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**UNEDITED VERSION**

**(October 2013)**

# **The Selection and Use of Essential Medicines**

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

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## Executive Summary

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

In accordance with its approved procedures ([http://www.who.int/entity/selection\\_medicines/committees/subcommittee/2/eeb1098%5B1%5D.pdf](http://www.who.int/entity/selection_medicines/committees/subcommittee/2/eeb1098%5B1%5D.pdf)) the Expert Committee evaluated the scientific evidence on the comparative effectiveness, safety and cost effectiveness of medicines in order to update the WHO Model List of Essential Medicines and the WHO Model List of Essential Medicines for Children. The Expert Committee considered 52 applications and 15 reviews and:

- approved the addition of 17 new medicines (10 to the Core List and 7 to the Complementary List) to the EML;
- approved the deletion of one medicine from the EML;
- approved new indications for three medicines already listed on the EML;
- approved the addition of a new dosage form or strength for four medicines already on the EML;
- approved two medicines to be moved from the Complementary List to the Core List, and one from the Core List to the Complementary List;
- rejected nine applications for the addition of a medicine to EML and deferred a decision in the case of further two applications;
- approved two medicines for neonatal care;

Some of the main recommendations made in order of their appearance on the Model List, were:

- Section 2 (Analgesics, Antipyretics, Non-Steroidal Anti-Inflammatory Medicines (NSAIDs), Medicines used to treat Gout and Disease Modifying Agents in Rheumatoid Disorders (DMARDs): renaming the section to Medicines for Pain and Palliative Care to emphasize the importance of the medicines used in palliative care. The Committee recognized the importance of palliative care not only in cancer but also in HIV/AIDS, MDR TB and severe congenital diseases. Therefore it moved these medicines from Section 8 (Antineoplastic, Immunosuppressives and Medicines used in Palliative Care) to Section 2 in both the EML and EMLc. Medicines needed for the treatment of other common symptoms in palliative care such as anorexia, nausea, constipation and diarrhoea were also included in Section 2. A new section, Medicines for Diseases of Joints (Section 30), was created to list the treatments for gout, disease modifying agents used in rheumatoid disorders and juvenile joint diseases that were deleted from Section 2.



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

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

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

■ ■ Section 6.5.3.1 (Antimalarial medicines - For curative treatment): addition of artesunate + mefloquine fixed-dose combination tablets for the treatment of malaria in adults and children in line with current WHO treatment guidelines. In making its decision, the Expert Committee noted that both medicines were listed separately in the EML and EMLc, and that evaluation in clinical trials had shown similar comparative efficacy of the separate tablets and the combination. There are products containing the fixed-dose combination that are approved by the WHO-UN prequalification programme. With this addition, three of the five fixed-dose combinations recommended by the WHO for the treatment of malaria are included in the Core List.

■ ■ Section 8.2 (Cytotoxic and adjuvant medicines): after considering the applications for addition of imatinib and trastuzumab, the Expert Committee decided that an urgent review of the sub-section is needed, using a process and structure similar to that used for the same section in the EMLc. This process would require identification of the treatable, public health relevant tumors in adults, and identification of the medicines required to treat those tumors, considering a stepwise development of cancer care systems in the overall context of health system development. The Expert Committee considered the two applications in detail and noted the high quality evidence showing relevant clinical benefits in support of both imatinib and trastuzumab but deferred the final specifications of the medicines and their inclusion till the review of the section of cytotoxics is completed.

■ ■ Section 11 (Blood Products and plasma substitutes): after considering the application for addition of Whole blood and red blood cells, the Expert Committee decided to restructure the section. The heading was changed to “Blood products and plasma substitutes of human origin”. Sub-section 11.1 was changed to “Blood and blood components” with fresh frozen plasma, red blood cell concentrates, platelets and whole blood. Sub-section was changed to 11.2 to “Plasma-derived medicinal products” with a sub-section of 11.2.1 of “Human

immunoglobulins” and a sub-section 11.2.2 of “Blood coagulation factors”. Sub-section 11.3 was changed to “Plasma substitutes”

■ ■ Section 21 (Ophthalmological Preparations): addition of bevacizumab injection to the Complementary List in a new section (Section 21.6 Anti-vascular endothelial growth factor preparations) of the EML. Neovascular Age-Related Macular Degeneration is a leading cause of blindness in the persons over 50 years and bevacizumab has been shown to be effective with an acceptable risk profile. The Expert Committee recommended the addition of bevacizumab, while noting the precautions needed for intravitreal administration.

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

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

■ ■ Section 29 (Specific Medicines for Neonatal Care): Chlorhexidine 7.1% solution or gel delivering 4% was added to the Core List for use in umbilical cord care in community settings. A new sub-section of Medicines administered to the mother (Section 29.2) was added and dexamethasone included for accelerated foetal lung maturation in anticipated preterm birth; the efficacy of steroids for this condition has been conclusively demonstrated. While alternative steroids with similar efficacy were available, dexamethasone was considered the most appropriate product based on availability and cost.

Other medicines added were: loratidine, loperamide (for adults only in the context of palliative care), hyoscine butyl bromide, gliclazide (to replace glibenclamide), azithromycin eye drops, latanoprost eye drops and ofloxacin eye drops, which were added to the Core List; and hydromorphone, oxycodone, fomepizole and prothionamide, which were added to the Complementary List.

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

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

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

All applications and documents considered by the Expert Committee remain available on the web site for the meeting at: [http://www.who.int/selection\\_medicines/committees/expert/19/en/index.html](http://www.who.int/selection_medicines/committees/expert/19/en/index.html).

<http://www.who.int/medicines/publications/essentialmedicines/en/index.html>

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## **Declaration of interests of Members of the 19th Expert Committee on the Selection and Use of Essential Medicines**

### Members reported the following interests:

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

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

Mr Andrew Gray disclosed remunerated consultancies for UNAIDS and WHO, relating to the preparation of a Strategic Report on Development and Cooperation in Pharmaceutical Sectors in BRICS Countries: Medicines for HIV/AIDS, TB, Malaria and Priority Medicines for NCDs, and the preparation of a systematic review and position paper on the interchangeability of lamivudine and emtricitabine. He declared having received support from Fresenius Kabi and Pfizer for continuing education presentations unrelated to any specific products. He also disclosed that he was involved as consultant pharmacist to the Centre for the AIDS Programme of Research in South Africa (CAPRISA), which was a site for National Institute of Health trials (ACTG and IMPAACT networks). The networks received donated trial medication from various manufacturers, including Abbott, Boehringer Ingelheim, Bristol Myers Squibb, Gilead, GlaxoSmithKline, Merck Sharpe and Dohme and Roche. In addition, he had been a co-investigator in a USAID and LIFELabfunded phase IIb clinical trial of a microbicide containing tenofovir (active ingredient supplied by Gilead, packed by Conrad). Mr Gray also disclosed that he was a member of an expert committee of the South African Medicines Control Council.

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



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

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

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

The temporary advisers present declared the following interests:

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

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

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

Prof. Gitanjali Batmanabane disclosed having previously worked for the Better Medicines for Children project in the SEARO office.

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

Dr Gilles Sama Kwende disclosed no potential conflicts of interest.

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

## **1. Introduction**

The 19<sup>th</sup> meeting of the WHO Expert Committee in Selection and Use of Essential Medicines was held from 8 to 12 March 2013, in Geneva, Switzerland.

The meeting was opened on behalf of the Director-General of the World Health Organization by Dr Marie-Paule Kieny, Assistant Director-General for Health Systems and Innovation. She welcomed the participants to the meeting and briefly summarised the history of Essential Medicines beginning with Member states requesting in the 1970s, a list of important medicines. The Essential Medicines Concept was elaborated in 1975 and the 1st WHO Model List of Essential Medicines was developed by the first Expert Committee in 1977. Today it is the 19th Expert Committee, revising the 17th WHO Model List of Essential Medicines which then becomes the 18th List.

She highlighted 3 changes that occurred during this period. The first was the evolution from an expert opinion-based process to an evidence-based one; secondly the WHO model list of essential medicines had gone from a list that chose from existing medicines to also recommending specific indications and, where necessary, what new formulations should be available based on health care needs. Finally and thirdly, it has progressed from a consultation of experts to including the wider global health community.

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

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

## 2. Open Session

This session of the meeting was chaired by Dr Marie-Paule Kieny, Assistant Director-General for Health Systems and Innovation on behalf of the Director-General and was attended by a number of interested parties. They were welcomed by Mr Kees de Joncheere, Director of the Department of Essential Medicines and Health Products.

