Blood coagulation factors*	
B02BD01	coagulation factor IX, II, VII and X in combination*	11.2
B02BD02	coagulation factor VIII*	11.2
B03	**Antianemic preparations**	
B03A	**Iron preparations***	10.1
B03AD	*Iron in combination with folic acid**	10.1
B03B	**Vitamin B_{12} and folic acid**	
B03BA	*Vitamin B_{12} (cyanocobalamin and analogues)*	

ATC code	ATC group/medicine or item	Section
B03BA03	hydroxocobalamin	10.1
B03BB	*Folic acid and derivatives*	
B03BB01	folic acid	10.1
B05	**Blood substitutes and perfusion solutions**	
B05A	**Blood and related products**	
B05AA	*Blood substitutes and plasma protein fractions*	
B05AA05	dextran*	11.1
B05B	**I.V. solutions**	
B05BA	*Solutions for parenteral nutrition*	
B05BA03	carbohydrates*	26.2
B05BB	*Solutions affecting the electrolyte balance*	
B05BB01	electrolytes*	26.2
B05BB02	electrolytes with carbohydrates*	26.2
B05BC	*Solutions producing osmotic diuresis*	
B05BC01	mannitol	16
B05D	**Peritoneal dialytics**	
B05DA	*Isotonic solutions**	*23*
B05X	**I.V. solution additives**	
B05XA	*Electrolyte solutions*	
B05XA01	potassium chloride	26.1; 26.2
B05XA02	sodium bicarbonate*	26.2
B05XA03	sodium chloride	26.2
B05XA05	magnesium sulfate	5
C	**CARDIOVASCULAR SYSTEM**	
C01	**Cardiac therapy**	
C01A	**Cardiac glycosides**	
C01AA	*Digitalis glycosides*	
C01AA01	simvastatin	12.6
C01AA05	digoxin	12.2; 12.4
C01B	**Antiarrhythmics, class I and III**	
C01BB	*Antiarrhythmics, class Ib*	
C01BB01	lidocaine	12.2
C01BD	*Antiarrhythmics, class III*	
C01BD01	amiodarone	12.2
C01C	**Cardiac stimulants excl. cardiac glycosides**	
C01CA	*Adrenergic and dopaminergic agents*	
C01CA04	dopamine	12.4
C01CA24	epinephrine (adrenaline)	3; 12.2; 25.1
C01D	**Vasodilators used in cardiac diseases**	
C01DA	*Organic nitrates*	
C01DA02	glyceryl trinitrate	12.1

ATC code	ATC group/medicine or item	Section
C01DA08	isosorbide dinitrate	12.1
C01E	**Other cardiac preparations**	
C01EA	*Prostaglandins*	
C01EA01	alprostadil*	29
C02	***Antihypertensives***	
C02A	***Antiadrenergic agents, centrally acting***	
C02AB	*Methyldopa*	
C02AB01	methyldopa (levorotatory)*	12.3
C02D	**Arteriolar smooth muscle, agents acting on**	
C02DB	*Hydrazinophthalazine derivatives*	
C02DB02	hydrazaline	12.3
C02DD	*Nitroferricyanide derivatives*	
C02DD01	nitroprusside*	12.3
C03	**Diuretics**	
C03A	**Low-ceiling diuretics, thiazides**	
C03AA	*Thiazides, plain*	
C03AA03	hydrochlorothiazide	12.3;12.4;16
C03C	**High-ceiling diuretics**	
C03CA	*Sulfonamides, plain*	
C03CA01	furosemide	12.4; 16
C03D	**Potassium-sparing agents**	
C03DA	*Aldosterone antagonists*	
C03DA01	spironolactone	16
C03DB	*Other potassium-sparing agents*	
C03DB01	amiloride	16
C07	**Beta blocking agents**	
C07A	**Beta blocking agents**	
C07AA	*Beta blocking agents, non-selective*	
C07AA05	propranolol	7.2
C07AB	*Beta blocking agents, selective*	
C07AB03	atenolol	12.1;12.2;12.3
C08	**Calcium channel blockers**	
C08C	**Selective calcium channel blockers with mainly vascular effects**	
C08CA	*Dihydropyridine derivatives*	
C08CA01	amlodipine	12.3
C08CA05	nifedipine	22.2
C08D	**Selective calcium channel blockers with direct cardiac effects**	
C08DA	*Phenylalkylamine derivatives*	
C08DA01	verapamil	12.1;12.2

ATC code	ATC group/medicine or item	Section
C09	**Agents acting on the renin-angiotensin system**	
C09A	**ACE inhibitors, plain**	
C09AA	*ACE inhibitors, plain*	
C09AA02	enalapril	12.3;12.4
D	**DERMATOLOGICALS**	
D01	**Antifungals for dermatological use**	
D01A	**Antifungals for topical use**	
D01AA	*Antibiotics*	
D01AA01	nystatin	6.3
D01AC	*Imidazole and triazole derivatives*	
D01AC02	miconazole	13.1
D01AE	*Other antifungals for topical use*	
D01AE02	methylrosanilinium chloride (gentian violet)*	13.2
D01AE12	salicylic acid	13.5
D01AE13	selenium sulfide	13.1
D01AE20	benzoic acid + salicylic acid*	13.1
D01B	**Antifungals for systemic use**	
D01BA	*Antifungals for systemic use*	
D01BA01	griseofulvin	6.3
D02	**Emollients and protectives**	
D02A	*Emollients and protectives*	
D02AB	*Zinc products**	13.3
D02AE	*Carbamide products*	
D02AE01	carbamide*	13.5
D04	**Antipruritics, incl. anthihistamines, anesthetics, etc.**	
D04AA	*Antihistamines for topical use*	
D04AA10	promethazine	1.3
D05	**Antipsoriatics**	
D05A	**Antipsoriatics for topical use**	
D05AA	*Tars**	13.5
D05AC	*Antracen derivatives*	
D05AC01	dithranol	13.5
D06	**Antibiotics and chemotherapeutics for dermatological use**	
D06A	**Antibiotics for topical use**	
D06AX	*Other antibiotics for topical use*	
D06AX04	neomycin*	13.2
D06B	**Chemotherapeutics for topical use**	
D06BA	*Sulfonamides*	
D06BA01	silver sulfadiazine	13.2
D06BB	*Antivirals*	

ATC code	ATC group/medicine or item	Section
D06BB04	podophyllotoxin*	13.5
D07	**Corticosteroids, dermatological preparations**	
D07A	**Corticosteroids, plain**	
D07AA	*Corticosteroids, weak (group I)*	
D07AA02	hydrocortisone	13.3
D07AC	*Corticosteroids, potent (group III)*	
D07AC01	betamethasone	13.3
D08	**Antiseptics and disinfectants**	
D08A	**Antiseptics and disinfectants**	
D08AC	*Biguanides and amidines*	
D08AC02	chlorhexidine	15.1
D08AE	*Phenol and derivatives*	
D08AE05	chloroxylenol	15.2
D08AG	*Iodine products*	
D08AG02	povidone-iodine*	15.1
D08AX	*Other antiseptics and disinfectants**	15.2
D08AX06	potassium permanganate	13.2
D08AX08	ethanol	15.1
D10	**Anti-acne preparations**	
D10A	**Anti-acne preparations for topical use**	
D10AE	*Peroxides*	
D10AE01	benzoyl peroxide	13.5
D10AX	*Other anti-acne preparations for topical use*	
D10AX05	aluminium diacetate	13.4
G	**GENITO URINARY SYSTEM AND SEX HORMONES**	
G01	**Gynecological antiinfectives and antiseptics**	
G01A	**Antiinfectives and antiseptics, excl. combinations with corticosteroids**	
G01AF	*Imidazole derivatives*	
G01AF02	clotrimazole	6.3
G02	**Other gynecologicals**	
G02A	**Oxytocics**	
G02AB	*Ergot alkaloids*	
G02AB03	ergometrine	22.1
G02AD	*Prostaglandins*	
G02AD06	misoprostol	22.1
G02B	**Contraceptives for topical use**	
G02BA	*Intrauterine contraceptives*	
G02BA02	plastic IUD with copper*	18.3.3
G02BA03	plastic IUD with progesteron*	18.3.5
G02BB	*Intravaginal contraceptives**	18.3.4

ATC code	ATC group/medicine or item	Section
G03	**Sex hormones and modulators of the genital system**	
G03A	**Hormonal contraceptives for systemic use**	
G03AA	*Progestogens and estrogens, fixed combinations*	
G03AA05	norethisterone and estrogen*	18.3.1
G03AA08	medroxyprogesterone and estrogen*	18.3.2
G03AB	*Progestogens and estrogens, sequential preparations*	
G03AB03	levonorgestrel and estrogen*	18.3.1
G03AC	*Progestogens*	
G03AC01	norethisterone*	18.3.2
G03AC03	levonorgestrel	18.3.1
G03AC06	medroxyprogesterone*	18.3.2; 18.7
G03B	**Androgens**	
G03BA	*3-oxoandrosten (4) derivatives*	
G03BA03	testosterone	18.2
G03C	**Estrogens**	
G03CA	*Natural and semisynthetic estrogens, plain*	
G03CA01	ethinylestradiol	18.4
G03D	**Progestogens**	
G03DC	*Estren derivatives*	
G03DC02	norethisterone	18.7
G03G	**Gonadotropins and other ovulation stimulants**	
G03GB	*Ovulation stimulants, synthetic*	
G03GB02	clomifene	18.6
G03X	**Other sex hormones and modulators of the genital system**	
G03XB	*Antiprogesterons*	
G03XB01	mifepristone	22.1
H	**SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS**	
H01	**Pituitary, hypothalamic hormones and analogues**	
H01B	**Posterior pituitary lobe hormones**	
H01BB	*Oxytocin and analogues*	
H01BB02	oxytocin	22.1
H02	**Corticosteroids for systemic use**	
H02A	**Corticosteroids for systemic use, plain**	
H02AA	*Mineralocorticoids*	
H02AA02	*fludrocortisone*	18.1
H02AB	*Glucocorticoids*	
H02AB02	dexamethasone	3; 8.3; 17.2
H02AB06	prednisolone	3; 8.3
H02AB09	hydrocortisone	3; 8.3
H03	**Thyroid therapy**	
H03A	**Thyroid preparations**	

ATC code	ATC group/medicine or item	Section
H03AA	*Thyroid hormones*	
H03AA01	levothyroxine sodium*	18.8
H03B	**Antithyroid preparations**	
H03BA	*Thiouracils*	
H03BA02	propylthiouracil	18.8
H03C	**Iodine therapy**	
H03CA	*Iodine therapy**	18.8
J	**ANTIINFECTIVES FOR SYSTEMIC USE**	
J01	**Antibacterials for systemic use**	
J01A	**Tetracyclines**	
J01AA	*Tetracyclines*	
J01AA02	doxycycline	6.2.2; 6.5.3.1; 6.5.3.2
J01B	**Amphenicols**	
J01BA	*Amphenicols*	
J01BA01	chloramphenicol	6.2.2
J01C	**Beta-lactam antibacterials, penicillins**	
J01CA	*Penicillins with extended spectrum*	
J01CA01	ampicillin	6.2.1
J01CA04	amoxicillin	6.2.1
J01CE	*Beta-lactamase sensitive penicillins*	
J01CE01	benzylpenicillin	6.2.1
J01CE02	phenoxymethylpenicillin	6.2.1
J01CE08	benzathine benzylpenicillin	6.2.1
J01CE09	procaine benzylpenicillin	6.2.1
J01CF	*Beta-lactamase resistant penicillins*	
J01CF02	cloxacillin	6.2.1
J01CR	*Combinations of penicillins, incl. beta-lactamase inhibitors*	
J01CR02	amoxicillin and enzyme inhibitor*	6.2.1
J01D	**Other beta-lactam antibacterials**	
J01DB	*First-generation cephalosporins*	
J01DB01	cefalexin	6.2.1
J01DB04	cefazolin	6.2.1
J01DD	*Third-generation cephalosporins*	
J01DD021	cefotaxime	6.2.1
J01DD02	ceftazidime	6.2.1
J01DD04	ceftriaxone	6.2.1
J01DD08	cefixime	6.2.1
J01DH	*Carbapenems*	
J01DH51	imipenem and enzyme inhibitor*	6.2.1
J01E	**Sulfonamides and trimethoprim**	

ATC code	ATC group/medicine or item	Section
J01EA	*Trimethoprim and derivatives*	
J01EA01	trimethoprim	6.2.2
J01EC	*Intermediate-acting sulfonamides*	
J01EC02	sulfadiazine	6.5.4
J01EE	*Combinations of sulfonamides and trimethoprim, incl. derivatives*	
J01EE01	sulfamethoxazole + trimethoprim	6.2.2; 6.5.4
J01F	**Macrolides, lincosamides and streptogramins**	
J01FA	*Macrolides*	
J01FA01	erythromycin	6.2.2
J01FA10	azithromycin	6.2.2
J01FF	*Lincosamides*	
J01FF01	clindamycin	6.2.2
J01G	**Aminoglycoside antibacterials**	
J01GA	*Streptomycins*	
J01GA01	streptomycin	6.2.4
J01GB	*Other aminoglycosides*	
J01GB03	gentamicin	6.2.2
J01GB04	kanamycin	6.2.4
J01GB06	amikacin	6.2.4
J01M	**Quinolone antibacterials**	
J01MA	*Fluoroquinolones*	
J01MA01	ofloxacin	6.2.4
J01MA02	ciprofloxacin	6.2.2
J01X	**Other antibacterials**	
J01XA	*Glycopeptide antibacterials*	
J01XA01	vancomycin	6.2.2
J01XD	*Imidazole derivatives*	
J01XD01	metronidazole	6.2.2
J01XE	*Nitrofuran derivatives*	
J01XE01	nitrofurantoin	6.2.2
J01XX	*Other antibacterials*	
J01XX04	spectinomycin	6.2.2
J02	**Antimycotics for systemic use**	
J02A	**Antimycotics for systemic use**	
J02AA	*Antibiotics*	
J02AA01	amphotericin B	6.3; 6.5.2
J02AC	*Triazole derivatives*	
J02AC01	*fluconazole*	6.3
J02AX	*Other antimycotics for systemic use*	
J02AX01	flucytosine	6.3

ATC code	ATC group/medicine or item	Section
J04	**Antimycobacterials**	
J04A	**Drugs for treatment of tuberculosis**	
J04AA	*Aminosalicylic acid and derivatives*	
J04AA01	p-aminosalicylic acid*	6.2.4
J04AB	*Antibiotics*	
J04AB01	cycloserine	6.2.4
J04AB02	rifampicin	6.2.3; 6.2.4
J04AB04	rifabutin	6.2.4
J04AB30	capreomycin	6.2.4
J04AC	*Hydrazides*	
J04AC01	isoniazid	6.2.4
J04AD	*Thiocarbamide derivatives*	
J04AD03	ethionamide	6.2.4
J04AK	*Other drugs for treatment of tuberculosis*	
J04AK01	pyrazinamide	6.2.4
J04AK02	ethambutol	6.2.4
J04AM	*Combinations of drugs for treatment of tuberculosis**	*6.2.4*
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**	
J04BA	*Drugs for treatment of lepra*	
J04BA01	clofazimine	6.2.3
J04BA02	dapsone	6.2.3
J05	**Antivirals for systemic use**	
J05A	**Direct acting antivirals**	
J05AB	*Nucleosides and nucleotides excl. reverse transcriptase inhibitors*	
J05AB01	aciclovir	6.4.1
J05AB04	ribavirin	6.4.3
J05AE	*Protease inhibitors*	
J05AE01	saquinavir (SQV)	6.4.2.3
J05AE02	indinavir (IDV)	6.4.2.3
J05AE03	ritonavir (r)	6.4.2.3
J05AE08	atazanavir	6.4.2.3
J05AE30	lopinavir + ritonavir (LPV/r)*	6.4.2.3
J05AF	*Nucleoside and nucleotide reverse transcriptase inhibitors*	
J05AF01	zidovudine (ZDV or AZT)	6.4.2.1
J05AF02	didanosine (ddI)	6.4.2.1
J05AF04	stavudine (d4T)	6.4.2.1
J05AF05	lamivudine (3TC)	6.4.2.1
J05AF06	abacavir (ABC)	6.4.2.1

ATC code	ATC group/medicine or item	Section
J05AF07	tenofovir disoproxil fumarate	6.4.2.1
J05AF09	emtricitabine	6.4.2.1
J05AG	*Non-nucleoside reverse transcriptase inhibitors*	
J05AG01	nevirapine (NVP)	6.4.2.2
J05AG03	efavirenz (EFV or EFZ)	6.4.2.2
J05AR	*Antivirals for treatment of HIV infections, combinations*	
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
J06	**Immune sera and immunoglobulins**	
J06A	**Immune sera**	
J06AA	*Immune sera*	
J06AA01	diphtheria antitoxin	19.2
J06AA03	snake venom antiserum*	19.2
J06B	**Immunoglobulins**	
J06BA	*Immunoglobulins, normal human*	
J06BA01	immunoglobulins, normal human, for extravascular admin*	11.2
J06BA02	immunoglobulins, normal human, for intravascular admin*	11.2
J06BB	*Specific immunoglobulins*	
J06BB01	anti-D immunoglobulin (human)	19.2
J06BB02	antitetanus immunoglobulin (human)	19.2
J06BB05	rabies immunoglobulin	19.2
J07	**Vaccines**	
J07A	**Bacterial vaccines**	
J07AE	*Cholera vaccines*	19.3
J07AF	*Diphtheria vaccines*	
J07AF01	diphtheria toxoid*	19.3
J07AH	*Meningococcal vaccines**	19.3
J07AJ	*Pertussis vaccines*	
J07AJ01	pertussis vaccine	19.3
J07AL	*Pneumococcal vaccines*	
J07AL01	*pneumococcus, purified polysaccharides antigen**	19.3
J07AM	*Tetanus vaccines*	
J07AM01	tetanus toxoid*	19.3
J07AN	*Tuberculosis vaccines*	
J07AN01	tuberculosis, live attenuated*	19.3
J07AP	*Typhoid vaccines*	
J07AP	typhoid vaccine	19.3

ATC code	ATC group/medicine or item	Section
J07B	**Viral vaccines**	
J07BA	*Encephalitis vaccines*	
J07BA02	encephalitis, Japanese, inactivated, whole virus	
J07BB	*Influenza vaccines*	
J07BB	influenza vaccine	19.3
J07BC	*Hepatitis vaccines*	
J07BC01	hepatitis B vaccine	19.3
J07BC02	hepatitis A vaccine	19.3
J07BD	*Measles vaccine**	
J07BD01	measles, live attenuated*	19.3
J07BE	*Mumps vaccines*	
J07BE01	mumps, live attenuated*	19.3
J07BF	*Poliomyelitis vaccine*	19.3
J07BG	*Rabies vaccine*	19.3
J07BH	*Rota virus diarrhea vaccines**	19.3
J07BJ	*Rubella vaccines*	19.3
J07BK	*Varicella zoster vaccines**	19.3
J07BL	*Yellow fever vaccines*	19.3
J07C	**Bacterial and viral vaccines, combined**	
J07CA	*Bacterial and viral vaccines, combined**	19.3
L	**ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS**	
L01	**Antineoplastic agents**	
L01A	**Alkylating agents**	
L01AA	*Nitrogen mustard analogues*	
L01AA01	cyclophosphamide	8.2
L01AA02	chlorambucil	8.2
L01AA06	ifosfamide	8.2
L01AX	*Other alkylating agents*	
L01AX04	dacarbazine	8.2
L01B	**Antimetabolites**	
L01BA	*Folic acid analogues*	
L01BA01	methotrexate	2.4; 8.2
L01BB	*Purine analogues*	
L01BB02	mercaptopurine	8.2
L01BC	*Pyrimidine analogues*	
L01BC01	cytarabine	8.2
L01BC02	fluorouracil	8.2; 13.5
L01C	**Plant alkaloids and other natural products**	
L01CA	*Vinca alkaloids and analogues*	