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

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

- Dr Willem Scholten (Consultant – Medicines and Controlled Substances, Geneva, Switzerland) - "Messages on WHO Essential Medicines: Pivotal for Access to Pain Management"
- Professor Lukas Radbruch (Incoming Chair of the International Association for Hospice and Palliative Care; Director, Department of Palliative Medicine, University Hospital Bonn, Germany) - "Relieving suffering: essential medicines in palliative care"
- Dr Leslie Lehmann (Clinical Director, Pediatric Hematopoietic Stem Cell Transplant Program, Dana/Farber/Children's Hospital Cancer Center Boston; Assistant Professor of Pediatrics, Harvard Medical School, Boston, USA) in collaboration with Ms Julie Torode (Deputy CEO, Union for International Cancer Control, Geneva, Switzerland) and Ms Mélanie Samsom (Global Advocacy Specialist, Union for International Cancer Control, Geneva, Switzerland) - "The case for support: addressing the needs of cancer patients worldwide in the WHO Model Essential Medicines List"
- Professor Tom Harrison and Professor Juan Luis Rodriguez Tudela (Global Action Fund for Fungal Infections, Geneva, Switzerland) - "Essential antifungals"
- Dr Harvey G. Klein (Department of Transfusion Medicine, Clinical Center, National Institutes of Health, Bethesda, USA) - "Blood is an Essential Medicine"
- Dr Gilles Folléa (Executive Director, European Blood Alliance, Brussels, Belgium) - "Addition of whole blood and red blood cells on the WHO essential medicine lists: an assessment of pros and cons from the European Blood Alliance"

- Dr Che Kit Lin (Chief Executive and Medical Director, Hong Kong Red Cross Blood Transfusion Service) - "Statement from International Transfusion Medicine Experts"

### 3. General items

#### 3.1 Defining public health relevance

The WHO definition of an 'essential medicine' currently is:

*"Essential medicines are those that satisfy the priority health care needs of the population".*

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

Public health relevance for a medicine has been variously interpreted by previous Expert Committees to include consideration of:

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

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

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

A potentially useful consideration is described in the report by Kanavos *et al*, on Value Based

Pricing (1). The authors note, with respect to antiretrovirals:

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

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

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

### 3.2 Medicines Information as a Global Public Good

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

Some commercial or not-for-profit drug information sources, for example the British National Formulary or Micromedex (a commercial drug information source) may provide information on the newer, unapproved indications, contraindications and adverse effects. However the information that is published by these organisations does not have the same legal and regulatory basis as a product information sheet supported by a manufacturer or product sponsor.

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

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

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

The Committee noted that it had previously considered evidence of efficacy and safety and a demonstrable public health as the main criteria for inclusion on the EML, and not whether the indication was approved by regulatory authorities in national settings (for example, ribavirin for haemorrhagic fever). The Committee noted that the inclusion of indications in regulatory documents (such as the label or package insert) was nearly always based on the request of the sponsor/applicant. The Committee was therefore in favour of an expanded role for WHO in ensuring that indications for which evidence existed, were recognized in product information documents. The Committee recommended that this issue be raised with the International Conference of Drug Regulatory Authorities (ICDRA).

### 3.3 Section 6 - Ivermectin

The Committee considered an application from the WHO Prevention of Blindness and Deafness (PBD) Unit for alteration of the listing of ivermectin in Section 6 of the EML. The manufacturer provides only 3mg oral solid dosage forms and not the 6mg strength currently listed. It was agreed that the listing should be amended to reflect this change.

### 3.4 Other

The Committee discussed and encouraged the Secretariat to evaluate different options for convening the Committee and modifying the Committee processes for updating the list. The Committee noted the necessity for more frequent meetings making use of facilities such as video- and tele-conferencing. The Committee also noted the large number of applications to be considered by this Expert Committee and suggested that the Secretariat consider whether there is a maximum number of applications that is feasible to consider in a single meeting.

The Committee recalled the decision made by the 17th Expert Committee with respect to applications for medicines for children: "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 noted that the number of applications for adult and paediatric medicines considered at this meeting was almost equal, but that the composition of the Committee did not reflect this distribution. The need to ensure adequate expertise must be carefully considered when composing future Expert Committees. A possible alternative would be to re-establish the subcommittee, as part of an overall reform of the working methods of the Committee.

The Committee also drew attention to another comment from the 17<sup>th</sup> Expert Committee report: "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." The applications submitted for the current meeting did not uniformly consider adult and child indications when relevant.



#### **4. Applications only for paediatric medicines**

##### Section 1: Anaesthetics

##### [Anaesthetics \(Review\) -- Children](#)

The 18<sup>th</sup> Expert Committee posted the question “What anaesthetics can be safely used in neonates?” A review on this topic, limited to general anaesthetics, was prepared by Dr Elizabeth Zisovska, Skopje, Republic of Macedonia.

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

A number of studies in immature animal models were reviewed and there was some evidence of degenerative effects of several anaesthetics on neuronal structure. However the relevance of these to neonates is not clear.(2, 3). Many general anaesthetics are not licensed for children, especially neonates. The reasons for this are complex but could be partly due to lack of safety or toxicity data in children, again especially in neonates.

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

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

- Minimization of physiological, humoral and behavioral signs of distress;
- Reduction of pain;
- Ablation of consciousness; and
- Maximization of perioperative outcomes.

The major issue is lack of appropriate studies and therefore evidence in neonates, a common problem in medicines for children. Hence any extrapolation from adult data need to be reviewed when data from neonates becomes available.

The review proposed that,

- halothane should not be the preferred inhalational anaesthetic in neonates; and that an age restriction of above one month be included in the listing;
- isoflurane is safe in neonates for induction and maintenance and should therefore be retained in the EMLc;
- nitrous oxide and oxygen both need to be retained in the EMLc;
- ketamine be retained in the EMLc, although a paediatric formulations would be useful to improve safety during administration;
- the use of propofol be restricted to patients aged over one month;
- thiopental be added to the EMLc, as it is licensed for use in neonates.

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

## Section 2: NSAIDs and DMARDs

### **2.2: Opioid analgesics**

#### [Hydromorphone \(Addition\) – Children](#)

#### [Oxycodone \(Addition\) – Children](#)

Two applications were submitted by Dr Willem Scholten, WHO Team Leader, Access to Controlled Medicines (until 31 October 2012); the first was for the addition of hydromorphone and oxycodone, as examples of the opioid class, to the EMLC.

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

These two applications were based on recommendations in the WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses published in 2012 and the WHO policy guidelines Ensuring Balance in National Policies on Controlled Substances, Accessibility and Availability of Controlled Medicines (8, 9). The listing was requested as a footnote to the square box appended to the morphine listing, which would read as “Examples for alternative opioids for morphine. Two or more alternatives should be available in addition to morphine.”

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

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

The Committee recommended that a square box symbol be added to the listing for morphine, with a note to the effect that this would be intended to include both hydromorphone and oxycodone.

***Morphine (New formulation) -- Children***

The second application submitted by Dr Willem Scholten, WHO Team Leader, Access to Controlled Medicines (until 31 October 2012), was for the addition of morphine granules and tablets (both slow-release) to the EMLc. The application also requested that the terminology be standardised to slow-release and requested that dosage and formulae for morphine oral solution be published as an Annexe in the TRS.

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

The WHO Guidelines on the Pharmacological Treatment Of Persisting Pain In Children With Medical Illnesses recommends morphine as the first-line strong opioid treatment for persisting moderate to severe pain (8). This application states that insufficient formulations as well as strengths of morphine are available to treat pain in paediatric groups ranging from infants to 12 years of age. Therefore, it proposes that slow-release granules, which would allow morphine to be administered as liquid in very small doses for infants, be added. The advantages of slow-release morphine are longer dose intervals, which could improve patient compliance by decreasing dose frequency. Additional points that were made relate to the inter-individual variation in the response to morphine and the need for titration for pain relief. As there is no upper dosage limit for opioid analgesics, the application also noted the need for high-end strengths of morphine to be added to the EMLc.

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

The Committee noted the requests that the standard term "slow-release" be used rather than "controlled-release", "modified-release" and "prolonged-release" and recommended that this term be implemented in the section on morphine. However, the application of the same approach in other sections would need a review of the applicability of this terminology for the full range of preparations in all therapeutic areas.

The Committee recommended the addition of morphine granules and slow release tablets to the EMLc and noted the dosage recommendations in the WHO Guidelines and the "Formulas for morphine oral solution" as included in the WHO Pharmacists Brochure, 2012 (8, 10).