ATC code	ATC group/medicine or item	Section
L01CA01	vinblastine	8.2
L01CA02	vincristine	8.2
L01CB	*Podophyllotoxin derivatives*	
L01CB01	etoposide	8.2
L01D	**Cytotoxic antibiotics and related substances**	
L01DA	*Actinomycines*	
L01DA01	dactinomycin	8.2
L01DB	*Anthracyclines and related substances*	
L01DB01	doxorubicin	8.2
L01DB02	daunorubicin	8.2
L01DC	*Other cytotoxic antibiotics*	
L01DC01	bleomycin	8.2
L01X	**Other antineoplastic agents**	
L01XA	*Platinum compounds*	
L01XA02	carboplatin	8.2
L01XB	*Methylhydrazines*	
L01XB01	procarbazine	8.2
L01XX	*Other antineoplastic agents*	
L01XX02	asparaginase	8.2
L01XX05	hydroxycarbamide	8.2
L02	**Endocrine therapy**	
L02B	**Hormone antagonists and related agents**	
L02BA	*Anti-estrogens*	
L02BA01	tamoxifen	8.3
L04	**Immunosuppressants**	
L04A	**Immunosuppressants**	
L04AD	*Calcineurin inhibitors*	
L04AD01	ciclosporin	8.1
L04AX	*Other immunosuppressants*	
L04AX01	azathioprine	2.4; 8.1
M	**MUSCULO-SKELETAL SYSTEM**	
M01	**Antiinflammatory and antirheumatic products**	
M01A	**Antiinflammatory and antirheumatic products, non-steroids**	
M01AE	*Propionic acid derivatives*	
M01AE01	ibuprofen	2.1, 29
M01C	**Specific antirheumatic agents**	
M01CC	*Penicillamine and similar agents*	
M01CC01	penicillamine	2.4; 4.2
M03	**Muscle relaxants**	
M03A	**Muscle relaxants, peripherally acting agents**	
M03AA	*Curare alkaloids*	

ATC code	ATC group/medicine or item	Section
M03AA01	alcuronium	20
M03AB	*Choline derivatives*	
M03AB01	suxamethonium	20
M03AC	*Other quaternary ammonium compounds*	
M03AC03	vecuronium	20
M04	**Antigout preparations**	
M04A	**Antigout preparations**	
M04AA	*Preparations inhibiting uric acid production*	
M04AA01	allopurinol	2.3
N	**NERVOUS SYSTEM**	
N01	**Anesthetics**	
N01A	**Anesthetics, general**	
N01AB	*Halogenated hydrocarbons*	
N01AB01	halothane	1.1
N01AF	*Barbiturates, plain*	
N01AF03	thiopental	1.1
N01AX	*Other general anesthetics*	
N01AX03	ketamine	1.1
N01AX13	nitrous oxide	1.1
N01B	**Anesthetics, local**	
N01BB	*Amides*	
N01BB01	bupivacaine	1.2
N01BB02	lidocaine	1.2
N01BB52	lidocaine, combinations*	1.2
N02	**Analgesics**	
N02A	**Opioids**	
N02AA	*Natural opium alkaloids*	
N02AA01	morphine	1.3; 2.2
N02B	*Other analgesics and antipyretics*	
N02BA	*Salicylic acid and derivatives*	
N02BA01	acetylsalicylic acid	2.1; 7.1
N02BE	*Anilides*	
N02BE01	paracetamol	2.1; 7.1
N03	**Antiepileptics**	
N03A	**Antiepileptics**	
N03AA	*Barbiturates and derivatives*	
N03AA02	phenobarbital	5
N03AB	*Hydantoin derivatives*	
N03AB02	phenytoin	5
N03AD	*Succinimide derivatives*	

ATC code	ATC group/medicine or item	Section
N03AD01	ethosuximide	5
N03AF	*Carboxamide derivatives*	
N03AF01	carbamazepine	5; 24.2.2
N03AG	*Fatty acid derivatives*	
N03AG01	valproic acid	5; 24.2.2
N04	**Anti-parkinson drugs**	
N04A	**Anticholinergic agents**	
N04AA	*Tertiary amines*	
N04AA02	biperiden	9
N04B	**Dopaminergic agents**	
N04BA	*Dopa and dopa derivatives*	
N04BA02	levodopa and decarboxylase inhibitor*	9
N05	**Psycholeptics**	
N05A	**Antipsychotics**	
N05AA	*Phenothiazines with aliphatic side-chain*	
N05AA01	chlorpromazine	24.1
N05AB	*Phenothiazines with piperazine structure*	
N05AB02	fluphenazine	24.1
N05AD	*Butyrophenone derivatives*	
N05AD01	haloperidol	24.1
N05AN	*Lithium*	
N05AN01	lithium*	24.2.2
N05B	**Anxiolytics**	
N05BA	*Benzodiazepine derivatives*	
N05BA01	diazepam	1.3; 5; 24.3
N05BA06	lorazepam	5
N06	**Psychoanaleptics**	
N06A	**Antidepressants**	
N06AA	*Non-selective monoamine reuptake inhibitors*	
N06AA04	clomipramine	24.4
N06AA09	amitriptyline	24.2.1
N06AB	*Selective serotonin reuptake inhibitors*	
N06AB03	fluoxetine	24.2.1
N06B	**Psychostimulants, agents used for ADHD and nootropics**	
N06BC	*Xanthine derivatives*	
N06BC01	caffeine citrate	29
N07	**Other nervous system drugs**	
N07A	**Parasympathomimetics**	
N07AA	*Anticholinesterases*	
N07AA01	neostigmine	20
N07AA02	pyridostigmine	20

ATC code	ATC group/medicine or item	Section
N07B	**Drugs used in addictive disorders**	
N07BA	*Drugs used in nicotine dependence*	
N07BA01	nicotine replacement therapy*	24.5
N07BC	*Drugs used in opioid dependence*	
N07BC02	methadone	24.5
P	**ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS**	
P01	**Antiprotozoals**	
P01A	**Agents against amoebiasis and other protozoal diseases**	
P01AB	*Nitroimidazole derivatives*	
P01AB01	metronidazole	6.5.1
P01AC	*Dichloroacetamide derivatives*	
P01AC01	diloxanide	6.5.1
P01B	**Antimalarials**	
P01BA	*Aminoquinolines*	
P01BA01	chloroquine	2.4; 6.5.3.1; 6.5.3.2
P01BA03	primaquine	6.5.3.1
P01BA06	amodiaquine	6.5.3.1
P01BB	*Biguanides*	
P01BB01	proguanil	6.5.3.2
P01BC	*Methanolquinolines*	
P01BC01	quinine	6.5.3.1
P01BC02	mefloquine	6.5.3.1; 6.5.3.2
P01BD	*Diaminopyrimidines*	
P01BD01	pyrimethamine	6.5.4
P01BD51	pyrimethamine, combinations*	6.5.3.1
P01BE	*Artemisinin and derivatives*	
P01BE02	artemether	6.5.3.1
P01BE03	artesunate	6.5.3.1
P01BE52	artemether, combinations*	6.5.3.1
P01C	**Agents against leishmaniasis and trypanosomiasis**	
P01CA	*Nitroimidazole derivatives*	
P01CA02	benznidazole	6.5.5.2
P01CB	*Antimony compounds*	
P01CB01	meglumine antimoniate	6.5.2
P01CB02	sodium stibogluconate	6.5.2
P01CC	*Nitrofuran derivatives*	
P01CC01	nifurtimox	6.5.5.1; 6.5.5.2
P01CD	*Arsenic compounds*	
P01CD01	melarsoprol	6.5.5.1
P01CX	*Other agents against leishmaniasis and trypanosomiasis*	

ATC code	ATC group/medicine or item	Section
P01CX01	pentamidine isethionate*	6.5.4; 6.5.5.1
P01CX02	suramin sodium	6.1.2; 6.5.5.1
P01CX03	eflornithine	6.5.5.1
P02	**Anthelmintics**	
P02B	**Antitrematodals**	
P02BA	*Quinoline derivatives and related substances*	
P02BA01	praziquantel	6.1.1; 6.1.3
P02BA02	oxamniquine	6.1.3
P02BX	*Other antitrematodal agents*	
P02BX04	triclabendazole	6.1.3
P02C	**Antinematodal agents**	
P02CA	*Benzimidazole derivatives*	
P02CA01	mebendazole	6.1.1
P02CA03	albendazole	6.1.1
P02CB	*Piperazine and derivatives*	
P02CB02	diethylcarbamazine	6.1.2
P02CC	*Tetrahydropyrimidine derivatives*	
P02CC01	pyrantel	6.1.1
P02CE	*Imidazothiazole derivatives*	
P02CE01	levamisole	6.1.1
P02CF	*Avermectines*	
P02CF01	ivermectin	6.1.2
P02D	**Anticestodals**	
P02DA	*Salicylic acid derivatives*	
P02DA01	niclosamide	6.1.1
P03	**Ectoparasiticides, incl. scabicides, insecticides and repellents**	
P03A	**Ectoparasiticides, incl. scabicides**	
P03AC	*Pyrethrines, incl. synthetic compounds*	
P03AC04	permethrin	13.6
P03AX	*Other ectoparasiticides, incl. scabicides*	
P03AX01	benzyl benzoate	13.6
R	**RESPIRATORY SYSTEM**	
R01	**Nasal preparations**	
R01A	*Decongestants and other nasal preparations for topical use*	
R01AA	*Sympathomimetics, plain*	
R01AA07	*xylometazoline*	28
R01AD	*Corticosteroids*	
R01AD05	budesonide	28
R03	**Drugs for obstructive airway diseases**	
R03A	*Adrenergics, inhalants*	

ATC code	ATC group/medicine or item	Section
R03AC	*Selective beta-2-adrenoreceptor agonists*	
R03AC02	salbutamol	25.1
R03B	**Other drugs for obstructive airway diseases, inhalants**	
R03BA	*Glucocorticoids*	
R03BA01	beclometasone	25.1
R03BB	*Anticholinergics*	
R03BB01	ipratropium bromide	25.1
R03C	**Adrenergics for systemic use**	
R03CA	*Alpha- and beta-adrenoreceptor agonists*	
R03CA02	ephedrine	1.2
R03CC	*Selective beta-2-adrenoreceptor agonists*	
R03CC02	salbutamol	25.1
R05	**Cough and cold preparations**	
R05D	**Cough suppressants, excl. combinations with expectorants**	
R05DA	*Opium alkaloids and derivatives*	
R05DA04	codeine	2.2; 17.5.3
R06	**Antihistamines for systemic use**	
R06A	**Antihistamines for systemic use**	
R06AB	*Substituted alkylamines*	
R06AB04	chlorphenamine	3
R07	**Other respiratory system products**	
R07A	**Other respiratory system products**	
R07AA	*Lung surfactants*	*29*
S	**SENSORY ORGANS**	
S01	**Ophthalmologicals**	
S01A	**Antiinfectives**	
S01AA	*Antibiotics*	
S01AA09	tetracycline	21.1
S01AA11	gentamicin	21.1
S01AD	*Antivirals*	
S01AD03	aciclovir	21.1
S01B	**Antiinflammatory agents**	
S01BA	*Corticosteroids, plain*	
S01BA04	prednisolone	21.2
S01E	**Antiglaucoma preparations and miotics**	
S01EA	*Sympathomimetics in glaucoma therapy*	
S01EA01	epinephrine	21.5
S01EB	*Parasympathomimetics*	
S01EB01	pilocarpine	21.4
S01EC	*Carbonic anhydrase inhibitors*	
S01EC01	acetazolamide	21.4

ATC code	ATC group/medicine or item	Section
S01ED	*Beta blocking agents*	
S01ED01	timolol	21.4
S01F	**Mydriatics and cycloplegics**	
S01FA	*Anticholinergics*	
S01FA01	atropine	21.5
S01FA06	tropicamide	14.1
S01H	**Local anesthetics**	
S01HA	*Local anesthetics*	
S01HA03	tetracaine	21.3
S01J	**Diagnostic agents**	
S01JA	*Colouring agents*	
S01JA01	fluorescein	14.1
S02	**Otologicals**	
S02A	**Antiinfectives**	
S02AA	*Antiinfectives*	
S02AA10	acetic acid	28
S02AA15	ciprofloxacin	28
V	**VARIOUS**	
V03	**All other therapeutic products**	
V03A	**All other therapeutic products**	
V03AB	*Antidotes*	
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
V03AB26	methionine*	4.2
V03AB31	potassium ferric hexacyanoferrate (II) ·2H2O (Prussian blue)	4.2
V03AC	*Iron chelating agents*	
V03AC01	deferoxamine	4.2
V03AF	*Detoxifying agents for antineoplastic treatment*	
V03AF01	*mesna*	*8.2*
V03AF03	*calcium folinate*	*8.2*
V03AN	*Medical gases*	
V03AN01	oxygen	1.1
V04	**Diagnostic agents**	
V04C	**Other diagnostic agents**	
V04CF	*Tuberculosis diagnostics*	
V04CF01	tuberculin, purified protein derivative (PPD)*	19.1

ATC code	ATC group/medicine or item	Section
V07	**All other non-therapeutic products**	
V07A	**All other non-therapeutic products**	
V07AB	*Solvents and diluting agents, incl. irrigating solutions**	26.3
V07AV	*Technical disinfectants**	15.2
V08	**Contrast media**	
V08A	**X-ray contrast media, iodinated**	
V08AA	*Watersoluble, nephrotropic, high osmolar X-ray contrast media*	
V08AA01	diatrizoic acid*	14.2
V08AB	*Watersoluble, nephrotropic, low osmolar X-ray contrast media*	
V08AB02	iohexol	14.2
V08AC	*Watersoluble, hepatotropic X-ray contrast media*	
V08AC02	iotroxic acid*	14.2
V08B	**X-ray contrast media, non-iodinated**	
V08BA	*Barium sulfate containing X-ray contrast media*	
V08BA01	barium sulfate with suspending agents*	14.2

* Medicine or item name differs slightly from the name used in the Model List.

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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	12.5
acetylsalicylic acid	N02BA01	2.1; 7.1
aciclovir	J05AB01	6.4.1
aciclovir	S01AD03	21.1
albendazole	P02CA03	6.1.1
alcuronium	M03AA01	20
allopurinol	M04AA01	2.3
aluminium diacetate	D10AX05	13.4
aluminium hydroxide	A02AB01	17.1
amidotrizoate*	V08AA01	14.2
amikacin	J01GB06	6.2.4
amiloride	C03DB01	16
amiodarone	C01BD01	12.2
amitriptyline	N06AA09	24.2.1
amlodipine	C08CA01	12.3
amodiaquine	P01BA06	6.5.3.1
amoxicillin	J01CA04	6.2.1
amoxicillin + clavulanic acid*	J01CR02	6.2.1
amphotericin B	J02AA01	6.3; 6.5.2
ampicillin	J01CA01	6.2.1
anti-D immunoglobulin (human)	J06BB01	19.2
antitetanus immunoglobulin (human)	J06BB02	19.2
antivenom immunoglobulin*	J06AA03	19.2
artemether	P01BE02	6.5.3.1
artemether + lumefantrine*	P01BE52	6.5.3.1
artesunate	P01BE03	6.5.3.1
ascorbic acid	A11GA01	27
asparaginase	L01XX02	8.2
atazanavir	J05AE08	6.4.2.3
atenolol	C07AB03	12.1;12.2;12.3
atropine	A03BA01	1.3; 4.2
atropine	S01FA01	21.5
azathioprine	L04AX01	2.4; 8.1
azithromycin	J01FA10	6.2.2

Medicine or item as in EML	ATC code	section
barium sulfate*	V08BA01	14.2
BCG vaccine*	J07AN01	19.3
beclometasone	R03BA01	25.1
benzathine benzylpenicillin	J01CE08	6.2.1
benznidazole	P01CA02	6.5.5.2
benzoic acid + salicylic acid*	D01AE20	13.1
benzoyl peroxide	D10AE01	13.5
benzyl benzoate	P03AX01	13.6
benzylpenicillin	J01CE01	6.2.1
betamethasone	D07AC01	13.3
biperiden	N04AA02	9
bleomycin	L01DC01	8.2
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
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
charcoal, activated*	A07BA01	4.1
chlorambucil	L01AA02	8.2
chloramphenicol	J01BA01	6.2.2
chlorhexidine	D08AC02	15.1
chlorine base compound*	D08AX	15.2
chloroquine	P01BA01	2.4; 6.5.3.1; 6.5.3.2
chloroxylenol	D08AE05	15.2
chlorphenamine	R06AB04	3
chlorpromazine	N05AA01	24.1
cholecalciferol*	A12AX	27
cholera vaccine	J07AE	19.3
ciclosporin	L04AA01	8.1
ciprofloxacin	J01MA02	6.2.2
ciprofloxacin	S02AA15	28
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

Medicine or item as in EML	ATC code	section
coal tar*	D05AA	13.5
codeine	R05DA04	2.2; 17.5.3
copper-containing device*	G02BA02	18.3.3
cyclophosphamide	L01AA01	8.2
cycloserine	J04AB01	6.2.4
cytarabine	L01BC01	8.2
dacarbazine	L01AX04	8.2
dactinomycin	L01DA01	8.2
dapsone	J04BA02	6.2.3
daunorubicin	L01DB02	8.2
deferoxamine	V03AC01	4.2
dexamethasone	H02AB02	3; 8.3; 17.2
dextran 70*	B05AA05	11.1
diaphragms*	G02BB	18.3.4
diazepam	N05BA01	1.3; 5; 24.3
didanosine (ddI)	J05AF02	6.4.2.1
diethylcarbamazine	P02CB02	6.1.2
digoxin	C01AA05	12.2; 12.4
diloxanide	P01AC01	6.5.1
dimercaprol	V03AB09	4.2
diphtheria antitoxin	J06AA01	19.2
diphtheria vaccine*	J07AF01	19.3
dithranol	D05AC01	13.5
DL-methionine*	V03AB26	4.2
dopamine	C01CA04	12.4
doxorubicin	L01DB01	8.2
doxycycline	J01AA02	6.2.2; 6.5.3.1; 6.5.3.2
efavirenz (EFV or EFZ)	J05AG03	6.4.2.2
efavirenz + emtricitabine + tenofovir	J05AR06	
eflornithine	P01CX03	6.5.5.1
emtricitabine	J05AF09	6.4.2.1
emtricitabine + tenofovir	J05AR03	
enalapril	C09AA02	12.3; 12.4
ephedrine	R03CA02	1.2
epinephrine (adrenaline)*	S01EA01	21.5
epinephrine (adrenaline)*	C01CA24	3; 12.2; 25.1
ergocalciferol	A11CC01	27
ergometrine	G02AB03	22.1
erythromycin	J01FA01	6.2.2
estradiol cypionate + medroxyprogesterone*	G03AA08	18.3.2
ethambutol	J04AK02	6.2.4
ethambutol + isoniazid*	J04AM03	6.2.4
ethambutol + isoniazid + pyrazinamide + rifampicin*	J04AM06	6.2.4
ethambutol + isoniazid + rifampicin	J04AM	6.2.4
ethanol	D08AX08	15.1
ethinylestradiol	G03CA01	18.4

Medicine or item as in EML	ATC code	section
ethinylestradiol + levonorgestrel*	G03AB03	18.3.1
ethinylestradiol + norethisterone*	G03AA05	18.3.1
ethionamide	J04AD03	6.2.4
ethosuximide	N03AD01	5
etoposide	L01CB01	8.2
factor IX complex (coagulation factors II, VII, IX, X) concentrate*	B02BD01	11.2
factor VIII concentrate*	B02BD02	11.2
ferrous salt*	B03A	10.1
ferrous salt + folic acid*	B03AD	10.1
fluconazole	J02AC01	6.3
flucytosine	J02AX01	6.3
fludrocortisone	H02AA02	18.1
fluorescein	S01JA01	14.1
fluorouracil	L01BC02	8.2; 13.5
fluoxetine	N06AB03	24.2.1
fluphenazine	N05AB02	24.1
folic acid	B03BB01	10.1
furosemide	C03CA01	12.4; 16
gentamicin	J01GB03	6.2.2
gentamicin	S01AA11	21.1
glibenclamide	A10BB01	18.5
glucose*	B05BA03	26.2
glucose with sodium chloride*	B05BB02	26.2
glutaral*	V07AV	15.2
glyceryl trinitrate	C01DA02	12.1
griseofulvin	D01BA01	6.3
haemophilus influenzae type b vaccine	J07CA04	19.3
haloperidol	N05AD01	24.1
halothane	N01AB01	1.1
heparin sodium*	B01AB01	10.2
hepatitis A vaccine	J07BC02	19.3
hepatitis B vaccine	J07BC01	19.3
human normal immunoglobulin	J06BA	11.2
hydrazaline	C02DB02	12.3
hydrochlorothiazide	C03AA03	12.3; 12.4; 16
hydrocortisone	A07EA02	17.3
hydrocortisone	D07AA02	13.3
hydrocortisone	H02AB09	3; 8.3
hydroxocobalamin	B03BA03	10.1
hydroxycarbamide	L01XX05	8.2
ibuprofen	M01AE01	2.1; 29
ifosfamide	L01AA06	8.2
imipenem + cilastatin*	J01DH51	6.2.1

Medicine or item as in EML	ATC code	section
indinavir (IDV)	J05AE02	6.4.2.3
influenza vaccine	J07BB	19.3
insulin injection (soluble)*	A10AB	18.5
intermediate-acting insulin*	A10AC	18.5
intraperitoneal dialysis solution*	B05DA	23
iodine*	A12CX	27
iohexol	V08AB02	14.2
ipratropium bromide	R03BB01	25.1
isoniazid	J04AC01	6.2.4
isoniazid + pyrazinamide + rifampicin*	J04AM05	6.2.4
isoniazid + rifampicin*	J04AM02	6.2.4
isosorbide dinitrate	C01DA08	12.1
ivermectin	P02CF01	6.1.2
Japanese encephalitis vaccine	J07BA02	19.3
kanamycin	J01GB04	6.2.4
ketamine	N01AX03	1.1
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
levamisole	P02CE01	6.1.1
levodopa + carbidopa*	N04BA02	9
levonorgestrel	G03AC03	18.3.1
levonorgestrel-releasing implant*	G02BA03	18.3.5
levothyroxine*	H03AA01	18.8
lidocaine	C01BB01	12.2
lidocaine	N01BB02	1.2
lidocaine + epinephrine (adrenaline)*	N01BB52	1.2
lithium carbonate*	N05AN01	24.2.2
lopinavir + ritonavir (LPV/r)*	J05AE30	6.4.2.3
lorazepam	N05BA06	5
Lugol's solution*	H03CA	18.8
magnesium hydroxide	A02AA04	17.1
magnesium sulfate	B05XA05	5
mannitol	B05BC01	16
measles vaccine*	J07BD	19.3
mebendazole	P02CA01	6.1.1
medroxyprogesterone acetate*	G03AC06	18.7
mefloquine	P01BC02	6.5.3.1; 6.5.3.2
meglumine antimoniate	P01CB01	6.5.2
meglumine iotroxate*	V08AC02	14.2
melarsoprol	P01CD01	6.5.5.1
meningococcal meningitis vaccine*	J07AH	19.3
mercaptopurine	L01BB02	8.2

Medicine or item as in EML	ATC code	section
mesna	V03AF01	8.2
metformin	A10BA02	18.5
methadone	N07BC02	24.5
methotrexate	L01BA01	2.4; 8.2
methyldopa*	C02AB01	12.3
methylrosanilinium chloride (gentian violet)*	D01AE02	13.2
methylthioninium chloride (methylene blue)	V03AB17	4.2
metoclopramide	A03FA01	17.2
metronidazole	J01XD01	6.2.2
metronidazole	P01AB01	6.5.1
miconazole	D01AC02	13.1
mifepristone	G03XB01	22.1
misoprostol	G02AD06	22.1
morphine	N02AA01	1.3; 2.2
mumps vaccine	J07BE01	19.3
naloxone	V03AB15	4.2
neomycin sulfate + bacitracin*	D06AX04	13.2
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
nitrous oxide	N01AX13	1.1
norethisterone	G03DC02	18.7
norethisterone enantate*	G03AC01	18.3.2
nystatin	D01AA01	6.3
ofloxacin	J01MA01	6.2.4
omeprazole	A02BC01	17.1
ondansetron	A04AA01	17.2
oral rehydration salts*	A07CA	17.5.1; 26.1
oxamniquine	P02BA02	6.1.3
oxygen	V03AN01	1.1
oxytocin	H01BB02	22.1
p-aminosalicylic acid*	J04AA01	6.2.4
pancreatic enzymes	A09AA02	17
paracetamol	N02BE01	2.1; 7.1
paromomycin	A07AA06	6.5.2
penicillamine	M01CC01	2.4; 4.2
pentamidine*	P01CX01	6.5.4; 6.5.5.1
permethrin	P03AC04	13.6
pertussis vaccine	J07AJ	19.3
phenobarbital	N03AA02	5

Medicine or item as in EML	ATC code	section
phenoxymethylpenicillin	J01CE02	6.2.1
phenytoin	N03AB02	5
phytomenadione	B02BA01	10.2
pilocarpine	S01EB01	21.4
pneumoccocal vaccine	J07AL	19.3
podophyllum resin*	D06BB04	13.5
poliomyelitis vaccine	J07BF	19.3
polyvidone iodine	D08AG02	15.1
potassium chloride	B05XA01	26.1; 26.2
potassium ferric hexacyanoferrate (II).2H_2O (Prussian blue)	V03AB31	4.2
potassium iodide*	H03CA	18.8
potassium permanganate	D08AX06	13.2
praziquantel	P02BA01	6.1.1; 6.1.3
prednisolone	H02AB06	3; 8.3
prednisolone	S01BA04	21.2
primaquine	P01BA03	6.5.3.1
procaine benzylpenicillin	J01CE09	6.2.1
procarbazine	L01XB01	8.2
proguanil	P01BB01	6.5.3.2
promethazine	D04AA10	1.3
propranolol	C07AA05	7.2
propylthiouracil	H03BA02	18.8
prostaglandin E*	C01EA01	29
protamine sulfate*	V03AB14	10.2
pyrantel	P02CC01	6.1.1
pyrazinamide	J04AK01	6.2.4
pyridostigmine	N07AA02	20
pyridoxine	A11HA02	27
pyrimethamine	P01BD01	6.5.4
quinine	P01BC01	6.5.3.1
rabies immunoglobulin	J06BB05	19.2
rabies vaccine	J07BG	19.3
ranitidine	A02BA02	17.1
retinol	A11CA01	27
ribavirin	J05AB04	6.4.3
riboflavin	A11HA04	27
rifabutin	J04AB04	6.2.4
rifampicin	J04AB02	6.2.3; 6.2.4
ritonavir (r)	J05AE03	6.4.2.3
rotavirus vaccine	J07BH01	19.3
rubella vaccine	J07BJ01	19.3
salbutamol	R03AC02	25.1
salbutamol	R03CC02	25.1
salicylic acid	D01AE12	13.5
saquinavir (SQV)	J05AE01	6.4.2.3

Medicine or item as in EML	ATC code	section
selenium sulfide	D01AE13	13.1
senna*	A06AB06	17.4
silver sulfadiazine	D06BA01	13.2
simvastatin	C01AA01	12.6
sodium calcium edetate*	V03AB03	4.2
sodium chloride	B05XA03	26.2
sodium fluoride	A12CD01	27
sodium hydrogen carbonate*	B05XA02	26.2
sodium lactate*	B05BB01	26.2
sodium nitrite	V03AB08	4.2
sodium nitroprusside*	C02DD01	12.3
sodium stibogluconate	P01CB02	6.5.2
sodium thiosulfate*	V03AB06	4.2; 13.1
spectinomycin	J01XX04	6.2.2
spironolactone	C03DA01	16
stavudine (d4T)	J05AF04	6.4.2.1
streptokinase	B01AD01	12.5
streptomycin	J01GA01	6.2.4
sulfadiazine	J01EC02	6.5.4
sulfadoxine + pyrimethamine*	P01BD51	6.5.3.1
sulfamethoxazole + trimethoprim	J01EE01	6.2.2; 6.5.4
sulfasalazine	A07EC01	2.4; 17.3
suramin sodium	P01CX02	6.1.2; 6.5.5.1
surfactant*	R07AA	29
suxamethonium	M03AB01	20
tamoxifen	L02BA01	8.3
tenofovir disoproxil fumarate*	J05AF07	6.4.2.1
testosterone	G03BA03	18.2
tetanus vaccine	J07AM	19.3
tetracaine	S01HA03	21.3
tetracycline	S01AA09	21.1
thiamine	A11DA01	27
thiopental	N01AF03	1.1
timolol	S01ED01	21.4
triclabendazole	P02BX04	6.1.3
trimethoprim	J01EA01	6.2.2
tropicamide	S01FA06	14.1
tuberculin, purified protein derivative (PPD)*	V04CF01	19.1
typhoid vaccine	J07AP	19.3
urea*	D02AE01	13.5
valproic acid	N03AG01	5; 24.2.2
vancomycin	J01XA01	6.2.2
varicella vaccine	J07BK01	19.3
vecuronium	M03AC03	20
verapamil	C08DA01	12.1; 12.2

Medicine or item as in EML	ATC code	section
vinblastine	L01CA01	8.2
vincristine	L01CA02	8.2
warfarin	B01AA03	10.2
water for injection*	V07AB	26.3
xylometazoline	R01AA07	28
yellow fever vaccine	J07BL	19.3
zidovudine (ZDV or AZT)	J05AF01	6.4.2.1
zinc sulfate	A12CB01	17.5.2

* Medicine or item name differs slightly from the name used in the Model List.

PART TWO

Second Meeting of the Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines

Second Meeting of the Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines

Geneva 29 September to 3 October 2008

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1. Introduction

The Second Meeting of the WHO Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines met in Geneva from 29 September to 3 October 2008. The meeting was opened on behalf of the Director-General by Dr Hans Hogerzeil, Director of the Department of Essential Medicines and Pharmaceutical Policies, who noted that this was the second meeting of the Subcommittee, following its original approval by the Executive Board in May 2007 (EB121.R2). He outlined the procedures of the meeting to participants, noting that the Subcommittee is not a representative one and that all members participate in their personal capacity and are not allowed to take instructions from any government or other authority.

The WHO Secretariat requested and received agreement from the Committee to hold an open session as part of its meeting (see Section 2). The purpose of the open session was to allow all stakeholders to participate in the discussions and to comment on issues relating to the WHO Model List of Essential Medicines for Children (EMLc). For Subcommittee members it provided an opportunity to receive, at first hand, additional information and opinion on matters under consideration. The discussions and considerations of the open session are reflected in the report of the meeting.

The full texts of the applications for changes, additions or deletions with all the evidence and references, as well as the external reviews and comments received are not included in the report but remain available on the WHO web site (http://www.who.int/selection_medicines/committees/subcommittee/2/en/index.html).

2. Open session

The open session was opened by Dr Hans Hogerzeil. He welcomed external participants and stated that all comments made during the session would be noted and taken into consideration by the Expert Subcommittee when formulating their recommendations.

The Secretariat provided an update on work undertaken since the first meeting of the Subcommittee in 2007, including progress made in relation to the World Health Assembly Resolution on Better Medicines for Children. This update included highlighting the global burden of disease mortality in children younger than five years of age, and some of the challenges of ensuring equitable access to essential medicines for children in different countries (for example, limits on logistical capacity in isolated island countries). Progress with work on the Resolution was also described, including the assessment of availability of medicines for children in several

countries, the revision of national medicines lists to include medicines for children, and the launch of an advocacy campaign, "Make Medicines Child Size" that aims to promote the development of appropriate high-quality essential medicines for children.

Participant statements were received from:

— Dr Kate Armstrong, President of CLAN (Congenital Adrenal Hyperplasia: Caring and Living as Neighbours);
— Dr Myriam Henkens, International Medical Coordinator of Médecins Sans Frontières (MSF);
— The representative of the Permanent Mission of Canada;
— Mrs Hanne Bak Pederson, UNICEF;
— Dr Rajiv Bahl, WHO Department of Child and Adolescent Health and Development.

Comments were received from UNICEF, reiterating the importance of the EMLc, and from the Child and Adolescent Health and Development Department of WHO, which welcomed the opportunity to be involved in the Subcommittee meeting to offer its perspective on several of the applications.

In their absence, the Secretariat read statements from Dr Armstrong and Dr Henkens. Dr Armstrong wished to emphasize the essential and global requirement for hydrocortisone and fludrocortisone as life-saving drugs in the management of congenital adrenal hyperplasia and adrenal insufficiency, and urged their inclusion on the EMLc. Médecins Sans Frontières sent a number of comments outlining its support for the inclusion of liposomal amphotericin B, doxycycline, oral salbutamol and quinolones on the Core List, but opposing the addition of lindane. The representative of the Permanent Mission of Canada posed a question to the Subcommittee regarding the proposal for the deletion of vitamin A 50 000 IU capsule.

3. Review of terms of reference

The Subcommittee reviewed the terms of reference provided to it by the Executive Board, which are reproduced below. Discussion of the terms of reference is included in this section of the report; amendments to the Model List of Essential Medicines for Children are discussed in Section 4.

The Executive Board:

1. DECIDES to establish as from June 2007 a temporary Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines, of no more than 15 members, with the following terms of reference:

- *to prepare a list of medicines for children, based on their clinical needs and the burden of disease, that the WHO Expert Committee on the*

Selection and Use of Essential Medicines can use to revise and regularly update the WHO Model List of Essential Medicines to include missing essential medicines for children;

- *to determine suitability criteria for dosage forms of medicines for children, with particular attention to conditions prevailing in the developing countries;*
- *to review the feasibility of manufacturing appropriate formulations for those priority medicines for which no dosage form for children currently exists, specifically considering requirements for use in resource-limited settings and availability of data on efficacy and safety in the appropriate age groups;*
- *to identify the clinical-research gaps regarding safety and efficacy of essential medicines for children in order to improve suboptimal prescribing and dosing, and to facilitate regulatory approval of paediatric formulations;*
- *to report to the Expert Committee on the Selection and Use of Essential Medicines in 2009.*

2. FURTHER DECIDES that the temporary Subcommittee shall terminate in 2009, after its report to the Expert Committee on the Selection and Use of Essential Medicines.

The Subcommittee evaluated its progress based upon the terms of reference given to it by the Executive Board. A summary of progress for each of the terms of reference is provided as follows:

Term of reference 1 — *prepare a list of medicines for children, based on their clinical needs and the burden of disease, that the WHO Expert Committee on the Selection and Use of Essential Medicines can use to revise and regularly update the WHO Model List of Essential Medicines to include missing essential medicines for children*

Through review and deliberations, the Subcommittee substantially increased and refined the information contained in the EMLc, which had been presented and approved in 2007. The proposed second WHO Model List of Essential Medicines for Children is provided as Annex 2 to this report, and will be submitted to the Expert Committee to review and approve at its next meeting. Further discussion of this List can be found below, under term of reference 5.

In spite of these accomplishments, work remains incomplete, largely due to the volume of information necessary to construct an EMLc that will meet the needs of the world's children. During its deliberations, the Subcommittee worked diligently to identify gaps while dealing with a wide range of information (relating to clinical pharmacology and therapeutics, clinical toxicology and pharmacovigilance) associated with medicine

products, their availability in formulations suitable for children in both developed and developing nations, and their suitability for use in children. The decisions reached and recommendations made by the Subcommittee were largely driven by considerations of therapeutic decision-making as opposed to generating lists of specific products. Decisions were based on review of available accumulated evidence whenever possible as opposed to simply reflecting current practice. The Subcommittee recognizes that when data are not available from paediatric clinical trials, there is still an imperative to make decisions based on the available information as it is unethical to deprive children of access to necessary treatment.

Term of reference 2 — *to determine suitability criteria for dosage forms of medicines for children, with particular attention to conditions prevailing in the developing countries*

Comments were received by the Subcommittee from Dr Sabine Kopp, representing the WHO Expert Committee on Specifications for Pharmaceutical Preparations, who discussed the development of a working paper entitled *Development of paediatric medicines: pharmaceutical development, points to consider*. A number of drafts had already been prepared and revised, following several comments that had been received. It was also noted that an informal working group had been established in collaboration with the National Institute of Child Health and Human Development, National Institutes of Health, USA, and others to ensure that the ongoing work of the Subcommittee satisfies the above terms of reference, particularly with regard to determining suitability criteria for dosage forms of medicines for children.

During its review of the EMLc, the Subcommittee identified a list of adult preparations that are frequently prepared extemporaneously for administration to children (Table 1). The Subcommittee recommended development of a set of guidelines on the use of extemporaneous preparations in children, including highlighting those medicines (not listed) that should never be prepared in an extemporaneous manner.

Table 1
Common extemporaneous preparations

Medicine	Existing form	Extemporaneous preparation
Acetic acid	Ear drops	Compounded
Anti-neoplastic medicines	Various	Preparation of lower dose forms or forms for alternative routes of administration
Artemether + lumefantrine	Tablet	Crushed tablet
Ethambutol	Tablet	Crushed for oral liquid
Fluconazole	Capsule	Opened for administration as liquid
Fludrocortisone	Tablet	Administered as liquid
Gentamicin	Eye drop	Combined with injection for higher strength
Hydrochlorthiazide	Tablet	Administered as liquid
Hydrocortisone	Tablet	Administered as liquid
Isoniazid	Liquid form	Administered rectally
Levothyroxine, propylthiouracil	Tablet	Administered as liquid
Midazolam	Injection	Administered as oral liquid
Morphine	Oral, injection	Preparation of liquids, dilution of injection
Peritoneal dialysis	Various	Preparation of different strengths/ formulations
Prostaglandins	Injection	Administered as liquid
Pyridostigmine	Tablet	Administered as liquid
Pyridoxine	Tablet	Administered as liquid
Sulfadoxine + pyrimethamine	Tablet	Crushed for liquid
Thiamine	Tablet	Administered as liquid

This report of the Subcommittee clearly reflects that work addressing suitability criteria for dosage forms is underway but is still far from complete. It was noted that specific recommendations for additions or amendments to the List were driven in large part by products that were identified as available in highly developed countries, with the assumption that they would be adopted and/or readily accepted for procurement or manufacture by developing countries. The Subcommittee also identified significant information gaps and research issues related to further development of dosage forms. In the absence of a mandate or mechanism for the Subcommittee to take the next steps to address these challenges, its recommendations must be considered, at this juncture, as suggestions for continued work by WHO.

Term of reference 3 — *to review the feasibility of manufacturing appropriate formulations for those priority medicines for which no dosage form for children currently exists, specifically considering requirements for use in resource-limited settings and availability of data on efficacy and safety in the appropriate age groups*

As regards this term of reference, the Subcommittee has achieved only a conceptual beginning. The recommendations made reflect expert opinion offered in the hope of providing direction to WHO that would enable it to leverage the resources required to ensure that appropriate paediatric medicine products are formulated and made widely available. When possible, specific recommendations for formulations were made (e.g. concentrations of drugs in parenteral solutions appropriate for use in neonates and young infants). The Subcommittee emphatically supports the need to address rational therapeutic use of these formulations and also, careful and critical assessment of their efficacy and safety. Furthermore, considerations of product safety must take into account not only the active ingredients but also excipients that may have intrinsic pharmacological activity.