Section 6: Anti-infective medicines

**6.2: Antibacterials 6.2.4: Antituberculosis medicines**

***Second-line antituberculosis medicines (Review) -- Children***

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

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

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

WHO groups the antituberculosis drugs into five groups, (11, 12). Group 1 is 'First-Line Oral Agents' (e.g. isoniazid, rifampicin) Group 2 'Injectable Agents' (e.g. kanamycin, amikacin), group 3 'Fluoroquinolones', Group 4 'Oral Bacteriostatic 2<sup>nd</sup>-Line Agents' (e.g. ethionamide, cycloserine) and finally Group 5 'Agents with unclear efficacy or concerns regarding usage' (e.g. clofazimine, linezolid). WHO guidelines recommend including a second-line injectable agent from Group 2, a fluoroquinolone from Group 3, and then adding additional drugs from Groups 4 and 5 to create a treatment regimen with at least 4-5 active drugs (12). These guidelines are generally consistent with those recommended by other organizations (13).

The Committee noted that the evaluation of the efficacy of antituberculosis drugs has generally relied on microbiologic, not clinical endpoints. Due to differences in the pathophysiology of TB in children, especially the paucibacillary nature of the majority of paediatric disease, and difficulties with obtaining sputum specimens, the evaluation of microbiologic endpoints in children is challenging. Evidence to inform the selection of agents for treating MDR-TB in children is essentially limited to outcome data from treatment cohorts and these confirm the efficacy of the medicines in groups 2-4.

The efficacy of ofloxacin, levofloxacin, and moxifloxacin against MDR-TB (defined as disease caused by *Mycobacterium tuberculosis* resistant to at least rifampicin and isoniazid) has been extensively evaluated *in vitro*, in animals, and in humans. Although multiple systematic reviews did not identify any randomized trials in MDR-TB, they did synthesize the data from many observational studies. A recent individual patient data (IPD) meta-analysis used reports identified in these systematic reviews to provide a more detailed analysis (14). This review included data from 9,153 patients, drawn from 32 observational cohorts, and reported improved treatment success with the use of a later-generation fluoroquinolones (FLQ) versus no FLQ (adjusted Odds Ratio [aOR] 2.8, 95% CI 1.3-6.1) and versus ofloxacin (aOR 2.1, 95% CI 1.2-3.9), and with the use of ofloxacin versus no FLQ (aOR 2.0, 95% CI 1.2-3.3). In a retrospective observational study comparing ofloxacin and levofloxacin for MDR-TB treatment in adults, levofloxacin was more efficacious, with increased treatment success in ofloxacin-susceptible isolates (96.2% for levofloxacin versus 87.5% for ofloxacin) and in ofloxacin-resistant isolates (78.6% for levofloxacin versus 45.5% for ofloxacin)(15). A systematic review of adults with XDR-TB reported that use of later-generation FLQs was associated with improved outcomes (16).

In a systematic review of children treated for MDR-TB, FLQs were an important component of the treatment regimen in all included studies, which had a pooled treatment success of 81.7% (17). More recently, in a cohort of children with MDR-TB in which a FLQ was a key component of the treatment regimen, 137/149 (92%) achieved a cure or probable cure (18).

The FLQs are generally well-tolerated by adults receiving the prolonged treatment required for MDR-TB. The data on extended administration of FLQs to children have not demonstrated serious adverse effects. Despite a lack of randomized trials of the FLQs in the treatment of MDR-TB in adults or children, their strong bactericidal and sterilizing activity, favourable pharmacokinetics and toxicity profile, have made them an important component of existing MDR treatment regimens. The WHO 2010 Rapid Advice on the Treatment of TB in Children makes a strong recommendation for the use of FLQs in the treatment of DR-TB (19). These recommendations did not specify which of the FLQ were preferred in children (19). Additional data are needed with regard to paediatric dosing of the FLQs in MDR-TB, particularly for levofloxacin and moxifloxacin. Pharmacokinetic data to inform the most appropriate dosing in children are urgently needed, and are likely to be forthcoming from ongoing studies. Existing formulations of these drugs are difficult to dose appropriately and to administer to children.

All three injectable medicines, kanamycin, amikacin, and capreomycin, are currently included in the EMLc. There is little data in children, though in a subgroup analysis in a systematic review of paediatric MDR-TB, treatment success was higher in studies in which patients received injectables compared to studies where they were uncommonly used (87.2% versus 62.6%,  $p=0.02$ )(17).

Ethionamide (ETH) is already included in the EMLc. ETH and prothionamide (PTH) have shown bactericidal activity *in vitro* against *M. tuberculosis*, with PTH MICs usually reported as either equal to or half that of ETH. In a trial in adults comparing ETH 500 mg in two divided doses versus PTH 500 mg in two divided doses, in combination with INH and streptomycin, there was no difference in treatment efficacy, with 98% and 96% respectively having negative cultures at 6 months (20). In an IPD meta-analysis of 9,153 patients with MDR-TB, use of ETH or PTH was associated with an increased odds of treatment success versus failure or relapse (aOR 1.7, 95% CI 1.3-2.3) and versus failure, relapse or death (aOR 1.7, 95% CI 1.4-2.1) (14). ETH was a component of the usual treatment regimens in all the cohorts included in a recent systematic review of children with MDR-TB, which reported a pooled treatment success of 81.7% (17). There is expected to be complete cross-resistance between ETH and PTH.

Cycloserine is already included in the EMLc. There are questions about the efficacy of cycloserine, and neurotoxicity is an important adverse event in treatment of MDR-TB in adults (21). Published paediatric experience consists of two small series in the 1960s, which described the use of cycloserine in combination with isoniazid in the treatment of 29 children, and which reported generally good outcomes and few adverse effects (22, 23). Because of the limited choices available for treatment, it remains an important option in the treatment of MDR-TB.

There is very little English-language literature on the use of terizidone (TZD) for TB. In combination with other drugs, TZD at a dose of 250 mg three times daily was shown to be well tolerated and effective for the treatment of urogenital TB in 51 adults (24).

Para-aminosalicylic acid (PAS) is already included in the EMLc. Though not a potent drug, its efficacy against *M. tb* has been well established in adults, particularly in protecting companion drugs against resistance. Based on existing data, experience, and

recommendations, many children with MDR-TB will be successfully treated without PAS, though for children with additional drug resistance, including Pre-XDR or XDR-TB, drug options are much more limited and PAS will be an important component of treatment regimens in that context.

The *in vitro* activity of linezolid against *M. tb* has been consistently demonstrated. Emerging data in adults and children have also shown it to be effective in difficult cases of DR-TB, with good long-term outcomes. Two systematic reviews in 2012 reported on the safety and efficacy of linezolid for the treatment of drug-resistant TB in adults. The first included 11 studies representing 148 patients (25). The pooled percentage of patients with treatment success was 67.9% (95% CI 58-79%). The second review included 207 patients in 12 studies, many but not all the same studies as the first review (26). Of 121 patients with definite treatment outcomes, 82% (95% CI 74-88%) had successful treatment outcomes, with 93% (95% CI 86-97%) having sputum smear conversion and 93% (95% CI 87-97%) having culture conversion. Two more recent cohorts have reported similar findings (27, 28). All 16 children on linezolid had culture conversion, most within 1-3 months, and 14 of 16 (87.5%) had a successful long-term outcome, with 1 lost-to-follow-up and 1 death (respiratory failure, culture-negative at the time of death). There are no formal recommendations for paediatric dosing of linezolid for DR-TB. Because of the high cost, toxicity, and good clinical outcomes with existing treatment regimens for children with MDR-TB, routine use of linezolid is not supported.

Clofazimine with its pharmacologic characteristics, ability to concentrate in macrophages, potential sterilizing activity, lack of cross-resistance with other agents, and its apparent ability to avoid developing resistance, is a potentially attractive option for treatment of DR-TB. In one study in adults, a 4-month intensive phase containing kanamycin, gatifloxacin, clofazimine, ethambutol, high-dose isoniazid, pyrazinamide, prothionamide, followed by a 5-month continuation phase containing gatifloxacin, ethambutol, pyrazinamide, and clofazimine, resulted in 87.8% cure with only 0.5% relapsing (29). Additional support for clofazimine includes the report of a cohort of adults with XDR-TB, in which more than 60% of patients had a successful treatment outcome with a clofazimine-containing regimen (30). The WHO 2008 guidelines recommend the use of Group 5 drugs, of which clofazimine is one, only when a regimen containing 4 drugs with likely activity cannot be created from Groups 1-4; no other specific recommendations regarding clofazimine is made.

The Committee recommended the following changes to update the complementary list in EMLc, based on WHO guideline recommendations, public health need and available evidence on efficacy and safety:

- to replace ofloxacin with levofloxacin, with an asterisk note to indicate that this would include ofloxacin and moxifloxacin
- to retain ethionamide, but with an asterisk note to indicate that this would include prothionamide.

The Committee noted that child-friendly formulations are urgently needed for some of the 2<sup>nd</sup>-line antituberculosis medicines in order to improve dosing and adherence.

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

#### *Streptomycin injections (To be moved to complementary list) -- Children*

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

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

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

According to the 2010 WHO Rapid Advice (19), streptomycin should not be used as part of first-line treatment regimens for children with pulmonary tuberculosis or tuberculous peripheral lymphadenitis. Streptomycin use is reserved for those with MDR TB with known susceptibility to this medicine.

The Committee accordingly decided to place streptomycin in the Complementary List of the EMLc. Its use for MDR TB will require specialist care and facilities.

#### **6.4.2: Antiretrovirals**

*Abacavir (New formulation); Abacavir + lamivudine (Addition); Efavirenz (New formulation); Lamivudine + nevirapine + zidovudine (New formulation); Lamivudine + stavudine (New formulation); Lamivudine + zidovudine (New formulation); Nevirapine (New formulation)*

Applications for additions and changes in formulations in order to update both the EML and EMLc were submitted by the Clinton Health Access Initiative, with the support of WHO HIV Department. At the time of the meeting, the current WHO guidelines for the treatment of people, both adults and children, living with HIV/AIDS were those issued in 2010 (31).

Expert Reviews were prepared by Dr Eva Njenga and Dr Liliana de Lima

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

Instead, the Expert Committee recommended that there should be an extraordinary meeting (possibly electronically) in order to consider a limited list of applications, specifically in order to align the List with the expected 2013 WHO guidelines, before the planned Committee meeting in 2015. Nonetheless, the Committee underscored the established

principle that the mention of a medicine in an approved WHO guideline did not automatically guarantee its inclusion in the List. Each such application would still be considered on its own merits, and in accordance with the principles that inform the selection of essential medicines.

#### **6.5.5: Antitrypanosomal medicines 6.5.5.1: African trypanosomiasis**

##### *Nifurtimox tablets (Addition) -- Children*

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

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

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

Nifurtimox-eflornithine combination therapy (NECT) is as effective as eflornithine alone for treating second stage African trypanosomiasis but has safety advantages and is easier to administer (infusion every 12 h for 7 days vs every 6 h for 14 days). Both are listed in the EML. Data from the seven HAT platform countries show that 59% of the adult patients were treated with the combination in 2010 (32) and 86% in 2011. Listing of both medicines in the EML has helped to scale up access to NECT.

Eflornithine is already listed in the EMLc for second stage African trypanosomiasis. . Nifurtimox is listed only for American trypanosomiasis in the EMLc, but for both American and African trypanosomiasis in the EML.

Additional data are now available from children and hence this application to include nifurtimox in EMLc to facilitate the combination therapy for sleeping sickness has been submitted. There are no RCTs to assess the combination of nifurtimox and eflornithine specifically in children. A clinical trial (multicenter, open label, phase IIIb) to assess NECT in field conditions was conducted in 6 sites in the Democratic Republic of Congo (DRC). Of a total of 629 patients included in the trial, 100 were children below 12 years of age, 14 were pregnant women and 33 were breastfeeding mothers. Ninety-eight percent of the 629 patients were alive and well on discharge (33). With a 24-month follow-up, similar cure rates were shown in children and adults, with close to 89% alive and well.

Results from a cohort study of patients from MSF treatment centers, including 120 children, also showed good results (34). Adverse reactions were common (60-90%), but severe events were relatively rare. A pharmacovigilance study of NECT reported the characteristics of adverse effects, the commonest being vomiting/nausea and abdominal pain followed by headache, musculoskeletal pains, and vertigo. Adverse event in children were similar to adults, but the major AE were less frequent (35).

Both NECT and eflornithine monotherapy have similar health system requirements, such as the need for intravenous infusion in a hospital setting. Nifurtimox is supplied free of charge



according to an agreement with WHO and, in practice, it is less costly to procure the combination rather than the individual components.

The Committee, considering the public health need for this combination in the affected countries, and the data on effectiveness and safety particularly in children, recommended that nifurtimox be added to the EMLc. This would also help countries to scale up treatment programmes for *T. brucei gambiense* second stage infection.

#### **6.5.5: Antitrypanosomal medicines 6.5.5.2: American trypanosomiasis**

##### **Benznidazole tablets (New formulation) -- Children**

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

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

A recent WHO report estimates that 10 million people worldwide are infected by *Trypanosoma cruzi*, mostly in the endemic areas of 21 Latin American countries, but also in non-endemic countries, as a consequence of population mobility (36). Most infections occur during childhood, and there are also congenital infections. However, until recently the only registered dosage form of benznidazole, the first line treatment for Chagas disease, was a 100 mg tablet, suitable for adults.

Despite the heterogeneity of studies presented in terms of objectives, geographic location, age ranges, numbers of children included in these studies, therapeutic schemes used, duration of post-treatment monitoring and the cure control tests deployed, there is clear evidence of the efficacy of benznidazole for the treatment of children infected by *T. cruzi*, including those less than a year old, and this evidence suggests that greater efficacy is associated with early treatment. Seroconversion rates vary from 87% at 36 months (37) (100% in the 0 to 3 months old group) to 100% (38) at 24 months in children up to two years old.

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

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

Taking into consideration the need for child-friendly formulations of benzimidazole, the Committee decided to add both the 12.5mg and 50 mg scored oral solid dosage forms to the EMLc.

## Section 8: Antineoplastic

### **8.4: Medicines used in palliative care**

#### **Palliative care (New section) -- Children**

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

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

This request was based on the WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses and the WHO policy guidelines Ensuring Balance in National Policies on Controlled Substances, Accessibility and Availability of Controlled Medicines (8, 9). The World Health Assembly in its Resolution 58.22 "On Cancer prevention and control" (2005), called on WHO to address access to opioid analgesics. Other international bodies, such as the International Narcotics Control Board and the UN Commission on Narcotic Drugs, have called for greater access for patients to these medicines.

It was noted that the opioids are currently listed under this section, as palliative care was initially addressed by the Cancer Control Programme more than 20 years ago. The Committee recognised that medicines in palliative care are needed for conditions other than for cancer such as in HIV/AIDS (39), MDR-TB (40) and severe congenital diseases (41). The present listing under section 8.4 (antineoplastic, immunosuppressive and medicines used in palliative care) may be interpreted by some countries as indicating that palliative care medicines are needed for use in cancer only. Listing palliative care medicines as a separate category would signify the importance of this group of medicines and promote their use in all conditions that require such care.

The Committee therefore recommended changing the title of Section 2 of the EMLc to "Medicines for Pain and Palliative Care". The corresponding change would also be made in the EML. In addition, the Committee recommended that the medicines for rheumatic conditions be moved from Section 2 to a new Section 30 (Medicines for Diseases of Joints).

## Section 11: Blood products and Plasma Substitutes

### **11.1: Plasma substitutes**

#### **Colloids (Review) -- Children**

At its 18th meeting the Committee requested a review to determine whether adults and children with Dengue fever should be treated with intravenous colloids rather than

crystalloids. The Committee also requested a review to determine whether plasma substitutes are essential medicines for children. It was not possible to address such a broad topic and therefore two reviews were commissioned by the secretariat on two common causes for volume replacement in children. The reviews considered by the Committee were:

1. "Colloids versus crystalloids for fluid resuscitation in Dengue fever patients – a review" prepared by *Dr. Pablo Perel, London School of Hygiene and Tropical Medicine, UK.*
2. "Are colloid solutions essential for the treatment of pediatric trauma or burn patients?" prepared by *Christina Huwer, Department of Violence and Injury, Prevention and Disability, World Health Organization, Geneva.*

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

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

#### Colloids versus crystalloids in Dengue fever

The purpose of the systematic review prepared for this meeting was to identify and synthesise the available evidence to assess the effect on mortality of using colloids compared to crystalloids for fluid resuscitation in patients with Dengue fever. Current recommendations for the management of Dengue patients with hypotensive shock include the administration of either crystalloids or colloids (42).

A recently published Cochrane systematic review found no evidence that colloids, in comparison to crystalloids, reduced the risk of death in critically ill patients (43). This review included 74 trials, 66 of which reported mortality data. Although trials involving patients with Dengue fever were included, the review did not report the results in these patients separately.

The present review identified five trials evaluating colloids versus crystalloids in children with shock associated with Dengue fever. Overall, the quality of the evidence for the effect of colloids versus crystalloids for fluid resuscitation was low. All of the included studies were underpowered to make any reliable assessment of the effect of colloids compared to crystalloids on mortality in Dengue patients. The review found no evidence that resuscitation with colloids reduced the risk of death compared to crystalloids (43-46).

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

### Colloids in paediatric trauma and burns

Fluid therapy plays an important role in the treatment of trauma patients with substantial blood loss as well as in patients with burn injuries. The review prepared for this meeting focused on these indications for the use of colloids in children. No evidence from RCTs could be identified(42, 47, 48). All articles reviewed indicated that there is very little evidence available currently for or against the use of colloids in children.