Term of reference 4 — *to identify the clinical-research gaps regarding safety and efficacy of essential medicines for children in order to improve suboptimal prescribing and dosing, and to facilitate regulatory approval of paediatric formulations*

The Subcommittee identified and prioritized clinical research and information gaps related to paediatric therapeutics, ranging from product availability to considerations of medicine selection and therapeutic use. Specific recommendations are provided in Boxes 1–4.

Box 1 lists areas in paediatric therapeutics where more information is clearly needed in order to consider further expansion of the EMLc so that the need for additional medicines for children can be met. Specific recommendations for systematic reviews and evidence syntheses to be conducted and then evaluated by the Subcommittee or the Expert Committee are listed with relative priority designated (H — high; M — medium and L — low). These are generally listed in the order of the sections of the Model List.

Box 1. Evidence syntheses/systematic reviews required

1. Appropriate medicines for pre-operative use in children H
2. Appropriate medicines for use in short-term procedures (conscious sedation) in children H
3. Review use of methylene blue in children M
4. Review use of oral iron/lead chelators M
5. Appropriate medicines for use in resuscitation in children H
6. Essential medicines for pain management in children H
7. Essential medicines for management of neuropathic pain in children including the role of lamotrigine, amitryptiline and gabapentin H
8. Essential medicines for management of juvenile inflammatory arthritis L
9. Review of safety and effectiveness of penicillamine compared to sodium calcium edentate L
10. Review of safety and effectiveness of anthelminthics in children H
11. Antimonials as essential medicines for leishmaniasis (core/complementary) H
12. Safety and efficacy of streptomycin in childhood tuberculosis H
13. Other questions identified in the report on tuberculosis medicines H
14. Essential cytotoxic therapies for the commonest tumours in childhood M
15. Review of safety/toxicity of gentian violet L
16. Safety of topical antibiotics including tetracycline ointment in neonates H
17. Alternatives to benzyl benzoate for scabies treatment in young children M
18. Identification of essential diagnostic (contrast) agents for use in children L
19. Essential diuretics for use in children H
20. Clinical use of ondansetron in children M
21. Choice and optimal use of laxatives in children H
22. Essential medicines for treatment of mental health conditions in children H
23. Identification of essential vitamin and mineral supplements (including iron and folic acid) especially in children with human immunodeficiency virus/tuberculosis/ malnutrition H
24. Review role of leukotriene antagonists in management of childhood allergic rhinitis L

In identifying priorities for immediate action, the Subcommittee concluded that there were several areas where existing data were available and could easily be formulated into proposals for consideration for addition to the EMLc. Specific recommendations for such action are summarized in Box 2 below.

Box 2. Examples of areas where data exist and applications could be immediately developed

1. Application for a non-sedating antihistamine for children (appropriate comparisons)
2. Application for heat stable protease inhibitors (lopinavir/ritonavir) for HIV management
3. Assess two new clinical trials on safety and efficacy of procaine penicillin in neonates
4. Comparison of sulfadiazine and co-trimoxazole in treatment of toxoplasmosis (possible deletion of sulfadiazine)
5. Review of liposomal amphotericin B as treatment of fungal infections in children
6. Applications for amiodarone, lignocaine and adenosine for use in children
7. Application for glucagon
8. Development of child-friendly equipment for medicine administration in sizes for all ages

Discussion emanating from the meeting of the Subcommittee revealed that there were unanswered questions arising from each application. It was also considered likely that the evidence syntheses and systematic reviews listed in Box 1 will produce additional research questions. These information gaps will require the conduct of specific research targeted to critical areas in paediatric therapeutics. A list of highlighted research issues identified during both meetings of the Subcommittee and at the research consultation held in October 2007 is contained in Box 3 below.

Box 3. Research gaps

1. Safety and efficacy of meropenem in neonates
2. Safety and efficacy of protease inhibitors in children weighing less than 10 kg
3. The use of rifabutin and rifapentine for children with tuberculosis co-infection in HIV
4. The role of pharmacotherapy, including amitryptyline, lamotrigine and gabapentin, in management of neuropathic pain
5. International controls over medicines used in palliative care and the need to allow better access in situations of medical need, including use in children
6. Malaria treatments, including fixed-dose combinations that are appropriate for children
7. Treatments for Chagas disease — need for safer treatment
8. Access to insulin
9. Supply chain issues relevant to the EMLc
10. Delayed adverse effects, especially effects on development
11. Factors that modify dose–response relationships in individuals and populations

In developing the updated EMLc, the Subcommittee identified the following specific products (Box 4) as being potentially useful for treatment of children. This is, however, not to be considered as a complete or exhaustive list as it is anticipated that in future deliberations of the Expert Committee additional paediatric products will be identified.

Box 4. Product gaps

1. Boosted heat-stable protease inhibitor fixed dose combinations based on existing products and appropriate dosage forms (e.g. sprinkles)
2. Inhaled beta-agonists and corticosteroids
   - — smaller packaging
   - — affordable canisters
3. Prostaglandin E oral formulation
4. Amphotericin B — appropriate strength for neonates
5. Appropriate insulin dosage forms for neonates
6. Appropriate strengths of oral and injectable morphine formulation for neonates
7. Oral liquid form of hydrocortisone
8. Mefloquine liquid formulation
9. Pyrimethamine liquid formulation
10. Chlorhexidine digluconate 7.1%
11. Phenobarbital sodium solution — appropriate strength and alcohol-free formulation
12. A multivitamin preparation suitable for general use in neonates and young children
13. An accessible, palatable and affordable preparation of zinc salts

As with the issues of paediatric formulations, the guidance given to the Secretariat regarding research priorities is, at present, directional as opposed to strategic. The Subcommittee further identified that for these clinical information and research gaps to be adequately addressed, it will be required that the areas of expertise represented by the current Subcommittee have an effective and dynamic interface with the working groups at WHO that are charged with developing treatment guidelines. Proof-of-concept for the utility of such an approach was offered by the example of recent efforts to address the development of a suitable fixed-dose formulation containing three drugs identified as standards of care for the treatment of tuberculosis in infants and children in the developing world.

Term of reference 5 — *to report to the Expert Committee on the Selection and Use of Essential Medicines in 2009*

The Subcommittee was pleased to report that significant progress had been made in the further development of the EMLc. The List had increased definition and expanded content, driven by the assessment of objective evidence. Two new sections are recommended: medicines for ear, nose and throat disease and medicines specifically for neonatal care. The first of these sections includes topical preparations needed for the management of ear, nose and throat disorders, conditions which are common in children throughout the world and cause significant morbidity, which were not included elsewhere in the EMLc.

In recognition of the high burden of disease occurring in neonates and young infants, the Subcommittee considered the preparation of an essential

medicines list for neonates. The Subcommittee proposed adding a section to the EMLc that specifies medicines that are uniquely required for the treatment of neonates. An annex listing medicines from the EMLc that were felt to be essential in treating a variety of neonatal conditions was also provided. In addition, medicines have been proposed for inclusion under the heading of palliative care.

Appropriate utilization of medicines on the EMLc will require purposeful and careful coordination with WHO programmes engaged in the development of treatment guidelines for children. This recommendation is offered as a direct result of the Subcommittee being aware that there are existing treatment guidelines which are not aligned with the best available evidence *(1)*. It is the contention of the Subcommittee that the EMLc can and must be used to support the continued development of paediatric-specific treatment guidelines for a variety of conditions and diseases. The Subcommittee also asserts that it is critical that the work undertaken thus far continues. Specifically, WHO should take a comprehensive, translational approach towards paediatric therapeutics, which focuses clearly on medicine use and the assessment of safety and efficacy associated with drug treatment. To attain this goal for the benefit of children around the world will require continuity of effort, widened engagement of professionals with paediatric expertise that spans the continuum of drug therapy (e.g. formulation development, drug delivery, clinical pharmacology and paediatric medicine) and adoption of a strategy that continues to place a priority on the value of providing children in all countries with the right to a healthy life.

Finally, the Subcommittee discussed the most effective and efficient mechanism to provide the continuity and level of engagement required to achieve the above-mentioned objectives.

To this end, the following recommendations are offered to the Expert Committee for consideration:

1. This report of the Subcommittee will be tendered to the Expert Committee for consideration, deliberation and adoption at the meeting to be held in March 2009.
2. For the foreseeable future, it is essential that the EMLc remain separate from the WHO Model List of Essential Medicines in order to maintain a critical focus on the needs of children.
3. The Secretariat should use available resources necessary to undertake reviews recommended by the Subcommittee and also to address information and research gaps of high priority for the paediatric medicines initiative. This may be done through the development of specific contracts and/or the establishment of strategic working groups that might be focused on a specific issue.

4. Consideration should be given to the appropriate constitution of future Expert Committees in order to meet the demands of United Nations Millennium Goals 4 and 6 to focus on paediatric priorities and Resolution WHA60.20. This would include further development and expansion of the EMLc and establishing plans for its continued maintenance.
5. To meet the critical needs of improving paediatric therapeutics throughout the world through an evidence-based approach, it is imperative that WHO continue to work effectively to define and address research gaps. Most importantly, WHO should create approaches to generate the new knowledge necessary for translation of discovery into rational therapeutic practices.

4. The WHO Model List of Essential Medicines for Children — by section

Section 4. Antidotes and other substances used in poisonings

Section 4 of the Model List of Essential Medicines concerns medicines used as antidotes and for the management of poisonings. The Subcommittee had requested further evaluation of the burden of disease and disability in children due to poisoning as well as applications for specific antidotes deemed critical for children. The Secretariat had therefore commissioned reviews of two key antidotes already on the Model List and the preparation of an application for inclusion of pralidoxime.

Comments were received from the South Asian Clinical Toxicology Research Collaboration and the WHO Department of Protection of the Human Environment.

Section 4.1 Non-specific

Charcoal, activated (review)

Core List

The Subcommittee considered the review of activated charcoal for the treatment of non-specific poisoning in children. The review was commissioned by the Secretariat and provided by Dr Jennifer A. Lowry from the University of Missouri-Kansas City and Children's Mercy Hospital, USA. Expert review comments were provided by Dr Helena L. Coelho and Professor Noël Cranswick.

Accidental poisonings in children are a significant problem, particularly throughout the developing world. The Subcommittee noted that there is a paucity of high-quality evidence for the efficacy of activated charcoal in children, and that the majority of the literature is based on a collection of

case-series and case-reports in adult patients. Position statements from the American Academy of Clinical Toxicology and the European Association of Poison Centres and Clinical Toxicologists were reviewed. They suggested that activated charcoal is most effective when given within the first hour following the ingestion of a poison, and that multi-dose activated charcoal should only be used following specific ingestions. The Subcommittee also considered comments from the South Asian Clinical Toxicology Research Collaboration which supported the inclusion of activated charcoal in the EMLc.

The Subcommittee considered that despite the limited evidence from controlled clinical trials for the efficacy of activated charcoal in children, when considered on balance with the low risk of adverse reactions and the limited alternatives for gastric decontamination, activated charcoal should remain on the EMLc.

Section 4.2 Specific

Acetylcysteine (review)

The Subcommittee reviewed the inclusion of N-acetylcysteine (NAC) on the EMLc as an antidote for paracetamol (acetaminophen) toxicity. A systematic review was commissioned by the Secretariat and provided by Dr D. Adam Algren from the University of Missouri-Kansas City and Children's Mercy Hospital. The expert comments were provided by Mrs Jenna Mohammed Ali Al-Fannah and Dr Helena L. Coelho. Comments were noted from members of the South Asian Clinical Toxicology Research Collaboration who supported the inclusion of oral NAC on the EMLc.

The review summarized the clinical evidence for use of NAC in adults and noted that no randomized efficacy trials have been conducted in children. There is significant clinical evidence in adult populations to suggest that oral and intravenous NAC are equally effective. The intravenous form of NAC can also be administered orally. A small study involving 25 paediatric patients demonstrated comparable efficacy between intravenous and oral NAC. Several observational studies involving the use of oral NAC showed a decrease in the incidence of hepatotoxicity in those patients in whom NAC therapy was initiated within 10 hours of ingestion. However these studies involved only small numbers of paediatric patients.

The Subcommittee noted that the major concern with regard to adverse effects in children is that intravenous infusion in children may be associated with hyponatraemia if excessive fluids are administered in conjunction with NAC and also, anaphylactoid reactions are associated with the parenteral formulation.

The Subcommittee agreed that NAC is considered the treatment of choice for paracetamol toxicity where the dose and/or paracetamol

plasma concentrations would suggest the risk of serious hepatotoxicity from an acute ingestion. It was agreed that intravenous NAC should remain on the List, and that the oral form should be added. The proposed WHO Model Formulary for Children may need to contain advice on appropriate use, including guidance on initiation of therapy and avoidance of unnecessary administration in the situation of sub-toxic doses of paracetamol.

Pralidoxime (inclusion)

Core List

The Subcommittee considered the proposal for inclusion of pralidoxime for the treatment of organophosphate poisoning in children. Expert comments were provided by Professor H.P.S. Sachdev. Atropine is currently the only antidote on the EMLc for acute organophosphate poisoning.

The Subcommittee noted that information on the prevalence of acute organophosphate poisoning in children is limited, although it is known to be an increasing problem worldwide, particularly in rural regions of developing countries.

The Subcommittee considered the evidence for the safety and efficacy of pralidoxime provided in the proposal. The proposal was based on five systematic reviews of studies involving adult patients *(2, 3, 4, 5, 6)*. There were no data in these reviews which described the use of pralidoxime in children. The study designs were of variable quality. Collectively, the data from the adult studies were unable to conclusively establish the effectiveness of pralidoxime in the treatment of organophosphate poisoning. The Subcommittee was made aware of two case-series describing the use of intravenous pralidoxime in children with organophosphate poisoning *(7, 8)*.

Comments from the South Asian Clinical Toxicology Research Collaboration, which had been involved in a large randomized controlled trial of pralidoxime in Sri Lanka, were noted: the Collaboration stated that data analysed thus far did not provide supporting evidence for the inclusion of pralidoxime in the EMLc.

The Subcommittee considered that at this time there was insufficient evidence to justify the inclusion of pralidoxime on the EMLc. It recommended that new trial data and the additional paediatric data be considered in March 2009.

For further revision of this section, the Subcommittee recommends the future consideration of additional iron and lead chelating agents and methylene blue as potential essential antidotes for paediatric use.

Section 6. Anti-infective medicines

At its first meeting in July 2007, the Subcommittee identified a number of questions about anti-infective medicines for children that needed further review. These included the need to obtain additional evidence and safety about products already on the EMLc as well as applications for new products.

Section 6.2 Antibacterials

Section 6.2.1 Beta-Lactam medicines

The Subcommittee considered reviews of efficacy and safety for procaine benzylpenicillin, ceftazidime and ceftriaxone, the carbapenems as a class, and a new application for cefelaxin.

Expert comments on the proposals were prepared by Mr Andy Gray, Dr Kalle Hoppu, Professor Prakash Mohan Jeena, Dr Peter Kazembe, Professor Harshi Sachdev, Dr Anita Zaidi and Dr Elizabeta Zisovska.

Comments were received from the WHO Department of Child and Adolescent Health and Development.

Cefalexin (inclusion)

A new proposal, commissioned by the Secretariat, for the inclusion of cefalexin on the EMLc was considered. Expert comments on cefalexin were provided by Mr Andy Gray and Dr Kalle Hoppu. It was noted that the WHO Department of Child and Adolescent Health and Development had suggested inclusion of cefalexin on the Complementary List.

The Subcommittee noted that the Expert Committee had previously considered an application for the addition of cefazolin and cefalexin in March 2007. At that time, cefazolin was added to the EMLc based on the high quality clinical evidence for its use in surgical prophylaxis. The proposal for cefalexin, on the other hand, was rejected on the basis of the limited evidence for its comparative effectiveness over other antibiotics already included on the EMLc, and concerns about inappropriate prescribing.

The new proposal stated that first-generation oral cefalosporins are generally inexpensive, easy to administer and commonly used in community outpatient settings. They provide good cover against the common organisms (e.g. *Staphylococcus aureus* and streptococci) that cause uncomplicated community-acquired respiratory, skin and soft tissue infections; however evidence for *superiority* over other antibiotics is limited.

The Subcommittee noted that evidence for clinical efficacy and safety of cefalexin in children was limited. Evidence presented in the proposal included a Cochrane systematic review *(9)* of 16 studies for the treatment

of impetigo, which included both children and adults. Other trials *(10, 11)* using cefalexin for the treatment of Group A streptococcal pharyngitis in children and adolescents showed equivalent clinical cure rates for cefalexin and penicillin. The efficacy of cefalexin in the treatment of urinary tract infections without proven culture sensitivity has not been demonstrated, and there are insufficient data available on the use of cefalexin for prevention of rheumatic fever or carditis.

After considerable deliberation, the Subcommittee found potential merits associated with the availability of cefalexin. These included evidence of effective treatment of skin and soft tissue infections produced by a variety of pathogens (with the exception of methicillin-resistant *Staphylococcus aureus*), the treatment of uncomplicated urinary tract infections produced by sensitive pathogens, and the perception that better palatability is associated with improved adherence to treatment regimens, particularly for prolonged treatment such as in the case of osteomyelitis. Also, it was recognized that cefalexin can often be safely administered to patients who demonstrate hypersensitivity reactions to penicillin. The Subcommittee therefore added cefalexin to the EMLc Core List.

Procaine benzylpenicillin (review)

The Subcommittee considered the review of procaine benzylpenicillin in neonates. The Subcommittee had previously raised concerns in October 2007 about its safety and efficacy in neonates, despite its widespread use in this age group. Expert reviews were provided by Dr Stuart MacLeod and Dr Gregory Kearns.

It was noted that (crystalline) benzylpenicillin is the preferred agent for treating serious infections such as neonatal sepsis and congenital syphilis. However several sets of guidelines (e.g. those of the American Academy of Pediatrics and the CDC Sexually Transmitted Diseases Treatment Guidelines) recommend intramuscular procaine benzylpenicillin as an alternative for use in the management of proven congenital syphilis. Only one randomized controlled trial demonstrating a significant reduction in rapid plasma reagin (RPR) titres, following treatment for congenital syphilis with either procaine benzylpenicillin or benzathine benzylpenicillin, was included in the review *(12)*.

The Subcommittee noted that although the *WHO Pocket book of hospital care for children* recommends intramuscular procaine benzylpenicillin in combination with gentamicin as an alternative treatment to (crystalline) benzylpenicillin for the management of neonatal sepsis and meningitis in neonates, there is no evidence for the efficacy of procaine benzylpenicillin in the management of early onset Group B sepsis, or in the community management of sepsis and pneumonia in neonates. It was also noted that

procaine benzylpenicillin has low cerebrospinal fluid penetration and, therefore, may be ineffective in treating infants who develop, or who are at risk of developing, bacterial meningitis. However, the Subcommittee also noted that procaine benzylpenicillin has been used as an alternative to (crystalline) benzylpenicillin as it can easily be administered in the community with once daily intramuscular dosing.

The Subcommittee took account of the safety concerns regarding the intramuscular administration of procaine benzylpenicillin in premature and low-birth-weight infants, including the reports of injection-site abscesses, muscle fibrosis and atrophy following intramuscular injection, particularly in premature and low birth weight neonates.

The Subcommittee noted that current studies of procaine benzylpenicillin given in combination with gentamicin as first-line treatment for infants with Gram-positive infections are under way and the results will be considered when they become available. The Subcommittee recommended: removal of the age restriction for procaine benzylpenicillin; a note added that it is not recommended as first-line treatment for sepsis and/or meningitis; but requested a further review of safety.