Volume replacement with colloids is considerably more expensive than with crystalloids. *The International Drug Price Indicator Guide* shows that the supplier median price for dextran 70 is almost 12 times higher than that for normal saline.

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

## Section 12: Cardiovascular medicines

### **12.2: Antiarrhythmic medicines**

#### [Antiarrhythmics \(Review\) -- Children](#)

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

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

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

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

Recognising that arrhythmias in children are rare and that they are typically managed in specialised settings, there does not appear to be a need for listing such products in the EMLc. Given that there is limited public health relevance of this section for children, the Committee decided to delete it from the EMLc.

## **12.6: Lipid-lowering agents**

### **Statins (Review) -- Children**

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

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

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

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

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

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

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

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

## Section 15: Disinfectants

### **15.1: Antiseptics**

#### **Chlorhexidine (New formulation) -- Children**

The application to include chlorhexidine digluconate 7.1% solution or gel, delivering 4% chlorhexidine for cord care was submitted by PATH, Chlorhexidine Working Group

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

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

An updated application was submitted for inclusion of the 7.1% concentration providing 4% free chlorhexidine formulation. There is a need to specify concentrations correctly: 20.0% chlorhexidine digluconate provides 11.3% free chlorhexidine, 7.1% provides 4.0% and 5.0% provides 2.8% .

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

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

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

There are still questions about the optimal treatment regimen, with respect to timing of application of chlorhexidine, as well as the number of applications. Compared with dry and clean care (mean 4.78 days), separation time of the umbilical cord was longer in the single (mean 6.90 days, difference = 2.10; 95% confidence interval: 1.85-2.35) and multiple (mean 7.49 days, difference = 2.69; 95% confidence interval: 2.44-2.95) cleansing groups in a cluster

randomized trial (60). This outcome may affect carer satisfaction, but the clinical importance is unclear.

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

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

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

## Section 24: Psychotherapeutic medicines

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

#### ***Chlorpromazine and haloperidol (Deletion) -- Children only***

The 18<sup>th</sup> Expert Committee noted the potential importance of these medicines in children for a variety of disorders, but requested a review of the entire section. The WHO Department of Mental Health and Substance Abuse reviewed the section and submitted applications for deletion of chlorpromazine and haloperidol from the EMLC; to increase the minimum age for the use of fluoxetine; and to include clozapine on the complementary list for the treatment of resistant schizophrenia in adults.

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

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

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

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

The Committee recognised that the indications for using haloperidol and chlorpromazine are very rare in children. Adverse events from these medicines may be more frequent in



children than in adults. However the Committee recognised the importance of ensuring that treatment of these severe psychiatric disorders in children is available and also noted that the application did not fully review all treatment options. The Committee therefore requested a specific review of the evidence for the benefits and risks of each medicine in the paediatric population, but decided not to make any changes to the List until such reviews had been considered.

#### **24.2: Medicines used in mood disorders 24.2.1: Medicines used in depressive disorders**

##### **Fluoxetine (Change to age restriction/Deletion from EMLC) -- Adults and Children**

Please refer section on Adults and Children (page 87).

Section 28: Ear, nose and throat medicines

##### **Montelukast (Addition) -- Children**

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

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

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

RCTs and observational studies suggest that LTRA as a class are effective in controlling symptoms related to allergic rhinitis. In a meta-analysis, the clinical efficacy of leukotriene receptor antagonists, including montelukast, in the treatment of patients with allergic rhinitis and nasal polyposis was compared with that of placebo, antihistamines, and nasal corticosteroids. The composite daily rhinitis symptoms scores in each trial were standardized and pooled. Among the trials included in the meta-analysis, 8 compared LTRAs with a placebo (5 montelukast trials, 2 zafirlukast trials, 1 L-649923 trial), 2 compared a LTRA and an antihistamine (both montelukast vs. loratadine), and 4 compared a LTRA with a nasal corticosteroid (montelukast vs. mometasone; montelukast vs. budesonide; montelukast vs. fluticasone and zafirlukast vs. beclomethasone). In the composite daily rhinitis symptom score, LTRAs decreased the score by 5% when compared to placebo, antihistamine decreased the score by 2% more compared to LTRAs and intranasal corticosteroids were the most effective decreasing the score by 12% compared to antihistamines (68). Two separate studies comparing montelukast, loratadine, or cetirizine to placebo groups in children showed some benefits in various symptom assessments relative to placebo, but no consistent benefit of one treatment type over the other. (69, 70).

Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines propose antihistamines and INS as preferred first line management. LTRAs are suggested either alone or in combination



therapies after the antihistamines and intranasal steroids. However, individual management options can vary.

A post-marketing report suggests an association between neuropsychiatric events (mood and behavioral adverse effects) and montelukast, the most commonly prescribed of the agents in the group. FDA confirmed the association with neuropsychiatric adverse reactions and in June 2009 requested that manufacturers add a precaution to the prescribing information (71). Such reactions can also occur in children (72-74).

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

#### Section 29: Specific medicines for neonatal care

##### *Dexamethasone (New indication) -- Children*

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

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

Preterm birth is the leading cause of neonatal deaths and the second most common cause of under-5 mortality, as well as a leading contributor to the global burden of disease, because of a significant risk of disability. Each year an estimated 15 million babies are born preterm, three-quarters in South Asia and Sub-Saharan Africa. Over 85% are moderate or late preterm, who are likely to survive without intensive care. However if access to basic care is limited, antenatal corticosteroids could make a considerable difference in mortality and morbidity, primarily through reducing the risk of respiratory distress syndrome (RDS).

There is high quality evidence that shows that antenatal corticosteroids reduce all cause neonatal mortality. A Cochrane review and meta-analysis of 18 trials (3956 infants) of antenatal corticosteroids found that the risk of neonatal mortality was reduced by approximately 30% (RR 0.69, 95% CI 0.58 to 0.81) (75). The same meta-analysis found that there was reduced incidence of RDS (RR 0.66, 95% CI 0.59 to 0.73, 21 studies, 4038 infants) and cerebroventricular hemorrhage (RR 0.54, 95% CI 0.43 to 0.69, 13 studies, 2872 infants). A meta-analysis of 4 RCTs (672 infants) from middle-income countries found a decrease in neonatal mortality following preterm birth (RR 0.47, 95% CI 0.35 to 0.64). No studies were found from low-income settings (76).

Two products have been used in the majority of trials, dexamethasone and betamethasone. No differences in effects have been found between the two products. A large trial that is powered to detect a difference is on-going, but results are not expected until 2015 (77).

The adverse effects of dexamethasone are well-defined. A retrospective cohort study compared pre-term babies exposed prenatally to dexamethasone to those not exposed, and

found no differences in verbal intelligence quotient, performance intelligence, body length, head circumference and body weight at 1, 3 and 6 years. (78).

Dexamethasone is recommended in WHO global clinical guidelines such as Managing Complications in Pregnancy and Childbirth: a guide for midwives and doctors (79). The National Institutes of Health (80), the American College of Obstetricians and Gynecologists (81), and the Royal College of Obstetricians and Gynecologists (82) have recommended antenatal corticosteroid treatment for women at risk for preterm delivery prior to 34 weeks of gestation in order to reduce the morbidity and mortality associated with preterm birth.

The most extensively studied regimens of corticosteroid treatment for the prevention of RDS are two doses of betamethasone 12 mg given intramuscularly 24 hours apart or four doses of dexamethasone 6 mg given intramuscularly 12 hours apart. Evidence for other dosing regimens, such as the commonly used two doses of betamethasone 12 mg given 12 hours apart, is sparse, but it would seem reasonable to use a regimen that delivers 24 mg of either drug within a 24–48-hour period (82).

Dexamethasone is generally inexpensive (< US \$1 per four-injection course) and widely available, making it the lowest-cost and most accessible means of preventing RDS and deaths due to preterm birth. Dexamethasone treatment is likely to be cost-effective in most settings, at an estimated cost per case (including the cost of syringes, needles, swabs, personnel and clinic visits) of US \$16.25 which is around one-third the cost of betamethasone treatment.

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

Given the compelling evidence of effectiveness and safety and cost-effectiveness, the Committee recommended the inclusion of dexamethasone in Section 29, under a new sub-heading of medicines for administration to the mother.

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

Section 2: NSAIDs and DMARDs

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

#### **Naproxen (Addition) -- Adults**

An application was submitted by Dr Patricia McGettigan, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, UK and Dr David Henry, Institute for Clinical Evaluative Sciences, Toronto, Canada for the inclusion of naproxen as an individual medicine, by virtue of it having the safest cardiovascular risk profile among non-steroid anti-inflammatory medicines (83).

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

Ibuprofen is specifically listed in the WHO Model List of Essential Medicines and not as a representative of the non-steroidal anti-inflammatory medicines (NSAID). This application requested the addition of naproxen due to its low cardiovascular risk. The application also

highlighted the extensive listing of diclofenac in National Essential Medicines Lists despite its high cardiovascular risk (84).

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

There was no comparison of analgesic effects between naproxen and ibuprofen provided in the application. The pricing data shows ibuprofen and naproxen to be similarly priced. There was also no comparison of naproxen with other NSAIDs in terms of adverse effects and toxicities in other systems (e.g. gastrointestinal). A review in 1999 stated that ibuprofen was associated with the lowest risk of side effects (85).

The increase in cardiovascular risk with ibuprofen is with the higher doses only and the Committee did not consider that there was adequate justification to include both ibuprofen and naproxen in the EML. However, the Committee noted that in high cardiovascular risk populations, it would be important to indicate that naproxen has the lowest cardiovascular risk. Given that the application focussed only on the cardiovascular outcomes for NSAIDs and not the comparative gastrointestinal outcomes or comparative analgesia, the Committee decided at this time to keep only ibuprofen on the list.

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

### **Section 2.3: Medicines used to treat gout**

#### **Colchicine (Re-instatement) -- Adults**

##### **Gout**

An application was submitted by Laboratoires Mayoly-Spindler, Chatou Cedex, France for reinstatement of colchicine for gout and addition for Familial Mediterranean Fever.

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

Colchicine was deleted from the WHO Model List of Essential Medicines in 2005 based on the fact that "Its usefulness for treating acute attacks is limited by its dose-dependent toxicity and the therapeutic margin is narrow." The 2005 Committee also noted that colchicine is not cheaper than ibuprofen and that it had not been procured to any great extent by international suppliers over the last five years. The Committee recommended that colchicine be deleted from the Model List because of its unfavourable benefit-risk ratio when compared with non-steroidal anti-inflammatory medicines (NSAIDs) for most people with gout. (86).

The application to reinstate colchicine was based on a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of a total of 185 patients published in 2010, that compared self-administered low-dose colchicine (1.8 mg total over 1 hour) and high-dose colchicine (4.8 mg total over 6 hours) with placebo. The endpoint of > 50% reduction of pain was observed in 37.8% in the low dose colchicine group, 32.7% in the high-dose group and 15.5% in the placebo group ( $p=0.005$  and  $p=0.034$ , respectively, versus placebo). Rescue therapy with NSAIDs was administered in the first 24 hours to 31.1% of patients in the low-dose group ( $p=0.027$  versus placebo), 34.6% in the high-dose group ( $p=0.103$  versus placebo), and 50.0% in the placebo group. With high-dose colchicine, 40 patients (76.9%) had diarrhea (OR 21.3 [95% CI 7.9-56.9]), 10 (19.2%) had severe diarrhea, and 9 (17.3%) had vomiting. With low-dose colchicine, 23.0% of the patients had diarrhea (OR 1.9 [95% CI 0.8-4.8]), none had severe diarrhea, and none had vomiting (87).

No clinical trials comparing NSAIDs with colchicine were provided in the application. Colchicine appears as a first-line treatment in both the European and British Society of Rheumatology recommendations but is seen as an effective alternative to NSAIDs (88, 89).

The Committee decided that if commonly available NSAIDs are as effective as colchicine in the treatment of gout, the necessity for a medicine useful only for gout is not clear. Additionally the application is based on a single trial that shows the low-dose to be as effective as the high-dose. Reinstating colchicine would require a comprehensive assessment of the comparative benefits and harms of the proposed lower dose regimen as well as information about the comparative costs.

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

### **Familial Mediterranean fever (FMF)**

FMF is a common auto-inflammatory disease in the Eastern Mediterranean region. It has traditionally been regarded as being inherited in an autosomal recessive manner, although some recent articles have reported a significant number of patients with only one mutation. FMF is divided in two main phenotypes. Type 1 is characterized by recurrent short episodes of inflammation and serositis including fever, peritonitis, synovitis, pleuritis and rarely pericarditis and meningitis. There is considerable variation in symptoms. Type 2 is characterized by amyloidosis as the first clinical manifestation of the disease in otherwise asymptomatic individuals (90). Mean age at clinical disease onset is 4 years (90% before 20 years) Amyloidosis that can lead to renal failure is the most severe complication of Type 2 FMF (91).

FMF generally affects Eastern Mediterranean people, mainly non-Ashkenazi Jews, Arabs, Armenians and Turks with a prevalence of 1/200 - 1/1000 population (92). However possibly due to extensive population movements, it has been reported throughout the world, including Japan (93).

The clinical trials of colchicine in Familial Mediterranean Fever were done in the early 1970s. (94-96). Subsequent work has focused on defining the appropriate dose, although there is no

clear recommendation yet. Paediatricians treating children with Familial Mediterranean Fever appear to be aware of the necessity to treat with colchicine as the national registry in Turkey showed that over 95% of the eligible patients were being prescribed colchicine with 80% reporting regular use (92).

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

The Committee therefore recommended that colchicine for Familial Mediterranean Fever not be included in the WHO EML.

### Section 3: Antiallergics and Medicines Used in Anaphylaxis

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

The 18th Expert Committee requested a comparative review of the safety and efficacy of chlorphenamine (which is in the EML and EMLc) compared with diphenhydramine, in order to inform the possible inclusion of diphenhydramine. Given the possible favorable clinical effects and side-effect profile of second generation systemic antihistamines (SGAHs), three over-the-counter, SGAHs (cetirizine, loratadine and fexofenadine) were also reviewed and compared to chlorphenamine and diphenhydramine (which are first generations antihistamines; FGAHs). The use in children and the elderly was specifically considered in the review and the National Essential Medicines Lists of 15 countries were checked for the availability of SGAHs. The review was prepared by Mr Harinder Chahal, Doctor of Pharmacy Candidate at the University of California, San Francisco.

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

Evidence of the efficacy and safety of these five antihistamines in allergic rhinitis and urticaria was provided. Overall, there is a lack of high quality data to compare the two FGAHs. The review found no RCTs that satisfactorily compared efficacy and safety of chlorphenamine and diphenhydramine for use in allergic rhinitis or urticarial conditions. The evidence from five RCTs comparing them with placebo or other medicines, show similar effectiveness and side effect profile of the two medications for both allergic rhinitis and urticaria (97).

Fifteen RCTs showed similar efficacy between the FGAHs and SGAHs in treating allergic rhinitis with significantly less side effects (in frequency and severity) with SGAHs. For treatment of urticaria, nine RCTs showed similar efficacy between FGAHs and SGAHs, with lower incidence of side effects with SGAHs. Six RCTs, three retrospective studies and one systematic review provide evidence establishing the superior safety profile of SGAHs over that of FGAHs (98). Significant sedation and psychomotor impairment is observed with FGAHs compared to SGAHs.

Due to the anticholinergic side effects and the reduced drug clearance in the elderly, the use of FGAHs in this population is strongly discouraged. Evidence from 5 RCTs, two pharmacokinetic studies, a systematic review and guidelines recommend against the use of FGAHs in infants and children, due to risk of sedation and death (97, 99).

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

The review also found that the monthly treatment cost with loratadine was lower than that for chlorphenamine and that 53% of the 15 LMICs surveyed already had an SGAH on their respective National EMLs.

The Committee considered the evidence on safety; the FGAHs are referred to as 'sedating' and the SGAHs as 'non-sedating'. This broad distinction is based on two primary differences between these medicine classes: 1) SGAHs are more specific to H-1 receptors compared to FGAHs and 2) FGAHs are able to cross the blood brain barrier as opposed to the SGAHs. These differences in receptor specificity and lipophilicity cause FGAHs to display significant central nervous system, cardiovascular system, and gastrointestinal system side-effects. These effects were seen during clinical trials.

Based on *considerations* of inferior safety, especially in children and elderly, and equal efficacy of SGAHs to FGAHs, the Committee decided to delete chlorphenamine from EML and EMLc and recommend addition of loratadine oral solid dosage form (10mg) and oral liquid (1mg/mL) to EML and EMLc, with a square box. An age restriction of 2 years and older for loratadine may be applied, although use below this age has occurred in some settings. (100-105).

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

##### [Fomepizole \(Addition\) -- Adults and Children](#)

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

Expert reviews were prepared by Dr Le Van Truyen and Dr Gilles Sama Kwende. Comments were received from Department of Evidence and Policy on Environmental Health Issues, WHO, Department of Pharmacology, Toxicology and Neuroscience, LSU health sciences Centre, Los Angeles, US, Dr Hans Perrson, Former Director of the Swedish Poisons Information Centre.