Ceftazidime (review)

Complementary List

The Subcommittee reviewed the inclusion of ceftazidime on the Complementary List. Expert comments were provided by Professor Prakash Mohan Jeena. In July 2007, the Subcommittee had identified the need to determine whether there were preferred alternatives for use in children.

It was noted that the review found limited evidence on efficacy and safety of use of ceftazidime in children and similarly limited information about the treatment of *Pseudomonas aeruginosa* in children. The main source of information was a systematic review of 57 trials comparing cefepime with other antibiotics, but only two had compared ceftazidime to cefepime in children: one was in patients with febrile neutropenia, the other in patients with urinary tract infections *(13)*.

The Subcommittee noted that there was no clinical evidence for the superiority of one antibiotic over the other for the treatment of *Pseudomonas aeruginosa* in cystic fibrosis, or as empirical treatment for ventilator-assisted pneumonia, and that ceftazidime was the antibiotic of choice in the treatment of *Burkholderia cepacia* infections in cystic fibrosis and of *Burkholderia pseudomallei* infections.

The Subcommittee also noted that there are no recommended age restrictions for the use of ceftazidime, and that it is the least expensive of

the antipseudomonal antibiotics according to the Management Sciences for Health International Drug Price Indicator Guide.

The Subcommittee agreed that although there was no evidence to support the superior efficacy or safety of ceftazidime over other antibiotics with a similar antibacterial spectrum, the drug should remain on the Complementary List of the EMLc.

Ceftriaxone

In response to safety concerns raised at the first meeting of the Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines in 2007, the Secretariat commissioned a review of the use and safety of ceftriaxone in neonates. Expert comments were provided by Professor H.P.S. Sachdev and Dr Elizabeta Zisovska.

The review identified four trials that had studied the use of ceftriaxone in neonates, for the treatment of sepsis and meningitis. The review noted that ceftriaxone can cause significant adverse reactions in neonates, including: a potentially fatal interaction with calcium; superinfections with candida and non-susceptible bacteria such as extended spectrum beta-lactamase producers; and kernicterus.

The Subcommittee considered whether the use of ceftriaxone should be contraindicated in premature infants younger than 41 weeks total age and the use restricted to infants ≥ 1 month of age. The Subcommittee noted that safety warnings had been issued by several regulatory authorities and Roche regarding interactions between ceftriaxone and calcium. Due to precipitation that can produce severe adverse effects, the administration of calcium and ceftriaxone in the same or different infusion lines or sites must be avoided. While current information suggests that a 48-hour period between administration of ceftriaxone and calcium is required, altered pharmacokinetics of the drug in neonates may require an even longer period separating the administration of the two drugs. Ceftriaxone use should be avoided in neonates with hyperbilirubinaemia consequent to potential disruption in bilirubin protein binding and the production of biliary sludging.

The Subcommittee recognized that a minimum age restriction was required for this medicine and therefore recommended that a note be inserted in the EMLc to restrict use to infants older than 41 weeks corrected gestational age. The use of ceftriaxone should be restricted to those who are being discharged from hospital who still require parenteral antimicrobial treatment and will not be receiving concomitant calcium treatment.

The Subcommittee also considered whether the medicine should be moved to the Complementary List, but on balance, decided to retain it in the Core

List because of the importance of rapid treatment for meningitis at first-line health-care facilities. Given the significant safety concerns associated with the use of this medicine in neonates, it was recommended that the Advisory Committee on Safety of Medicines evaluate the use of ceftriaxone in infants and children at its next meeting.

Carbapenems (review)

Complementary List

The Subcommittee considered the review of carbapenems, which was commissioned following the 2007 meeting to identify potential alternatives to the currently listed imipenem–cilastatin. Expert comments were provided by Dr Anita Zaidi.

The Subcommittee noted that the majority of evidence for the safety and efficacy of meropenem and imipenem–cilastatin comes from a systematic review of studies in adults, which demonstrated that meropenem produced a marginally better clinical and bacteriological cure rate than imipenem *(14)*. The limited evidence from studies in children suggested that the efficacy and safety of meropenem and imipenem–cilastatin were comparable for most indications other than meningitis *(15)*. The Subcommittee noted that meropenem was the only carbapenem that could be used for treatment of meningitis, due to its low propensity to cause seizures even at high doses. Imipenem–cilastatin is contraindicated for meningitis.

Although the cost of meropenem is higher than that of comparators, the Subcommittee took into account that studies done in the Russian Federation, the UK and the USA have shown that the overall cost of therapy for patients with severe infection in intensive care units is lower for meropenem than for imipenem–cilastatin and conventional combination antibacterial therapy *(16)*.

The Subcommittee noted that meropenem is not currently licensed for neonates. While the *British National Formulary* (BNF) for Children 2008 does give dosages for meropenem in neonates, these recommendations do not appear to be firmly supported by data from controlled clinical trials of pharmacokinetics or drug safety in this subpopulation. Imipenem–cilastatin is the only carbapenem currently approved by regulatory authorities for use in all age groups.

The Subcommittee recommended that for all infections caused by drug-resistant pathogens known or believed to be sensitive to a carbapenem, meropenem can be considered as an alternative to imipenem–cilastatin. Given its association with the production of seizures, imipenem–cilastatin is contraindicated for use in infants and children with meningitis. In such situations, meropenem is the preferable agent. Until complete data on

meropenem in young infants and neonates are available, it is recommended that imipenem–cilastatin be retained on the EMLc but that a note should be inserted to recommend the use of meropenem where appropriate.

Section 6.2.2 Other antibacterials

Macrolides

At the meeting of the Subcommittee in July 2007, the question of differences in efficacy and safety between the macrolides, particularly with regard to their use in neonates, was raised. It was also noted that, with the exception of the treatment of trachoma, there was no evidence for the superiority of azithromycin over other macrolides or beta-lactams. It was therefore decided that azithromycin should remain restricted to the specified indication of trachoma and that a review should be commissioned by the Secretariat to summarize the evidence regarding the use of macrolides in children, with particular regard to safety and efficacy in neonates. Azithromycin and erythromycin were the only macrolides on the EMLc.

Expert review comments were provided by Mrs Jehan Mohammed Ali Al-Fannah and Dr Jacqueline Deen.

Comparative evidence for efficacy

There is no evidence for the superiority of azithromycin over other macrolides for the treatment of *Bordetella pertussis* or *Campylobacter jejuni*. However guidelines from the American Academy of Pediatrics and the Centers for Disease Control and Prevention (CDC) recommend azithromycin as the preferred macrolide for treatment of *Bordetella pertussis* infections. Azithromycin is the macrolide of choice for trachoma treatment in children older than six months, and the efficacy of azithromycin for the treatment of trachoma has been demonstrated in several randomized controlled trials identified in the review. This is consistent with the current recommendation in WHO guidelines *(17)*.

A Cochrane Review *(18)* did not find any evidence for the superiority of azithromycin in the treatment of community-acquired pneumonia over other antibiotics such as amoxicillin–clavulanic acid or erythromycin. There is no evidence that azithromycin is superior to other antibiotics for the treatment of Legionnaires' disease, acute otitis media or sinusitis.

Clarithromycin is recommended for the treatment and prophylaxis of disseminated *Mycobacterium avium intracellularum* infection in children infected with HIV according to the US CDC guidelines. However data on the use of clarithromycin in children are scanty and it is not recommended for this indication in children aged less than 20 months. It may also be effective for the treatment of pertussis, Legionnaires' disease, and *Helicobacter pylori* but there is no evidence for its superiority over the other macrolides.

Comparative evidence for safety

Erythromycin is administered 3 or 4 times per day. Azithromycin is administered as a single daily dose. Adverse events reported for erythromycin may include epigastric distress, hepatic dysfunction and drug interactions. In neonates, its use may be associated with infantile hypertrophic pyloric stenosis (IHPS) that may be dose-dependent, and occurs at a rate of between 5 and 10%. For this reason, other macrolides have often been recommended for use in neonates despite the absence of strong evidence for their safety or efficacy in this age group. Intravenous use of erythromycin has been associated with thrombophlebitis, cardiac arrhythmias, and auditory impairment. There are no systematic reviews comparing the tolerability of erythromycin with that of other macrolides.

The Secretariat identified four trials that directly compared azithromycin with erythromycin *and* reported adverse effects: two from the Cochrane Review of antibiotics for community-acquired pneumonia in children *(19, 20)*, one from the Cochrane Review of antibiotics for pertussis *(21)* and the fourth, a trial by Langley et al. *(22)*, not included in either review, by far the largest direct comparison of azithromycin with erythromycin in the treatment of pertussis in 477 children.

As reported in the study by Langley et al. (*22*), the clinical and bacterial efficacy of the two treatments was the same. However gastrointestinal events were reported significantly more frequently in the group treated with erythromycin (41.2%) than in the group that received azithromycin (18.8%). Children randomized to azithromycin were also much more likely to have complied with antimicrobial therapy during the treatment period (90% versus 55%).

Only one study directly comparing clarithromycin with erythromycin was found *(23)* in which clarithromycin was shown to lead to significantly fewer adverse events (34/76) than erythromycin (48/77, $p = 0.035$].

Comparative evidence in neonates

Erythromycin has been approved for use in neonates for the treatment of eye infections and pneumonia caused by *Chlamydia trachomatis.*

Azithromycin has not been approved for use in children under six months old, and evidence for its efficacy and safety is limited to a single study of 13 neonates, which found azithromycin to be effective and safe in this age group. Guidelines from the CDC and the American Academy of Pediatrics recommend the use of azithromycin in children under one month for the treatment of *Bordetella pertussis* infections.

Clarithromycin is not licensed nor recommended for use in neonates.

Currently, the cost of azithromycin is US$ 0.53/DDD, that of erythromycin US$ 0.10/DDD and of clarithromycin US$ 0.44/DDD for solid dosage forms based on the Management Sciences for Health International Drug Price Indicator Guide.

The Subcommittee noted that:

— Azithromycin remains the antibiotic of choice for the treatment of trachoma.
— The drug interaction profile for the macrolides differs with erythromycin and clarithromycin producing inhibition of CYP3A activity sufficient to alter the pharmacokinetics of drugs that are CYP3A4/5 substrates. Azithromycin appears to be devoid of drug interactions with CYP3A substrates.
— There remains limited evidence for the superiority of one macrolide over another in the management of other infections. They are best considered as clinically interchangeable in terms of efficacy.
— There are minimal data on the comparative safety of the macrolides. Azithromycin is favoured, but this is not clinically significant.
— The available data on efficacy and safety of macrolides in children under six months are primarily for erythromycin; data for azithromycin and clarithromycin in children younger than six months are scanty. Despite this lack of quality evidence, guidelines from the CDC and the American Academy of Pediatrics continue to recommend the use of azithromycin in children in this age group for the treatment and prophylaxis of *Bordetella pertussis*, as azithromycin may be better tolerated and easier to administer. There is the potential for resistance to develop if azithromycin is overused or used inappropriately.

It was therefore agreed that azithromycin remain on the EMLc with a note regarding its appropriate indication, that oral erythromycin be retained, but without annotation, and that intravenous erythromycin be deleted.

Fluoroquinolones (review)

In 2007, the Subcommittee reviewed the listing of fluoroquinolones for use in children and, given the concerns about the potential for the overuse and inappropriate use of fluoroquinolones outside the recommended indications, a review on the efficacy, safety and rational use of fluoroquinolones in children was requested. Expert comments were provided by Professor Dai Yao Hua and Dr Jacqueline Deen.

The review commissioned by the Secretariat cited a Cochrane Review of quinolones for treatment of typhoid fever *(24)* in which three of the trials were exclusively in children (comparisons were: ofloxacin with cefixime, norfloxacin with ceftriaxone, and ofloxacin for two versus three days). The

overall conclusion of the Cochrane Review was that there was no evidence for the superiority of quinolones in the treatment of typhoid fever in children over other antibiotics such as ceftriaxone or cefixime.

It was noted that evidence for the use of oral ciprofloxacin in the management of shigella, salmonella and other gastrointestinal infections consists mostly of case-series and case-reports. The Zimbabwe, Bangladesh, South Africa Study group has conducted a multicentre, double-blind randomized controlled trial *(25)* in which 235 children with shigella were randomly assigned to receive oral ciprofloxacin for a 3- or 5-day course. All children were microbiologically cured and all isolates were sensitive to ciprofloxacin. Several countries have recently reported increased resistance to fluoroquinolones in the management of these conditions.

No randomized controlled trials evaluating efficacy of a fluoroquinolone in the management of meningitis in children were identified, and data on clinical efficacy of fluoroquinolones in neonates and pre-term infants are scanty. An additional search of the literature undertaken by the Secretariat identified two further studies not included in the review: a matched case–control study *(26)* in which 30 neonates were treated with parenteral ciprofloxacin for 14 days. When controlled for birth weight and gestation, cartilage size was not affected by ciprofloxacin. The second, a prospective long-term follow-up study carried out in Bangladesh *(27)* and involving 48 preterm infants of less than 33 weeks gestation concluded that ciprofloxacin was a safe therapeutic option for newborns with sepsis produced by multi-resistant organisms, with no differences in growth and development observed in the ciprofloxacin-treated group during treatment or follow-up.

It was noted that there are no data comparing the superiority of the other quinolones such as gatifloxacin and moxifloxacin over ciprofloxacin in children.

The application included a review of the findings in animals and compared this to a summary of findings in children (31 reports, > 7000 children) where arthropathy was found to be reversible, without long-term sequelae, and not convincingly correlated with the use of fluoroquinolones in children. The Subcommittee noted the recent warnings issued by the US Food and Drug Administration about the risk of arthropathy in adult patients older than 65 years and the risk of tendon rupture associated with protracted treatment in adults over 60 years of age.

The Subcommittee agreed that:

— Evidence for the clinical efficacy and superiority of fluoroquinolones over other antibiotics in children is limited, particularly within the neonatal and preterm period.

— Ciprofloxacin remains the fluoroquinolone for which there is the most evidence for use and safety in children.
— Inappropriate use of fluoroquinolones has the potential to rapidly increase the emergence of resistance.

The Subcommittee concluded that sufficient evidence is available to support the use of ciprofloxacin as a second-line treatment for specific, severe infections in paediatric patients. Given patterns of use, it was decided that ciprofloxacin should remain the only fluoroquinolone on the EMLc as there is evidence for ciprofloxacin to be used in other infections. The statement regarding Shigella should be deleted. It was also recommended that the safety issues pertaining to use of fluoroquinolone in neonates and children be considered by the Advisory Committee on the Safety of Medicines at its next meeting.

Tetracycline (review)

The use of tetracyclines in children was reviewed by the Subcommittee. The inclusion of tetracycline on the EMLc for use in treating severe cholera had previously been reviewed by the Subcommittee in July 2007, at which time the square box had been deleted as there was no evidence to support the use of other tetracyclines for this indication. The Secretariat was requested to commission a review to address this question. Expert comments were provided by Professor Tony Nunn.

The evidence identified in the review for the efficacy of tetracyclines in treating children was mostly gathered in children over 8 years of age, and the majority of the available evidence is for the use of doxycycline. No evidence was found for the use of other tetracyclines in the management of severe cholera.

The Subcommittee recognized that doxycycline and tetracycline have been recommended as the treatment of choice in Rickettsial infections. The reviewers cited a Cochrane Review of therapy for scrub typhus involving four trials, which demonstrated no difference between the use of doxycycline and tetracycline, or between tetracycline and chloramphenicol in the management of scrub typhus *(28)*.

Minimal evidence was identified in the review for the efficacy of tetracyclines in the management of *Mycoplasma pneumoniae*, leptospirosis, or for the prophylaxis against *Plasmodium falciparum* and anthrax in children.

The Subcommittee acknowledged that children under 8 years of age may develop permanent brown discolouration of their teeth, enamel defects and hypoplasia following the use of tetracyclines, which may be related to dose and duration of therapy. It was noted that a small amount of evidence exists that doxycycline may have less adverse effect on teeth than the other

tetracyclines. In one study, only six out of 300 children and premature infants exposed to doxycycline developed discolouration of their teeth. A further small study, not identified in the review, showed absence of tooth staining in 30 children aged between 2 and 8 years who received doxycycline treatment *(29)*.

The Subcommittee agreed that doxycycline is a useful antibiotic for the management of a wide range of infections as well as in the prophylaxis against infections of public health importance, and therefore removed the restricted indication for cholera. It was noted that evidence for the efficacy and safety of other tetracyclines in children is limited, and therefore agreed that doxycycline be included in the EMLc without a square box. An age restriction (over 8 years) should be applied when the tetracyclines are used to treat non-life-threatening infections.

Gentamicin (review)

The Subcommittee reviewed the inclusion of gentamicin on the EMLc as concerns had previously been raised regarding potential ethnic differences in ototoxicity associated with this drug. Expert reviews were provided by Dr Peter Kazembe and Dr Anita Zaidi.

It was noted that most of the available evidence for the safety of aminoglycosides in children is for gentamicin. The review identified a Cochrane systematic review of 11 studies (n = 574 subjects) *(30)* that assessed the safety and efficacy of a once-daily dose of gentamicin in neonates less than 28 days old being treated for sepsis. No ototoxicity or nephrotoxicity was seen in any of the patients, however limited numbers of preterm infants were included in these studies.

A second meta-analysis *(31)* of 24 randomized controlled trials compared once-daily dosing regimens with more frequent dosing in terms of patients with hearing loss (assessed through both clinical and formal auditory testing). There were no cases of clinical hearing impairment; however on auditory testing, 2.3% of children treated with once-daily doses of gentamicin were found to have auditory loss, compared with 2% of children treated with multi-dose administration of gentamicin (10/436 versus 8/406, relative risk 1.16; 95% confidence intervals (CI) 0.48–2.84). The majority of trials included in this meta-analysis were of small sample size, and although the two regimens seemed equivalent with respect to ototoxicity, only half of the studies actually incorporated formal audiometric testing. It was noted that less than 2% of children in either treatment group in this systematic review were found to have primary nephrotoxicity.

Another systematic review of 16 trials *(32)* comparing daily gentamicin dosing with multi-dosing in neonates aged less than 30 days on initiation of

treatment demonstrated only one episode of ototoxicity in 210 neonates. No significant difference in toxicity between the two dosing regimens was seen.

The Subcommittee noted that there is limited evidence for the occurrence of otoxicity in preterm infants following gentamicin use, although the majority of measurements for toxicity are carried out in the immediate post-treatment period only.

It was noted that toxicity correlates with gentamicin concentration in plasma and with duration of use. The Subcommittee could find no documentation supporting an ethnic predilection for gentamicin toxicity in Chinese populations either within China or in other countries. The Subcommittee agreed that the majority of evidence demonstrates a low incidence of ototoxicity and nephrotoxicity following the use of gentamicin in children, but noted that there is a paucity of evidence for the occurrence of toxicity following aminoglycoside use in preterm infants, or on long-term follow-up. Systematic reviews failed to show a difference in incidence of gentamicin–associated ototoxicity with varying dosing regimens. On balance, given its broad potential for use in infections with Gram–negative organisms, it was agreed that gentamicin should remain as the aminoglycoside on the EMLc.

Sulfadiazine (review)

The Subcommittee considered the review of sulfadiazine for the treatment of toxoplasmosis in children. It had been noted in 2007 that sulfadiazine was not licensed for the treatment of toxoplasmosis in children, and therefore a review of its use in children with particular regard to the treatment of toxoplasmosis was requested. Expert reviews were provided by Dr Stuart MacLeod and Dr Tony Nunn.