Fomepizole is used for the treatment of toxic alcohol and glycol poisoning, principally methanol and ethylene glycol, in adults and children. Ethylene glycol poisoning occurs worldwide due to ingestion of substances such as antifreeze, screen wash and fuel additives, and account for the majority of accidental or intentional poisoning. Methanol poisoning is

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

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

Prospective observational studies, clinical trials and retrospective case reviews have demonstrated fomepizole to improve outcomes by improving renal function, preventing visual impairment associated with methanol poisoning, and preventing metabolic acidosis (106, 107). In a retrospective case series, ethanol and fomepizole were equally effective but fomepizole provided practical advantages such as ease of administration, and monitoring, and a better adverse events profile (108) (109-113). However, no high quality studies currently exist that directly compare fomepizole with ethanol.

Fomepizole is approved by the US FDA for these indications and is recommended by American and European Associations of Clinical Toxicologists. Ethanol is not FDA approved for this indication.

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

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

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

Section 6: Anti-infective medicines



## **6.2: Antibacterials 6.2.2: Other antibacterials**

### *Isoniazid + pyridoxine + sulfamethoxazole + trimethoprim (Addition) -- Adults and Children*

An updated application to include the FDC of isoniazid+pyridoxine+sulfamethoxazole+trimethoprim was submitted by the WHO HIV Department.

An application for addition of this product had been submitted to the 18<sup>th</sup> Committee. The addition was not made at that time since the product was not commercially available at that time.

An expert review was prepared by Mr Andrew Gray

Based on known activities of the component medicines, the FDC is anticipated to be of use in preventing tuberculosis, bacterial pneumonia, malaria, isosporiasis and other infections and to reduce mortality and hospitalizations among adults and children living with HIV/AIDS (PLHIV).

WHO has listed this FDC in the 10th Invitation for Expression of Interest for HIV medicinal products. Therefore a product once available and prequalified by WHO would provide a reliable and safe source for this FDC.

Current WHO Guidelines recommend both cotrimoxazole preventive therapy (CPT) and isoniazid preventive therapy (IPT) as part of the standard package of care for PLHIV (114). In most settings CPT is recommended indefinitely while IPT is recommended for at least 6 months. CPT prevents *Pneumocystis jiroveci* pneumonia, cerebral toxoplasmosis, bacterial pneumonia, diarrhoea, *Isospora belli* infections, malaria, and other infections and its use has led to a significant reduction in mortality in clinical trials in low and high-income countries. IPT prevents active tuberculosis in HIV-infected persons. Pyridoxine is recommended in all HIV-infected persons receiving INH. It may be difficult for countries to procure and distribute pyridoxine with INH. Including pyridoxine in the FDC ensures that all patients on IPT are on concomitant pyridoxine, thereby preventing INH-induced neuropathy.

The efficacy of CPT and IPT are compromised by lapses in adherence. FDCs have the potential to improve adherence and reduce pill burden. Access to the FDC has also been proposed as a means to address the lower uptake of IPT uptake compared with CPT.

The data on efficacy and safety presented were largely from studies of the individual components or prophylactic IPT and CPT regimens. These regimens are clearly effective for improving outcomes in PLHIV. The safety profiles of the components are also well characterized. Though rare, the risk of Stevens- Johnson syndrome with CPT does need to be taken into account. All of the constituent elements of this proposed FDC are already included in the WHO Model EML.

The application contained no new evidence compared to the application presented to the previous Expert Committee.



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

This application provided no additional information that could justify a different conclusion from that reached by the previous Committee and therefore the Committee recommended that the proposed FDC not be included in EML.

#### **6.2: Antibacterials 6.2.4: Antituberculosis medicines**

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

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

There are an estimated 630,000 prevalent cases of multi-drug resistant tuberculosis (MDR-TB) globally (115), but appropriate treatment remains a problem. Bedaquiline is the first new drug with a novel mechanism of action (ATP synthase inhibition) for TB in more than 40 years. The proposed use of this medicine is for those newly diagnosed with MDR pulmonary TB over 18 years of age, as part of combination therapy, preferably as directly-observed therapy (DOT). Total duration of treatment is 24 weeks.

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

The WHO/Stop TB Department noted the accelerated approval by the US FDA, and in December 2012 a rapid interim guidance on the potential use of bedaquiline for the treatment of MDR-TB was being developed but this was not available to the Committee.

The Committee noted that available trial data consisting of 2, Phase IIb trials suggested that bedaquiline is effective in MDR pulmonary TB in adults. Primary efficacy analysis was based on a modified intention to treat population, which excluded subjects who had drug susceptible TB, XDR-TB or unconfirmed MDR-TB (based on susceptibility tests taken prior to randomization), or had missing or negative baseline cultures, or who were positive at baseline, but had no post-baseline culture results. The modified Intention To Treat (mITT) population was composed of 132 subjects (66 in each of the bedaquiline and placebo groups). The median time to culture conversion was 83 days (95%CI: 56-97) in the bedaquiline group compared to 125 days (95%CI: 98-168) in the placebo group.

Twelve deaths were reported in total; of these, 10/79 (12.7%) came from the bedaquiline group and 2/81 (2.5%) from the placebo group ( $p=0.017$ ) (ITT analysis). In the bedaquiline group, 8 of the 10 deaths occurred in culture converters. TB was the cause of death in the two placebo arm deaths and in 5 of the 10 bedaquiline-arm deaths (all occurred off

bedaquiline treatment). Counting deaths strictly at the 120 weeks cut-off point reveal nine deaths in the bedaquiline and one death in the placebo group. There was no discernible relationship between death and culture conversion, relapse, microbiological response, susceptibility to drugs used in the MDR-TB background medication regimen, HIV status, or severity of disease. The reason(s) for the imbalance were not clear.

The Committee considered that further efficacy and safety data from clinical trials conducted in different backgrounds are needed and concerns regarding its registration in the US (116). Bedaquiline is also not currently available commercially outside of the USA and is only expected to be available in some countries by the end of 2013. The cost in high-burden countries is as yet unknown.

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

### **6.3: Antifungal medicines**

#### ***Amphotericin B (To be moved to core list); Flucytosine (To be moved to core list) -- Adults and Children***

The WHO HIV Department submitted applications to move amphotericin B and flucytosine to the core list in EML and EMLc.

Dr Suzanne Hill reviewed both amphotericin B and flucytosine, Dr Gilles Sama Kwende and Dr Hany Abdel-Aleem reviewed flucytosine. Comments were received from Dr Myriam Henkens, International Medical Coordinator, MSF

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

WHO Rapid Advice guidelines on the diagnosis, prevention and management of cryptococcal meningitis in HIV-infected adults and children, were published in December 2011(117). Amphotericin-based regimens were recommended as preferred in three of the five regimens. A two-week regimen of amphotericin B plus flucytosine is recommended as the preferred option. Where amphotericin is unavailable, or cannot be monitored safely, the treatment guidelines recommend flucytosine in conjunction with high dose fluconazole. The guidelines with flucytosine cannot be followed in many parts of Africa currently because flucytosine is not available.

A cost-effectiveness analysis that also analysed mortality from pooled clinical trial data show that regimens containing amphotericin were consistently superior (118). The addition of flucytosine to amphotericin B during induction therapy, compared to amphotericin B alone, was found to be associated with increased rates of CSF sterilization, a reduced risk of relapse, and a non-significant reduction in mortality at two weeks and a significant reduction at 10 weeks (118).

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

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

The evidence provided to the Committee included a published cost-utility analysis cited in the WHO Guidelines (118). The Committee noted that there were several problems with the analysis that meant it was difficult to interpret the results. The estimates of survival from different treatment regimens were extrapolated from 10 weeks to 1-3 years based on several different cohorts that may or may not be valid for deriving incremental survival benefit. "QALYs" were calculated on the basis of Karnofsky performance scores from patients treated with antiretroviral treatment (a completely different intervention), and these scores were then used to calculate incremental changes in estimated life years. This is not a valid approach to calculating quality adjusted life years (QALY), which should be based on an implied trade-off between survival and quality of life. It was difficult to rely on the results of the analysis as presented so the Committee decided that its decision should be weighted by other factors.

Given the obvious public health need, the potential to promote availability of effective combinations in countries with heavy disease burden and the evidence of safety in the context where the products will be used, the Committee decide to move these products to the Core List. It considered that transferring these medicines to the Core List may improve availability. The Committee strongly recommended that WHO monitor the change in availability over the next 5 years.

#### **6.4.2: Antiretrovirals**

*Abacavir + lamivudine (Addition); Atazanavir + Ritonavir (Addition); Tenofovir Disoproxil Fumarate+ Lamivudine (Addition); Tenofovir Disoproxil Fumarate+ Lamivudine+ Efavirenz (Addition) -- Adults*

As described above (page 31), decisions on these applications were deferred.