Evidence cited in the Secretariat's review to support the efficacy of sulfadiazine in the management of toxoplasma encephalitis included a Cochrane Review *(33)* and several other randomized controlled trials involving adults with HIV *(34)*, however there was limited evidence for its superiority over trimethoprim–sulfamethoxazole for this indication. Studies of the management of congenital toxoplasmosis included several longitudinal cohort studies *(35, 36, 37),* which demonstrated sulfadiazine to be an efficacious and safe treatment for infected neonates. An improved outcome was seen in the majority of infected infants who were treated with combination sulfadiazine therapy; however outcome was shown to be dependent on the duration of treatment and the degree of disability at birth. The Subcommittee noted that there was no evidence to support the use of sulfadiazine in the treatment of nocardia or other infections.

Sulfadiazine treatment appeared to be well tolerated, with adverse reactions reported in approximately 5% of patients. No systematic reviews comparing

oral versus intravenous sulfadiazine were identified, however it was noted that the majority of guidelines, including the CDC and the British National Formulary 2006, recommend oral sulfadiazine in the management of toxoplasmosis. The majority of an oral dose is rapidly absorbed from the gastrointestinal tract and therefore no justification for an intravenous form could be made.

The Subcommittee agreed that there was sufficient evidence for the clinical efficacy and safety of oral sulfadiazine in children for the treatment of congenital toxoplasmosis. It was decided that intravenous sulfadiazine should be removed from the EMLc and the oral tablet formulation should be deleted from Section 6.2.2 of the EMLc and moved to Section 6.5.4 (antitoxoplasmosis medicines). The need for an oral liquid formulation of sulfadiazine was also identified.

Section 6.2.4 Antituberculosis medicines (review)

At the July 2007 meeting, the Subcommittee noted that the fixed-dose combinations (FDCs) listed for the first-line treatment of tuberculosis in children needed to be reviewed to determine whether the currently recommended strengths were appropriate for children. The Secretariat commissioned a review of pharmacokinetic studies, and this was presented and considered at an informal meeting in July 2008. The report of the meeting is on the Subcommittee web site; the review of pharmacokinetic studies has not yet been published. A review of studies of ethambutol use in children was published in 2006 *(38)*.

The recommendations for doses of pyrazinamide, isoniazid and rifampicin based on the assessment of the medical literature reviewed at the meeting are quoted below:

1. The panel recommends that the dose of PZ in children above 3 months of age should be 35 mg/kg (range 30–40) per day. The maximum daily dose should not exceed the recommended adult daily dose. If data are accessible, further analysis of the IPD from recent PK studies may increase the confidence in this recommendation.
2. The panel recommends that the dose of isoniazid in children above 3 months of age for treatment or prophylaxis (treatment of latent TB infection) should be 10 mg/kg (range 10–15) per day. The maximum daily dose should not exceed the recommended adult daily dose.
3. The panel recommends that the dose of RMP in children above 3 months of age should be 15 mg/kg (range 10–20) per day. Dosages at the higher ranges may be preferable for children under 10 kilograms, and children with HIV infection or malnutrition. The maximum daily dose should not exceed the recommended adult daily dose.

The Subcommittee then considered what type of FDC product would be needed to ensure sufficient flexibility to enable accurate administration of age-specific doses of each component medication. The three-drug formulation proposed at the meeting in July 2008 (isoniazid 100 mg/pyrazinamide 350 mg/rifampicin 200 mg) was considered, but is not endorsed at present. The Subcommittee realizes that additional work is underway, which, when completed, should provide a more refined assessment of what the composition and properties of an ideal formulation should be.

Although the EMLc listed three FDC products for children, no prequalified products existed in the strengths listed. The Subcommittee considered whether the FDCs on the EMLc should be retained. Taking into consideration the public health importance of ensuring that treatment for tuberculosis is effective and noting that no products are currently prequalified, the Subcommittee recommended deletion of the existing FDCs on the grounds of potential underdosing, with the associated risk of treatment failure, and lack of suitability, as multiple tablets of the existing strengths would be needed to ensure effective doses. The Subcommittee supported the urgent need for further research and reviews on this topic to define optimal doses, and recommended that the Expert Committee should consider progress on this at its meeting in March 2009.

Section 6.4.2 Antiretrovirals (new formulations)

At its meeting in 2007, the Subcommittee considered that FDCs for children with HIV were clearly essential and endorsed three FDCs already on the adult list of essential medicines as appropriate for older children (listed in alphabetical order):

lamivudine + nevirapine + stavudine: 150 + 200 + 30 mg
lamivudine + nevirapine + zidovudine: 150 + 200 + 300 mg
lamivudine + zidovudine: 150 + 300 mg.

In addition, the Subcommittee considered but rejected a number of applications for FDC products for the treatment of children with HIV:

lamivudine + nevirapine + stavudine, 40 + 70 + 10 mg, and 20 + 35 + 5 mg, Ranbaxy
lamivudine + nevirapine + zidovudine tablet, 30 + 60 + 60 mg, Ranbaxy
lamivudine + zidovudine, 150 + 300 mg scored tablet, GlaxoSmithKline.

Three new applications were submitted at this meeting, for the following combinations:

lamivudine + nevirapine + stavudine dispersible tablets 30 + 50 + 6 mg and 60 + 100 + 12 mg, Cipla
lamivudine + nevirapine + zidovudine tablet 30 + 50 + 60 mg, Matrix Laboratories

lamivudine + zidovudine tablet 30 + 60 mg, Matrix Laboratories.

Expert reviews were provided by Mr Andy Gray and Dr Peter Kazembe; comments were received from the WHO Department of HIV/AIDS.

The key problem for specifying FDCs is determining the appropriate doses of the components so that they are suitable for all children. For HIV, "ideal doses" of components for first-line treatment have now been identified by an expert group working with the WHO Department of HIV. These are published on the WHO web site. The most recent update of the "ideal dosing table" is at: http://www.who.int/hiv/paediatric/Sum_WHO_ARV_Ped_ARV_dosing.pdf.

The Subcommittee noted that the two applications from Matrix presented no clinical evidence apart from bioequivalence studies. The applications were based on the recommended doses in the WHO guidelines, and the clinical evidence supporting these recommendations is summarized in an extensive report at: http://www.who.int/hiv/paediatric/External_report_dosing_paediatric_ARVs.pdf.

Both products are consistent with the "ideal products" listed in the dosing table. Both have been registered in India and are under review by the WHO Prequalification Programme.

The application from Cipla was more complete, and as well as summary results of bioequivalence studies, included a limited review of the relevant clinical literature. The doses of the components are consistent with the WHO "ideal dose" recommendations for the lower-strength product; the higher-strength product is not listed in the WHO table. Both products had been prequalified by WHO. The main concern with this combination is the toxicity of stavudine, although this problem is well defined. The Subcommittee noted the comments from the WHO Department of HIV/AIDS that zidovudine-containing combinations are generally preferred.

The Subcommittee recommended that as the proposed combinations containing zidovudine exist and comply with WHO's "ideal dose" requirements, they should be added to the EMLc. The quality of any individual product will have to be determined by regulatory review. The role of stavudine-containing combinations needs to be considered. While they may well be essential at present during the scale-up process of antiretroviral treatment for children, their long-term usefulness is unclear. The Subcommittee therefore recommends that the combinations containing stavudine should be included on the EMLc, but reviewed again in the future. The Subcommittee also extensively discussed the roles of ritonavir-boosted lopinavir in paediatric HIV therapy and agreed that evolving safety data and the issue of how development influences the dose–plasma concentration–

effect relationship for all medicines be considered in the determination of appropriate paediatric doses. In addition, the Subcommittee identified the need for heat-stable formulations of ritonavir-boosted protease inhibitors.

Section 6.5 Antiprotozoal medicines

Section 6.5.2 Antileishmaniasis medicines

Liposomal amphotericin B (inclusion)

The Subcommittee considered the application submitted by the WHO Department of Control of Neglected Tropical Diseases (NTD) for listing liposomal amphotericin B in the EMLc, for the treatment of visceral leishmaniasis. Expert reviews were prepared by Dr Shalini Sri Ranganathan (non-attending Temporary Adviser) and Dr Anita Zaidi.

The Subcommittee noted that the incidence of this infection is increasing in different parts of the world and that children account for a significant proportion of those with visceral leishmaniasis in disease-endemic areas. Morbidity and mortality related to this infection are substantial. Resistance to conventional therapy has been recorded, but there is inadequate information regarding the magnitude of this problem.

The available data, although not of good quality, suggest that liposomal amphotericin B is effective for the treatment of visceral leishmaniasis and is safe in children *(39, 40)*. However, the Subcommittee is concerned that there are insufficient data to show how liposomal amphotericin B compares with the original formulation of this drug in terms of efficacy and safety in the treatment of visceral leishmaniasis. The Subcommittee noted that the different dosages and schedules tested have shown a good response and hence there could be flexibility in the dosage schedule. Several regimens have used a total dose of approximately 20 mg/kg and WHO recommends this dosage *(41)*. The duration of in-patient therapy can vary, but is shorter than that with conventional therapies.

Safety data suggest that liposomal amphotericin B may be better than other therapies, but there is a paucity of good quality data on which to base conclusions.

The cost of therapy with liposomal amphotericin B can be significantly higher than that of conventional therapies. The Subcommittee was made aware of the preferential pricing offer which could help in addressing the issues of cost and availability associated with the procurement of liposomal amphotericin B in developing countries.

The Subcommittee has noted that liposomal amphotericin B is being used as first-line therapy in some high-income countries. In other countries it is considered as second-line therapy, mainly due to cost. The Subcommittee

decided that liposomal amphotericin B should be added to the Core List of the EMLc for the treatment of visceral leishmaniasis. When the cost of the liposomal formulation is similar to that of the original formulation of amphotericin B, the liposomal formulation may be preferable in the light of data on other fungal infections that support a lower incidence of nephrotoxicity. It also recommended that good quality clinical data on the safety and efficacy of liposomal amphotericin B in children with visceral leishmaniasis be collected prospectively.

Section 8. Antineoplastic, immunosuppressives and medicines used in palliative care

At its meeting in 2007, the Subcommittee noted that access to cytotoxic medicines for children was an important public health issue, and that a review of the cytotoxics listed and of the medicines for palliative care should be commissioned.

Section 8.2 Cytotoxic medicines (review)

The Subcommittee reviewed the documents received. Expert comments were provided by Professor Noël Cranswick and Professor Dai Yao Hua. Additional comments were made by Dr Ian Magrath, International Network for Cancer Treatment at Institut Pasteur, Brussels, Belgium, and Dr Judith Margolin, Baylor College of Pharmacy, USA.

The documents included a brief overview of sample protocols used for acute lymphoblastic leukaemia (ALL) and a review of the uses of methotrexate. No detailed evidence was provided concerning the efficacy, relevance or appropriate dosage of the medicines in children, the relative merit of one over the other, or any assessment of use within the developing world. Cytotoxic management of other common paediatric malignancies was also absent from the review. However, it was noted that oral dexamethasone is an essential component of the majority of paediatric oncological protocols, including ALL protocols of the United Kingdom, Children's Oncology Group 1882 (North America), Berlin-Frankfurt-Munster and China, Hong Kong Special Administrative Region.

The review of methotrexate included a description of its use in the management of ALL and several studies were identified in which methotrexate was proven to be an effective therapy for ALL in children. Although intrathecal methotrexate forms part of standard care in the management of meningeal leukaemia and lymphomatous meningitis in children throughout the world, the evidence for efficacy in children for this indication included in the application was limited. Its use in other indications was also evaluated and the Subcommittee noted that side-effects

of methotrexate may be significant and multiple. It was also noted that the evidence that the benefits of methotrexate outweigh the harms when used as an immune modulator in the management of conditions such as juvenile rheumatoid arthritis, uveitis, inflammatory bowel disease, systemic lupus erythematosus (SLE), psoriasis and sarcoidosis was unclear.

The Subcommittee agreed that overall, the documents did not provide sufficient evidence to enable it to make an informed decision as to which cytotoxics should be included on the EMLc. A more extensive review of the relative merits of these treatment approaches is required, particularly with regard to the situation in developing countries. The comments from the INCTR suggested potential modifications to the EMLc that had already been made (e.g. deletion of levamisole and chlormethine) and potential additions without any detailed assessment. They also note that certain cytotoxic medicines not included on the EMLc e.g. ifosfamide, mesna and hydroxyurea are used in the management of paediatric cancers (e.g. chronic myeloid leukaemia, lymphomas and sarcomas), whereas other drugs that are on the EMLc (e.g. fluorouracil) are rarely used in children.

An important question is the relevance of including cytotoxics on the WHO EMLc. On the one hand, countries that can afford to provide such care will develop protocols and formularies based on international standards, and presumably will have expertise available to administer the medicines appropriately. The relevance of the WHO EMLc to these countries may be limited. On the other hand, deletion of all medicines and an indication that countries should make their own judgement is likely to be a significant barrier to access in some countries, as well as providing no guidance to those countries wishing to start treatment programmes. The importance of treatment of HIV-related tumours in children, for example, is likely to increase and the availability of treatment is also likely to increase given donor priorities. In addition to the cost of treatment, most therapies are associated with significant side-effects requiring intensive support and monitoring, and contributing to high individual patient costs. Diagnostic precision is also important.

The Subcommittee considered how best to advance the provision of evidence-based information on selection and use of these medicines, including, potentially, the development of appropriate treatment guidelines so that it becomes a useful resource to countries. It was noted that this will require expanded consultation with experts and expert groups (e.g. the Children's Oncology Group) to determine the most common paediatric malignancies, the medicines used to treat them and the evidence (outcome-driven) suggesting their efficacy in improving both the quantity and quality of life.

It was therefore decided that the current list of cytotoxic medicines should remain unchanged at this stage.

Section 8.4 Medicines used in palliative care (inclusion)

The Subcommittee considered the review of medicines for palliative care commissioned by the Secretariat to ensure that appropriate medicines for the pharmacological management of the most prevalent and distressing symptoms in children with life-threatening and life-limiting conditions worldwide are included in the EMLc. Expert comments were provided by Dr Robert Peterson and Dr Shalini Sri Ranganathan.

The Subcommittee noted that malignancy and HIV/AIDS were identified as the most common causes of childhood mortality appropriate to palliative care worldwide and that the 10 most frequent symptoms and symptom clusters (fatigue and weakness, pain, anorexia and weight loss, delirium and agitation, breathlessness, nausea and vomiting, constipation, depression, excess respiratory tract secretions and anxiety) had been identified based on available data.

The Subcommittee noted that the evidence to support efficacy and safety of medicines used in the management of these symptoms was generally weak and therefore, several recommendations in the proposal were based on experience from clinical practice. It also noted that several medicines proposed for addition to the EMLc were not listed in the International Drug Price Indicator Guide and availability worldwide can be an issue.

For some of the medicines identified in the proposal but already included in other sections of the EMLc, the Subcommittee was of the general opinion that the child-friendly dosage forms recommended need to be included in the EMLc. These are oral dexamethasone, oral liquid ibuprofen (for bone pain), a rectal solution form of diazepam and variable dosage forms of morphine. The Subcommittee acknowledged that availability of these dosage forms may be a problem in some parts of the world but considered that including them on the EMLc was one important way to promote improved availability and access.

To ensure appropriate first- and second-line management of nausea and vomiting due to different pathophysiological mechanisms, the proposal suggested that antiemetics with different mechanisms of action are required. The review proposed the following medicines: cyclizine (tablet: 50 mg; injection: 50 mg/ml), an antihistaminic antimuscarinic antiemetic that is effective for vomiting centre-mediated nausea and vomiting and levomepromazine (tablet: 25 mg; injection: 25 mg/ml) for chemo-receptor trigger zone-mediated nausea and vomiting. Although there is a lack of

documented data on efficacy and safety, these two medicines are currently being used for this indication in some developed countries. Availability, especially of levomepromazine, may be a problem in many parts of the world. On balance, given that there is substantially more experience with the use of cyclizine, the Subcommittee recommended that it should be added to the EMLc in the dosage forms recommended specifically for use in palliative care.

The Subcommittee noted that the proposal recommends that laxatives are required for managing constipation, one of the most troublesome symptoms in palliative care. The options proposed were:

— docusate sodium (capsule: 100 mg; oral liquid: 50 mg/5 ml) as a faecal softening agent for use in children;
— senna (oral liquid 7.5 mg/5 ml) as a stimulant laxative.

The Subcommittee agreed that docusate sodium seems to be better tolerated and cheaper than lactulose, which is often the only available alternative, and therefore recommended its inclusion. The Subcommittee also noted that current clinical practice supports the use of a stimulant laxative, senna, in the management of opioid-induced constipation and hence the oral syrup was included in the EMLc for use in palliative care.

For the management of respiratory tract secretions, the proposal suggested that hyoscine hydrobromide may provide some benefit in terminal care. Despite the absence of data from large paediatric studies, the Subcommittee felt that the drug should be added to the EMLc. The Subcommittee particularly noted the potential usefulness of the patch presentation as an appropriate dosage form for use in children and decided, therefore to include the intravenous form and transdermal patch.

Midazolam is useful for managing anxiety and terminal agitation and delirium. The Subcommittee noted that there is insufficient evidence for the superiority of one benzodiazepine over another. However, the use of intravenous midazolam as a short-acting benzodiazepine is valuable, and the Subcommittee also noted that the intravenous form has been administered orally. It therefore recommended that midazolam should be included in the section on palliative care medicines for children.

Amitriptyline (10 mg tablet) is listed in the EML but was not endorsed for use in the treatment of depression in children at the meeting in 2007. The Subcommittee noted that this medicine is used in children for neuropathic pain and although there is, as for most other palliative care medicines in children, a lack of formal studies, it appears to be safe and effective. Hence the Subcommittee recommended that this medicine should be added to the EMLc specifically for use in palliative care.

The Subcommittee considered the general principle of whether medicines listed for palliative care should also have indications of age restrictions. On the one hand, it was noted that for several of the medicines added to the EMLc in this section evidence of efficacy and safety at all ages was not available. Specifically:

— cyclizine is not licensed for use in children under 6 years;
— docusate sodium is not licensed for use in children under 6 months;
— senna is not licensed for use in children under 2 years.

The Subcommittee considered that the licensed indications may not always reflect existing evidence, and also noted the importance of access to these products for children in need of palliative care, and therefore decided not to indicate age restrictions on the use of these products for this purpose.

Section 12. Cardiovascular medicines

Quinidine (review)

Complementary List

The Subcommittee considered the review of quinidine that proposed its deletion from the EMLc. At its meeting in 2007, the Subcommittee identified antiarrhythmics as a class of medicines for which further information was required before any could be endorsed as essential in children. Expert comments were provided by Dr Helena L. Coelho and Professor Noël Cranswick.

The Subcommittee noted that there was a paucity of data on the need for, and use of, antiarrhythmics in children generally, but acknowledged that the effects of quinidine are likely to be similar to those observed in adults. In adults, there is good evidence to show that quinidine suppresses atrial fibrillation *(42)*. However, there is also high quality evidence to show that use of this medicine is associated with higher rates of potentially fatal adverse events such as Torsade de Pointes *(43)* and that mortality is higher in those who use this medicine than in controls. Adverse events can even occur at therapeutic and sub-therapeutic serum levels and occasionally without marked prolongation of the QT interval. There is also the possibility of dangerous interactions of the drug with commonly used medicines.

Regulatory authorities have not approved this medicine for paediatric use. In the absence of evidence to establish public health need and efficacy and safety, the Subcommittee recommended that quinidine not be included in the EMLc.

Rheumatic fever and rheumatic heart disease (review)

The Subcommittee considered the review of antibiotics for the prevention and treatment of rheumatic fever and rheumatic heart disease in children,

commissioned to determine whether the antibiotics currently listed are appropriate and adequate.

The Subcommittee noted that the burden due to rheumatic fever and rheumatic heart disease is high, especially among children in less developed countries. Antibiotics are proven to be effective in primary prevention, treatment of acute rheumatic fever and for secondary prophylaxis.

For all three situations, benzathine benzyl penicillin is recommended as the first-line therapy *(44)*. Evidence shows that this antibiotic can reduce recurrences and that IM therapy is better than oral therapy for this outcome *(45)*. However, oral phenoxymethyl penicillin is an alternative if injections are unacceptable or not possible. In patients with hypersensitivity to penicillins, erythromycin is the recommended antibiotic. These three antibiotics are listed in the current EMLc.

The Subcommittee recommended that the antibiotics listed currently in the EMLc (as shown below) are adequate for the prevention and treatment of rheumatic fever and rheumatic heart disease:

— benzathine benzyl penicillin:
  powder for injection: 900 mg (= 1.2 million IU) in 5-ml vial;
  1.44 g (= 2.4 million IU) in 5-ml vial.
— phenoxymethyl penicillin:
  powder for oral liquid: 250 mg (as potassium salt) in 5 ml;
  tablet: 250 mg (as potassium salt).
— erythromycin:
  capsule or tablet: 250 mg (as stearate or ethyl succinate);
  powder for oral liquid: 125 mg (as stearate or ethyl succinate).

Section 13. Dermatological medicines (topical)

Dermatological medicines (review)

The Subcommittee considered the review of dermatological medicines prepared by the International League of Dermatological Societies (ILDS). Expert comments were provided by Dr Shalini Sri Ranganathan and Professor Harshi Sachdev. Additional comments were provided by Médecins Sans Frontières.

Diseases of the skin are common in children and are among the leading reasons for visits to primary health care services *(46)*. Several different topical and systemic medicines are required to treat the varied conditions affecting the skin. The Subcommittee noted that the review identified 10 diseases as priorities and that recommendations for addition and deletion were made in addition to retaining most of the medicines already in the EMLc.

The Subcommittee noted that the review by the ILDS recommends that the following medicines are retained:

— miconazole and Whitfield's ointment (benzoic acid + salicylic acid) (Section 13.1);
— silver sulfadiazine 1% cream, gentian violet 0.5% in alcohol or water and potassium permanganate 1/10 000 aqueous solution (Section 13.2);
— 1% hydrocortisone cream and 0.1% betamethasone cream and calamine lotion (Section 13.3);
— Salicylic acid preparations, benzoyl peroxide 5% cream or lotion and urea 5% or 10% cream or ointment (Section 13.5);
— 10–25% benzyl benzoate, permethrin cream/solution (Section 13.6).

Polyvidone iodine 10% solution and chlorhexidine solution listed in Section 15.1, are also useful for topical treatment of skin diseases.

Cloxacillin, amoxicillin, erythromycin, doxycycline, benzyl penicillin, griseofulvin aciclovir, chlorphenamine, cefalexin and ivermectin are also required for managing skin diseases resulting from infectious causes and are listed in other sections of the EMLc.

The Subcommittee noted that the review recommended the addition of the following medicines — econazole cream (13.1); tetracycline 3% ointment (13.2); lindane cream/lotion (13.6); crotamiton ointment (13.6); petrolatum and oral terbinafine.

As miconazole ointment or cream is listed in the EMLc with a square box, addition of econozole is not required.

Although topical tetracycline may be useful for certain skin conditions, there are insufficient clinical data on its efficacy and safety in children to determine whether it should be listed. The Subcommittee noted the recommendation that neomycin sulfate + bacitracin ointment (13.2) be deleted from the EMLc. Information from the review suggested that neomycin + bacitracin is associated with allergic manifestations and better topical applications are currently available. The Subcommittee concluded that insufficient information is currently available and proposed a review of the comparative effectiveness and safety of common antibiotics for the treatment of skin infections in neonates, particularly pyoderma and omphalitis.

The Subcommittee noted that resistance to first-line scabicides and pediculocides has appeared, so there is a need for alternative therapy. However, it was concerned about the safety profile of lindane and in the absence of a more detailed assessment of its safety, decided not to include it on the EMLc at this time. While crotamiton appears to be safe in children, data to support its effectiveness in comparison with permethrin were not

provided and would need to be considered before it could be added to the EMLc.

The Subcommittee felt that there was insufficient evidence to determine that petrolatum met the criteria of an essential medicine and hence it was not included on the EMLc.

There is evidence that oral terbinafine is useful in treating *tinea capitis*, commonly seen in children. The Subcommittee reconsidered the prior review of oral antifungals in children (2007) and concluded that there was an insufficient basis for including oral terbinafine on the EMLc at that time.

The Subcommittee noted the recommendation that dithranol preparation (13.5) be deleted from the EMLc given its caustic potential. This recommendation was accepted.

Section 15. Disinfectants and antiseptics

Chlorhexidine (new formulation)

The Subcommittee considered the application to include 4% chlorhexidine in the EMLc for topical cord care in settings where risk of umbilical cord infections is high. Expert comments were provided by Dr Jacqueline Deen and Dr Gregory Kearns.

The Subcommittee noted that the risk of umbilical cord infections is higher in areas where neonatal mortality rates are already very high and that these infections contribute significantly to neonatal mortality. Cord infection rates are higher in areas where home delivery rates are high, where clean delivery is not universally guaranteed and where traditional practices of cord care increase the risk of infection. There is a general consensus that in unclean deliveries, topical antiseptics for cord care may be of use in preventing infections.

Systematic reviews do not show superiority of any one antiseptic. However, a recent large community-based cluster randomized trial in Nepal *(47)*, showed that chlorhexidine 4% reduces incidence of omphalitis as compared to dry care. A reduction in neonatal mortality was also observed when treatment was started within 24 hours of birth. Another recent trial in Italy *(48)* failed to confirm these findings. One possible explanation for the discrepancy in the trial results is the different standards of perinatal care in the two countries.

Chlorhexidine is currently listed in the EMLc, with a square box, as solution 5% (digluconate) for dilution, in Section 15.1 (antiseptics). The Subcommittee noted that for the randomized controlled trial which showed benefit, the chlorhexidine 4% was prepared for use by diluting a 20% commercially available solution *(47)*. The options are therefore to add a

20% solution of chlorhexidine digluconate and specify it for dilution or add 7.1% as proposed in the application. In the absence of a commercially available 7.1% solution, the Subcommittee decided to include a 20% solution as digluconate on the EMLc, specifying the dilution required in the proposed WHO Model Formulary for Children.

Section 17. Gastrointestinal medicines

Pancreatic enzymes (inclusion)

The Subcommittee reviewed the application for the inclusion of pancreatic enzymes on the EMLc, for the management of severe pancreatic insufficiency. Expert comments were provided by Professor Harshi Sachdev and Dr Elizabeta Zisovska.

The Subcommittee noted that the majority of paediatric patients with pancreatic insufficiency suffer from cystic fibrosis, although several other conditions (e.g. chronic pancreatitis and post-gastric surgery) may also contribute to this condition. It was acknowledged that cystic fibrosis occurs worldwide, and that pancreatic insufficiency may be present in up to 90% of these patients. The resulting malnutrition may lead to a multitude of negative clinical outcomes, including lower life expectancy, poor growth, increased susceptibility to infections, and deterioration in lung function.

The Subcommittee noted that the application cited several good quality randomized trials, which appeared to support the use of pancreatic enzymes for treatment of pancreatic insufficiency in cystic fibrosis. A significant difference in mean protein and fat absorption was seen when comparing placebo to pancreatic enzyme replacement therapy; however the aim of the majority of studies was to evaluate different doses and formulations. Two randomized controlled studies *(49, 50)* carried out by the manufacturer of Creon, Solvay, were described, where a co-efficient of fat absorption (CFA) of up to 89.1% following Creon treatment was observed. Similar efficacy was demonstrated between different preparations included in the application.

Limited studies involving the use of pancreatic enzyme therapy in the management of conditions other than cystic fibrosis were included in the application, and the Subcommittee noted that evidence for safety and efficacy in infants younger than six months was limited.

It was the conclusion of the Subcommittee that sufficient evidence exists for the efficacy and safety of pancreatic enzyme replacement therapy in children, with resulting improvement in morbidity and mortality of patients with severe pancreatic insufficiency. Given the need for the dose to be monitored and titrated according to clinical response, it was agreed that pancreatic enzymes should be included on the Complementary List.

Further discussion by the Subcommittee focused on the recent warnings about phthalates in the formulations and their potential safety implications.

Section 17.2 Antiemetic medicines (review)

At its 2007 meeting, the Subcommittee requested a review of the choice of antiemetics for inclusion on the EMLc. The Secretariat commissioned a review, considered below. It was noted that antiemetic medications are not currently included in any of the major guidelines (American Academy of Pediatrics, CDC or WHO) for use in children with acute gastroenteritis. Expert comments were provided by Professor Prakash Mohan Jeena.

The commissioned review included a number of systematic reviews evaluating the effectiveness of antiemetics in the management of acute gastroenteritis in children. It was noted that although the studies demonstrated ondansetron to be significantly superior to placebo in preventing vomiting, none of the studies supported the routine use of antiemetic medications in the management of acute gastroenteritis in children. The Subcommittee also noted that the majority of studies reported a significant increase in side-effects associated with the use of antiemetics.

Overall there was insufficient evidence to support the routine use of antiemetic medications in the management of children with gastroenteritis, and potentially a high risk of associated adverse events, negating any significant benefit to children. However, the Subcommittee noted that antiemetic medicines were important in the context of post-operative nausea and vomiting as well as in conjunction with chemotherapy. It therefore recommended that before deleting the existing medicines, a further assessment of this class of drugs in post-operative patients and those receiving cancer chemotherapy, should be carried out, especially with regard to newer products, such as 5-HT3 antagonists.

Section 18. Hormones, other endocrine medicines and contraceptives

Hydrocortisone and fludrocortisone (inclusion)

The Subcommittee considered the application for the inclusion of the adrenal hormones fludrocortisone and hydrocortisone to the EMLc. Expert comments were provided by Dr Stuart MacLeod and Professor Tony Nunn. Numerous external comments in support of the proposal were received from health professionals, associations and individuals.

The Subcommittee noted that hydrocortisone and fludrocortisone are used in the management of primary and secondary aldosterone deficiency caused by congenital adrenal hyperplasia and Addison disease, that both medications are licensed for use in all ages, and that treatment should be

of lifelong duration. It was noted that fludrocortisone is currently the only mineralocorticoid available for aldosterone replacement in congenital adrenal hyperplasia, and that consequently there are no comparative efficacy or safety studies for the management of mineralocorticoid deficiency in congenital adrenal hyperplasia.

The application identified a retrospective study of 484 patients from five European countries, which demonstrated a decrease in mortality rate from 11.9% in untreated patients to 4.3% in those patients who were treated with fludrocortisones *(51)*.

Only one small study *(52)* of nine patients comparing hydrocortisone with prednisone for the management of congenital adrenal hyperplasia was included in the application. It showed that prednisolone had significantly greater adverse effects on growth than hydrocortisone. It was acknowledged however that the use of other glucocorticoids such as dexamethasone and prednisolone is generally avoided in children due to adverse effects on growth.

The Subcommittee agreed that fludrocortisone and hydrocortisone are both essential medicines for the management of congenital adrenal hyperplasia and adrenal insufficiency in children, and included them on the EMLc.

Section 24. Psychotherapeutic medicines (review)

At its meeting in July 2007, the Subcommittee requested a review of the section on psychotherapeutic medicines to determine what was essential in addition to the products considered at that meeting. In particular the sections on anxiety and sleep disorders, obsessive-compulsive disorders and panic attacks, and substance abuse were highlighted as needing further review. The Secretariat commissioned a review, published for discussion at the meeting. Expert comments were provided by Dr Kalle Hoppu and the WHO Department of Mental Health and Substance Abuse.

The Subcommittee decided that the review is best considered as a preliminary overview; as has been pointed out by the WHO Department of Mental Health and Substance Abuse, there is a need for more detailed summaries of evidence to be prepared before the suggested additions of medicines to the EMLc could be supported. It was difficult to support addition of any new medicines on the basis of the information presented.

The Subcommittee recommended that a review be undertaken by the Secretariat to identify the most common mental health disorders in children that require medication and that this information should be used as the basis for further development of this section of the EMLc. The Subcommittee recommended retaining chlorpromazine and haloperidol at present but

recognized that their patterns of use support inclusion on the Complementary List. There was no change to the listing of fluoxetine.

Section 25. Medicines acting on the respiratory tract

Salbutamol (review)

Oral salbutamol is currently included on the list in liquid and tablet formulation. In July 2007, the Subcommittee noted that these formulations are rarely used in the management of childhood asthma in many countries and requested a review of the evidence for the use of these forms, with particular emphasis on young children with viral-related wheeze. A review was subsequently received by the Secretariat. Expert comments were provided by Professor Noël Cranswick and Mr Andy Gray.

Given the superiority of inhaled salbutamol over oral salbutamol for the management of asthma, the lack of evidence for the use of bronchodilators in bronchiolitis, and the paucity of evidence for the use of oral salbutamol in children with viral wheeze, the Subcommittee agreed that at present, oral salbutamol should only be considered for use when treatment with inhaled asthma medications is not feasible. The EMLc was annotated to reflect this recommendation.

Surfactant (inclusion)

The Subcommittee reviewed the application for the inclusion of surfactant on the EMLc for the prophylaxis and management of primary respiratory distress syndrome in preterm infants, and secondary surfactant deficiency in infants. Expert comments were provided by Professor Noël Cranswick and Dr Elizabeta Zisovska.

High quality evidence demonstrating that both prophylactic and rescue surfactant improve clinical outcome in premature neonates was identified in the application. This included a Cochrane systematic review *(53)* of seven randomized controlled trials in which clinical outcomes were assessed following prophylactic administration of synthetic surfactant to premature infants aged between 25 to 34 weeks gestation, and with birth weights between 500 and 1350 grams. The meta-analysis showed a statistically significant decrease in the risk of pneumothorax, a decrease in the risk of pulmonary interstitial emphysema, and a decrease in risk of neonatal mortality. However an increased risk of developing patent ductus arteriosus and pulmonary haemorrhage was demonstrated.

The Subcommittee noted that the European Consensus Guidelines recommend the use of natural over synthetic surfactant as a prophylactic approach in infants of less than 27 weeks gestation, and for those between 26 and 30 weeks gestation if intubation is required in the delivery room or

if no prenatal corticosteroids have been received. The American Academy of Pediatrics guidelines suggest that surfactant should be given to infants with respiratory distress syndrome as soon as possible after intubation, regardless of gestational age or exposure to prenatal corticosteroids.

A systematic review *(54)* which included 11 trials showed that although the use of natural rather than synthetic surfactant resulted in a significant reduction in the risk of pneumothorax and mortality, there was a trend towards an increase in overall intraventricular haemorrhage following the use of natural surfactant.

The Subcommittee noted that limited evidence is available to determine the optimal method of surfactant administration and that high-quality evidence is lacking for the use of surfactant in other conditions such as persistent pulmonary hypertension of the newborn, congenital diaphragmatic hernia, neonatal pulmonary haemorrhage and meconium aspiration syndrome.

Despite evidence for an increased risk of patent ductus arteriosus, pulmonary haemorrhage and intraventricular haemorrhage following treatment with surfactant therapy, the benefits of use in management of respiratory distress syndrome in the neonatal population clearly outweigh the risks. Costs of surfactant were noted to be high. The Subcommittee concluded that the application had identified high quality evidence for the use of surfactant in the management of respiratory distress syndrome in premature infants. It was added to the EMLc and placed in a new section devoted to neonatal medicines and categorized as a Complementary medicine given the nature of its use.

Section 27. Vitamins and minerals

Retinol

The WHO Department of Child and Adolescent Health and Development commissioned a review of the evidence of potential benefit of prophylactic/routine administration of vitamin A to neonates and infants younger than six months, with a view to updating the current recommendations about its use. The proposal to delete the 50 000 IU formulation currently on the EMLc arose from the results of the review. Expert comments were provided by Dr Stuart MacLeod and Dr Robert Petersen.

The two reports, *(55)* provided as confidential drafts to the Subcommittee, were the manuscript version of the systematic review of neonatal vitamin A supplementation *(56)* and the report to WHO on the benefits and safety of vitamin A supplementation in the first six months of life *(57)*. Both are comprehensive systematic reviews and both found that the existing evidence shows no benefit of routine supplementation in terms of mortality or morbidity in these age groups. The Subcommittee noted that

administration of this drug to young infants has been associated with an increased occurrence of bulging fontanelle.

Five additional Cochrane Reviews were identified examining administration of vitamin A to other subgroups of children: low birth weight infants, children with cystic fibrosis, children with measles, for prevention of lower respiratory tract infections, and non measles pneumonia in children under seven years of age *(58, 59, 60, 61, 62)*.

In low-birth-weight children, most studies reported use of intramuscular vitamin A. There was a trend towards benefit in terms of survival and reduced oxygen requirement, but most of the outcomes analysed were not statistically significant. No studies were identified in the review of cystic fibrosis. In the review of treatment of measles, vitamin A was administered at doses of 100 000 or 200 000 IU and was found to reduce mortality. The reviews of non-measles pneumonia and lower respiratory tract infections found no evidence of benefit of vitamin A supplementation in children under seven years of age.

The Subcommittee considered that there was no clear need for a 50 000 IU oral dose for routine prophylaxis against vitamin A deficiency during the first six months of life. The 50 000 IU dosage form is also not appropriate for routine supplementation in children over six months of age for whom the recommended dose is 100 000 or 200 000 IU. Therefore the only potential use for the low-dose capsule would be for the outpatient treatment of clinically proven vitamin A deficiency in neonates and infants under six months of age; a condition that is exceedingly rare. The Subcommittee recommended that the 50 000 IU dosage form be deleted from the EMLc.

New section 28. Ear, nose and throat conditions in children

The Subcommittee considered the review that was commissioned to identify essential medicines for the treatment of ear, nose and throat conditions in children. Expert comments were provided by Dr Kalle Hoppu and Professor Prakash Mohan Jeena.

Based primarily on South African guidelines and WHO guidelines for treating ear, nose and throat conditions in children, the priority conditions identified were acute croup, epiglottitis, epistaxis, otitis externa, otitis media (acute and chronic), rhinosinusitis and sore throat. The Subcommittee noted that many medicines required for treating these conditions were already listed. However, several more needed to be considered for addition. These included preparations for both topical and systemic use. There was a lack of documented evidence for the efficacy and safety of most of the medicines that needed to be considered for addition. Most available data came from

studies in adults or from those involving both adults and children. However, these medicines are recommended in widely accepted guidelines.

The Subcommittee noted that there is evidence to show that antibiotic ear drops are of benefit in the treatment of otitis externa. There is evidence to suggest that quinolone ear drops are superior to other otic antimicrobial formulations. The Subcommittee considered the importance of the available information regarding combination antimicrobial agent—corticosteroid formulations for the treatment of otitis externa *(63)* and found no compelling evidence to support the inclusion of combination products.

The Subcommittee therefore recommended that acetic acid ear drops and ciprofloxacin ear drops be added to the EMLc, the ciprofloxacin ear drops with a square box annotation.

The Subcommittee decided that based on available evidence, the inclusion of a nasal corticosteroid could be recommended. Further, the Subcommittee recommended the inclusion of a decongestant nasal spray/nose drops, listing xylometazoline with a square box annotation. Topical ephedrine was not included in recognition of its potential for abuse.

The Subcommittee requested a full proposal for a non-sedating antihistamine.

New section 29. Essential medicines for neonates

The Subcommittee reviewed the application for inclusion of a separate section for essential medicines for neonates. In October 2007, the Expert Committee recommended that:

1. The Subcommittee should consider whether it would be appropriate to develop a separate section of the EMLc for neonates.
2. If a separate section is recommended, should it be retained for the "master" list? and
3. How should work in this neglected area be proritized?

The Secretariat prepared the review that was considered by the Subcommittee. Expert comments were provided by Professor Noël Cranswick and Dr Gregory Kearns. The general issues noted were:

— There was a paucity of high quality evidence for the use of medications in the neonatal period and the subsequent off-label and unlicensed use in this population are major problems.
— A more detailed and systematic review of the available evidence for efficacy and safety of the medicines recommended for neonates may be required.
— Medicines were categorized as *recommended* essential medicines for neonates, *missing* essential medicines for neonates, medicines *requiring*

further review before a recommendation for use in neonates can be made, and medicines *not* recommended for neonates.

The Subcommittee noted that the medicines currently missing from the EMLc, and recommended exclusively for use in neonates were:

— *Intravenous ibuprofen or indomethacin* — injectable non-steroidal anti-inflammatory medicines for use in the management of patent ductus arteriosus in preterm infants. It was noted that there is evidence that ibuprofen and indomethacin are equivalent in efficacy for this indication *(64)*. This meta-analysis, not included in the application, of 11 trials comparing the treatments for management of patent ductus arteriosus in the preterm infant, showed that ibuprofen was as effective as indomethacin in closing the patent ductus arteriosus. No significant differences were found in the incidence of complications, except that there was less renal impairment associated with ibuprofen.
— *Prostaglandin E1 or E2 injection* — used to maintain patency of the ductus arteriosus when a cyanotic lesion or interrupted aortic arch presents in a newborn. No systematic reviews of the efficacy of prostaglandin in the management of patent ductus arteriosus were identified, but this therapy is recommended in most clinical treatment guidelines.
— *Surfactant* — See Section 25 — Medicines acting on the respiratory tract.

Given that the review by the Secretariat identified only four medicines for exclusive use during the neonatal period, the Subcommittee recommended inclusion of a new section for these specific medicines. The medicines were:

— caffeine citrate, already included under Section 25;
— ibuprofen injection, to be included in this new section of the EMLc, with a square box to indicate that indomethacin may be an appropriate alternative;
— prostaglandin E1 or E2 injection;
— surfactant (see Section 25).

Given that caffeine citrate is recommended for use in health facilities generally and does not need to be administered in an intensive care unit, it was considered that it should remain on the Core List. The other medicines were included on the Complementary List.

The Subcommittee then considered additional aspects of the use of other medicines, already on the EMLc, in neonates. Comments were received from the WHO Child and Adolescent Health and Development Department, which questioned the need to include chloramphenicol, vitamin A, zinc sulfate and aciclovir 3% for neonates.

There is no evidence for the efficacy of oral zinc in children under six months of age. A recent review from the Cochrane Collaboration identified 18 randomized controlled trials that compared zinc with placebo in young children. This included two large trials that were conducted in children aged less than six months with acute diarrhoea, and showed no evidence of an effect on any of the outcomes *(65)*.

Evidence for the efficacy of chloramphenicol specifically in the neonatal population is limited. A Cochrane Review showed equivalent efficacy of ceftriaxone or cefotaxime with conventional antibiotics (including chloramphenicol) when given for the management of acute bacterial meningitis *(66)*.

Neonates with suspected herpes simplex virus infection, including those with skin, eye or mouth disease, should be treated with intravenous aciclovir. There is no evidence for the efficacy of topical aciclovir in the management of neonatal herpes infections.

On the basis of the review, medicines on the EMLc used in neonatal care were identified and are included in Appendix B to this report. The Subcommittee considered that a separate list of medicines for neonates could cause unnecessary confusion and that an annex listing medicines that can be safely used in neonates was the best option at the present time.

5. Summary of recommendations

Section 4. Antidotes and other substances used in poisonings

4.2 Specific

— NAC oral solution added.

Section 6. Anti-infective medicines

6.2.1 *Beta-lactam medicines*

— **cefalexin** — capsule, tablet and powder for dilution added.
— **cefotaxime** — added to Complementary List for use in hospitalized neonates.
— **ceftazidime** — request for review removed.
— **ceftriaxone** — insertion of note to restrict use to infants older than 41 weeks corrected gestational age; note added regarding avoidance of use in administration with calcium and in infants with hyperbilirubinaemia; request for review removed.
— **imipenem–cilastin** — note added stating that meropenem is indicated for the treatment of meningitis in children over the age of 3 months; request for review removed.

— **procaine benzylpenicilli**n — age restriction removed; note added that it is not recommended as first-line treatment for sepsis and/or meningitis; request for review removed.

6.2.2 ***Other antibacterials***

— **azithromycin** — age restriction removed.
— **ciprofloxacin** — removal of note stating that it is for use only in Shigella infections; IV and oral liquid formulation added; request for review removed.
— **doxycycline** — age restriction added limiting use to children over 8 years of age with non-life threatening conditions; removal of note regarding use only in treatment of cholera; request for review removed; 50-mg tablet and oral liquid added.
— **erythromycin** — intravenous formulation deleted; request for review removed.
— **gentamicin** — request for review removed.
— **sulfadiazine** — intravenous form deleted; oral form moved from Section 6.2.2 to Section 6.5.4.

6.2.4 ***Antituberculosis medicines***

— Deletion of fixed-dose combination antituberculosis medications (rifampicin + isoniazid, rifampicin + isoniazid + pyrazinamide).

6.4.2.3 ***Protease inhibitors***

— Addition of new doses of fixed-dose combination tablets for antiretroviral medicines.

6.5.2 ***Antileishmaniasis medicines***

— Liposomal amphotericin B added to the Core List of antileishmaniasis medicines.

Section 8. Antineoplastic, immunosuppressives and medicines used in palliative care

8.4 Medicines used in palliative care

Ten new medicines added (amitriptyline, cyclizine, dexamethasone, diazepam, docusate sodium, hyoscine hydrobromide, ibuprofen, midazolam, morphine and senna).

Section 10. Medicines affecting the blood

10.2 Medicines affecting coagulation

— Heparin sodium strength 20 000 IU deleted.

Section 12. Cardiovascular medicines

12.5 Antithrombotic medicines

— Antithrombotic medicines section deleted.

Section 13. Dermatological medicines (topical)

13.5 Medicines affecting skin differentiation and proliferation

— Dithranol preparation deleted.

Section 15. Disinfectants and antiseptics

15.1 Antiseptics

— 20% chlorhexidine digluconate solution added.

Section 16. Diuretics

— Spironolactone — strength changed to 5 mg/5 ml; 10 mg/5 ml; 25 mg/5 ml (previously 1–20 mg/ml).

Section 17. Gastrointestinal medicines

— Pancreatic enzymes added to the Complementary List.

Section 18. Hormones, other endocrine medicines and contraceptives

18.1 Adrenal hormones and synthetic substitutes

— Fludrocortisone and hydrocortisone added to the List.

18.5 Insulins and other antidiabetic agents

Insulin injection strength 40 IU/ml deleted.

Section 24. Psychotherapeutic medicines

24.1 Medicines used in psychotic disorders

— Chlorpromazine and haloperidol moved to the Complementary List.

Section 25. Medicines acting on the respiratory tract

25.1 Antiasthmatic and medicines for chronic obstructive pulmonary disease

— Oral salbutamol — note added that treatment should only be considered when inhaled asthma therapy is not feasible.

Section 26. Solutions correcting water, electrolyte and acid–base disturbances

26.2 **Parenteral**

— Glucose (4%) with sodium chloride (0.18%) deleted.
— Potassium chloride strength 7.5% and 15% added, 11.2% deleted.

Section 27. Vitamins and minerals

— Retinol — 50 000 IU dosage form of vitamin A deleted.

Section 28. Ear, nose and throat conditions in children

— New ear, nose and throat section created.
— Acetic acid drops, budesonide, ciprofloxacin drops and xylometazoline spray added.

Section 29. Essential medicines for neonates

— New section created for specific medicines in neonatal care.
— Caffeine citrate moved to this section from Section 25.2.
— Surfactant, prostaglandins and intravenous ibuprofen added.
— Medicines used in neonatal care identified and included in Appendix B.

Table 1. Age restriction table

— New additions — ceftriaxone, xylometazoline.
— New deletions — azithromycin, clindamycin, procaine benzylpenicillin.

Summary of new reviews/applications requested during the meeting of the Subcommittee:

— Appropriate medicines for use in resuscitation in children.
— Essential medicines for management of neuropathic pain in children, including the role of lamotrigine, amitriptyline and gabapentin.
— Review of liposomal amphotericin B as a treatment for fungal infections in children.
— Antimonials as essential medicines for leishmaniasis, and whether they should be on the Core or Complementary List.
— Safety and efficacy of streptomycin in childhood tuberculosis.
— Review of safety of topical antibiotics, including tetracycline ointment in neonates.
— Clinical use of ondansetron in children.
— The role of leukotriene antagonists in the management of childhood allergic rhinitis.
— Application for heat-stable protease inhibitors for management of HIV.

— Comparison of sulfadiazine and co-trimoxazole in the treatment of toxoplasmosis.
— Application for glucagon.
— Development of child-friendly equipment for medicine administration for all ages.
— Review of use of methylene blue in children.
— Review of use of oral iron/lead chelators in children.
— Assessment of two new clinical trials on safety and efficacy of procaine benzylpenicillin in neonates.

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Appendix A

Declaration of interests of Subcommittee members

The members of the Subcommittee reported the following:

Professor Noël Cranswick reported being an investigator on trials for GlaxoSmithKline, Quintiles, Novartis, Uriach, Biomarin and Biota but not for any products or related products to those being considered at the meeting, and also reported holding shares in Biota through a family trust.

Mr Andy Gray reported having accepted travel support and honoraria from AstraZeneca, Aspen Pharmacare for continuing professional development lectures and being a study pharmacist for the International Clinical Trials Unit and Center for the AIDS Programme of Research in South Africa in KwaZulu-Natal. He also reported being a director of a government funding agency for biotechnology, and being a member of the Scheduling and Naming Committee of the Medicines Control Council of South Africa.

Dr Kalle Hoppu reported receiving lecture fees from Norit Pharmaceuticals Netherlands, Leiras Ltd. Finland (2005) and Oy Swedish Orphan Ab Finland (2008). Dr Hoppu reported providing consultation advice once to Lundbeck A/S Denmark, provided through the Clinical Research Institute Helsinki University Central Hospital Ltd/Finnish Investigators Network for Paediatric Medicines.

Dr Gregory Kearns reported providing consultancy services for Abbott, Biodelivery Sciences, Santarus, Mead Johnson, Wyeth Pharmaceuticals, Cubist Pharmaceuticals, Schwarz Pharma, Proctor and Gamble, Orexigen, Tyco Healthcare, Altana Pharma and Centocor. In addition, Dr Kearns reported that his employer holds research contracts related to child health with the private sector. He also serves as a member of the US Food and Drug Administration Clinical Pharmacology Advisory Committee, and provides consultation to the National Institutes of Health regarding paediatric drug development.

Professor Prakash Mohan Jeena declared being a principal investigator on a trial of protease inhibitors in HIV (GlaxoSmithKline) and receiving travel support and honoraria for lectures from GlaxoSmithKline, Wyeth and Sanofi-Pasteur. He also chaired the essential drugs programme for children in South Africa.

Dr Anita Zaidi reported that her department received research funding from Wyeth Pharmaceuticals and GlaxoSmithKline for work on vaccines.

Dr Peter Kazembe reported that his employing institution received some funding from The Abbot Fund, through Baylor College of Medicine, USA.

Mrs Jehan Mohammed Ali Al-Fannah and Dr Helena L. Coelho and reported no conflict of interest.

The Temporary Advisers reported the following:

Dr Stuart MacLeod reported serving as Executive Director of the Child and Family Research Institute, Vancouver, and as Associate Dean (Research) University of British Columbia, Canada. Both institutions hold child health research contracts with the private sector, but he is not principal investigator on any of these contracts. He has also provided consultation and has served on advisory committees for federal and provincial governments in Canada.

Dr Robert Peterson reported receiving travel expenses to attend the Board meetings of the Institute for Regulatory Science, Centre for Medicines Research International, and also for being a member of the Expert Drug Advisory Committee of the Canadian Agency for Drug and Health Technology Assessment.

Professor H. P. S. Sachdev reported receiving honoraria for speaking at the National Probiotic Symposium (India, 2007) and the National Indian Academy of Paediatrics Conference (2007) on the use of probiotics and zinc to treat diarrhoea. He has also served on policy committees established by the Government of India.

Professor Anthony Nunn provided advice to the European Medicines Agency and the UK Government Commission on Human Medicines. He receives research support for the study of medicines in children from the UK National Institute of Health Research.

Dr Jacqueline Deen served as a paid consultant to GlaxoSmithKline to develop a training module until May 2008. Her employer, the International Vaccine Institute receives funding from the Bill and Melinda Gates Foundation, other foundations and vaccine producers. Dr Deen is currently an investigator in a malaria trial being conducted in Africa, funded by the Wellcome Trust.

Professor Dai Yao Hua and Dr Elizabeta Zisovska reported no conflict of interest.

Dr Shalini Sri Ranganathan was a non-attending Temporary Adviser who reported no conflict of interest.

For the purposes of this declaration, the participants noted that many of them worked in departments that received funding from other commercial entities but they were not directly involved in these projects. Several participants have held positions in academic or learned societies that have provided general direction on matters pertinent to child health.

Appendix B

Essential medicines that can be used in neonates

CORE	
oxygen	Inhalation (medicinal gas) (*Section 1.1*)
lidocaine	Injectable solution: 1%; 2% (hydrochloride) in vial Topical forms: 2% to 4 % (hydrochloride) (*Section 1.2*)
diazepam*	Injection: 5 mg/ml in 2-ml ampoule (*Section 1.3*) * Preparations without benzyl alcohol should be used for neonates
morphine	Injection: 10 mg (as morphine hydrochloride or morphine sulfate) in 1-ml ampoule (*Sections 1.3 and 2.2*) Oral liquid: 10 mg (as morphine hydrochloride or morphine sulfate)/5 ml (*Section 2.2*)
paracetamol	Oral liquid: 125 mg/5 ml Suppository: 60 mg (*Section 2.1*)
epinephrine	Injection: 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule (*Sections 3 and 25.1*)
calcium gluconate	Injection: 100 mg/ml in 10-ml ampoule (*Section 4.2*)
naloxone	Injection: 400 micrograms (as hydrochloride) in 1-ml ampoule (*Section 4.2*)
phenobarbital	Injection: 200 mg/ml (phenobarbital sodium) (*Section 5*)
phenytoin	Injection: 50 mg/ml in 5-ml ampoule (as sodium salt) Oral liquid suspension: 25 mg to 30 mg/5 ml (*Section 5*)
amoxicillin as trihydrate (as sodium salt)	Powder for oral liquid: 125 mg (anhydrous)/5 ml; 250 mg (anhydrous)/5 ml (*Section 6.2.1*)
ampicillin	Injection: 500 mg (as sodium salt) in vial (*Section 6.2.1*)
benzylpenicillin (penicillin G)	Powder for injection: 600 mg (= 1 million IU); (sodium or potassium salt) in vial (*Section 6.2.1*)
cefotaxime	Powder for reconstitution: 500 mg (*Section 6.2.1*)
ceftriaxone [a]	Powder for reconstitution: 250 mg (as sodium salt) in vial (*Section 6.2.1*) [a] not in infants <41 weeks corrected gestational age
cloxacillin	Injection: 500 mg (as sodium salt) in vial (*Section 6.2.1*)
procaine benzylpenicillin	Suspension for intramuscular injection 1 g (*Section 6.2.1*)
☐ erythromycin*	Powder for oral liquid: 125 mg (as stearate or ethyl succinate) in 5 ml (*Section 6.2.2*)
gentamicin	Injection: 10 mg (as sulfate)/ml in 2-ml vial (*Section 6.2.2*) Solution (eye drops): 0.3% (as sulfate) (*Section 21.1*)
fluconazole	Injection: 2 mg/ml in vial Oral liquid: 50 mg/5 ml (*Section 6.3*)
nystatin	Oral liquid: 50 mg/5 ml or 100 000 IU/ml (*Section 6.3*)

CORE	
zidovudine	Oral liquid: 50 mg/5 ml Solution for injection: 10 mg/ml (*Section 6.4.2.1*)
nevirapine	Oral liquid: 50 mg/5 ml. (*Section 6.4.2.2*)
phytomenadione	Injection: 1 mg/ml in 5 ml-ampoule (*Section 10.2*)
methylrosanilinium chloride (gentian violet)	Aqueous solution: 0.5% (*Section 13.2*)
oral rehydration salts	glucose: 75 mEq sodium: 75 mEq or mmol/L chloride: 65 mEq or mmol/Ll potassium: 20 mEq or mmol/L citrate: 10 mmol/L osmolarity: 245 mOsm/L glucose: 13.5 g/L sodium chloride: 2.6 g/L potassium chloride: 1.5 g/L trisodium citrate dihydrate+: 2.9 g/L + trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/L. However, as the stability of this latter formulation is very poor under tropical conditions, it is only recommended when manufactured for immediate use. (*Sections 17.5.1 and 26.1*)
antitetanus immunoglobulin	500 IU vial (*Section 19.2*)
caffeine citrate	Injection: 20 mg/ml (equivalent to 10 mg caffeine base/ml) Oral liquid: 20 mg/ml (equivalent to 10 mg caffeine base/ml) (*Section 25.2*)
glucose	Injectable solution: 10% (*Section 26.2*)
potassium chloride	Solution for injection: 7.5% (equivalent to K 1 mmol/ml and Cl 1 mmol/ml) (*Section 26.2*)
sodium chloride	Injectable solution: 0.9% isotonic (equivalent to Na^+ 154 mmol/l, Cl^- 154 mmol/l) (*Section 26.2*)
water for injection	Solution for injection: 2-ml; 5-ml; 10-ml ampoules. (*Section 26.3*)
cholecalciferol	Oral liquid: 400 IU/ml (*Section 27*)
COMPLEMENTARY	
atropine sulfate	Injection: 1 mg (as sulfate) in 1-ml ampoule (*Sections 1 and 4*)
hydrocortisone	Powder for injection: 100 mg (as sodium succinate) in vial (*Sections 3 and 8.3*)
imipenem + cilastatin	Powder for injection: 250 mg (as monohydrate) + 250 mg (as sodium salt) in vial (*Section 6.2.1*)
metronidazole	Injection: 500 mg in 100-ml vial (*Sections 6.2.2 and 6.5.1*)

CORE	
vancomycin	Powder for injection: 250 mg (as hydrochloride) in vial (*Section 6.2.2*)
amikacin	Solution for injection: 50 mg/ml (*Section 6.2.4*)
aciclovir	Solution for injection: 250 mg/10 ml (*Section 6.4.1*)
amphotericin B	Injection: 50 mg in vial (*Section 6.5.2*)
digoxin	Injection: 100 micrograms/ml Oral liquid: 50 micrograms/ml (Section 12.4)
dopamine	Injection: 40 mg/ml as hydrochloride in 5-ml vial (*Section 12.4*)
ranitidine	Injection: 25 mg/ml in 2-ml ampoule (*Section 17.1*)
insulin	Injection: 100 IU/ml in 10-ml vial (*Section 18.5*)

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This report presents the recommendations of the WHO Expert Committee responsible for updating the WHO Model List of Essential Medicines. The first part contains a review of the report of the meeting of the Expert Subcommittee on the Selection and Use of Essential Medicines, held in October 2008. It also provides details of new applications for paediatric medicines and summarizes the Committee's considerations and justifications for additions and changes to the Model List, including its recommendations. Part Two of the publication is the report of the second meeting of the Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines. Annexes include the revised version of the WHO Model List of Essential Medicines (the 16th) and the revised version of the WHO Model List of Essential Medicines for Children (the 2nd). In addition there is a list of all the items on the Model List sorted according to their Anatomical Therapeutic Chemical (ATC) classification codes.

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