*Antiretrovirals (Formulations to be considered for possible deletion) -- Adults and Children*

As described above (page 31), decisions on these applications were deferred.

### **6.4.3: Other antivirals**

#### *Oseltamivir (Deletion) -- Adults and Children*

An application to delete oseltamivir from the WHO Model List of Essential Medicines was submitted by Acute Respiratory Infections Cochrane Review group.

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

Oseltamivir was added to the EML and EMLc in 2010, with notes to indicate conditions of use in compliance with the WHO treatment guidelines. These notes specified that oseltamivir should be used only in patients with severe or progressive clinical illness with confirmed or suspected influenza pandemic (H1N1) 2009 and for the treatment of patients with confirmed or suspected but uncomplicated illness due to pandemic influenza virus infections who were in higher risk groups, most notably for pregnant women and children under 2 years of age.

The effect of oseltamivir in reducing complications of influenza was originally reported in a pooled analysis of 10 manufacturer-sponsored randomized trials of oseltamivir for treatment of seasonal influenza (119). This analysis and an independent re-analysis of 11 RCTs (120) found that oseltamivir treatment reduced the risk of lower respiratory tract complications requiring antibiotic treatment by 28% overall (95% CI 11%–42%) and by 37% among patients with confirmed influenza infections (95% CI 18%–52%).

The application proposed deletion of oseltamivir from the Model List citing a systematic review done by the applicants (121), re-examining the evidence base for neuraminidase inhibitors which found that the only benefit was reduction in time to first alleviation of symptoms. The application also argued that due to limitations in the design, conduct and reporting of the trials data, there was insufficient detail to assess credibility of the possible effect of oseltamivir on complications and viral transmission. The applicants also noted the significant publication and reporting bias in trials of oseltamivir.

The Committee recalled that the addition of oseltamivir to the essential medicines list in 2011 was on the basis of consideration of not only the randomized trials but also systematic reviews of observational studies (122). The Committee had also been provided with some unpublished data in relation to use and dose of oseltamivir in children. The observational studies reported outcomes that were relevant to the assessment of effectiveness and safety in the context of pandemic influenza, and also in populations that were not included in the trials (for example pregnant women).

The meta-analysis of observational data examined by the Supplementary meeting of the Committee in 2010 was published as an independent systematic review and meta-analyses of 74 studies (122) and the few studies providing effects with adjustment for confounders suggest that, in high-risk populations, oral oseltamivir may reduce mortality (odds ratio, 0.23 [95% CI, 0.13 to 0.43]; (low-quality evidence), hospitalization (odds ratio, 0.75 [CI, 0.66 to 0.89]; (low-quality evidence), and duration of symptoms (33 hours [CI, 21 to 45 hours]; (very low-quality evidence) compared with no treatment. This very large effect on mortality was taken into account when deciding whether to include oseltamivir for treatment.

The Committee also acknowledged an additional recent systematic review and meta-analysis (123) of observational data from 90 studies (80 reported exclusively laboratory confirmed diagnoses) that assessed the impact of neuraminidase inhibitor treatment on severe outcomes in hospitalized patients during the 2009–2010 Influenza A(H1N1) pandemic. There was a non-significant reduction in mortality associated with NAI treatment (at any time) versus none (OR, 0.72; 95% CI 0.51 to 1.01), a significant reduction for early treatment ( $\leq 48$  hours after symptom onset) versus late (OR 0.38; 95% CI 0.27 to 0.53) and for early treatment versus none (OR 0.35; 95% CI 0.18 to 0.71). This study and the previously reviewed studies, did not provide compelling evidence to alter the current assessment of safety and benefit.

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

The Committee noted that the WHO guidelines assessed the quality of the clinical evidence in relation to oseltamivir as low. While noting the limitations of the evidence, the previous decision to include oseltamivir on the EML took account of the magnitude of the effect on mortality and hospitalization, principles of equity, lack of alternative and the severity of infection and strongly recommended it for restricted use (124).

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

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

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

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

#### [Pegylated interferon \(Addition\) -- Adults](#)

An application for addition was submitted by Médecins Sans Frontières - Access Campaign, Rue de Lausanne 78, P.O Box 116, 1211 Geneva, Switzerland .

Expert reviews were prepared by Dr Nicola Magrini and Dr Kuruvilla Prasad Mathews. Comments were received from the Global Hepatitis Program, WHO, AIDS Treatment Organisations, multiple Civil Society Organisations and Patient Groups.

Peginterferon is a covalent conjugate of recombinant interferon alfa-2 with polyethylene glycol (PEG). The 2a and 2b formulations differ in the size and nature of covalently attached PEG which results in differences in pharmacokinetics and doses.

Globally, approximately 150 million people are infected with hepatitis C (HCV) and it is estimated that 350,000 people die each year from HCV-related liver disease (125). The goal of therapy is to produce a sustainable virological response (SVR). This can potentially result in reversal of liver injury, prevent serious consequences such as cirrhosis, end stage liver disease, hepatocellular carcinoma and death.

As compared to standard interferon-alfa alone, interferon-alfa in combination with ribavirin increased SVR from 10-20% to 40-60% (126, 127). The long-acting pegylated formulation in combination with ribavirin has further increased SVR rates to 50-60% for genotype 1 and 80% for genotype 2 and 3 (128, 129). Based on a recent meta-analysis, treatment success rates in low and middle-income countries are similar to those obtained in high-income countries (130). Head-to-head randomized controlled trials, including the large, randomized IDEAL trial (n = 3070), demonstrated similar SVR rates for peginterferon-alfa-2a and alpha-2b (41% vs. 39% in IDEAL), in combination with ribavirin (131). While peginterferon alfa-2a or -2b in combination with ribavirin has been the standard of care for chronic hepatitis C, the new direct-acting oral antiviral agents (sofosbuvir and daclatasvir) are more effective but currently expensive (132, 133). The Committee noted that there are several more direct acting antivirals in development.

Pegylated interferons + ribavirine are associated with a range of adverse events often requiring dose reduction and discontinuation. Adverse events that resulted in treatment termination were reported in 39 studies and were present in 4% (95%CI: 3-5)(130). Peginterferon- $\alpha$ -2a and - $\alpha$ -2b appear to be similarly tolerated (127).

Before treatment patients need to be screened, have RNA measurements and genotyping (which require high level laboratory support), liver biopsy facilities are required and subsequently facilities to detect and manage complications are also needed.

WHO is currently developing guidelines for Screening, Care and Treatment of Hepatitis C. Other expert bodies such as NICE (134), European Association for the Study of the Liver (135) and the American Association for the Study of Liver Disease (136) recommend peginterferon alfa 2a or 2b with ribavirin for treatment of Hepatitis C. Ribavirin is already listed in the EML and EMLc for viral haemorrhagic fevers.

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

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

### **6.5.3: Antimalarial medicines 6.5.3.1: For curative treatment**

#### **Artesunate + mefloquine (Addition) -- Adults and Children**

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

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

Artesunate (AS) and mefloquine (MQ) are well established for the treatment of malaria and are listed in the EML and EMLc, with notes advocating for their use in combination therapy. The combination (ASMQ) is recommended by WHO as one of 5 fixed-dose combinations for the treatment of uncomplicated falciparum malaria. The combination of AS and MQ is the first-line therapy for *Plasmodium falciparum* malaria in the national policies of some Asian and South American countries.

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

Evaluations of the FDC in clinical studies have shown similar comparative efficacy to that demonstrated with separate tablets of AS and MQ (137, 138). Reported adverse events were also comparable between the FDC and separate tablets. There is some evidence to suggest that transmission is decreased in places where ASMQ is used (139).

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

WHO does not recommend the use of AS+MQ in African children due to concerns about toxicity, including vomiting. To address these concerns DNDi is sponsoring a multicentre, open-label, prospective, randomised, controlled, Phase IV study in Africa (Tanzania, Burkina Faso and Kenya) to assess the efficacy, safety and pharmacokinetics of ASMQ FDC versus artemether-lumefantrine in approximately 1000 children with uncomplicated *P. falciparum* malaria (140) .

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



**6.5: Antiprotozoal medicines 6.5.5: Antitrypanosomal medicines 6.5.5.1: African trypanosomiasis**

***Nifurtimox + eflornithine (Review) -- Adults and Children***

Please refer to page 32: Application Nifurtimox (Addition) – Children.

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

**8.2: Cytotoxic and adjuvant medicines**

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

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

The Committee therefore decided to consider the applications in detail, and their deliberations are set out below. However, given the need to restructure the current published List of Essential medicines as noted above, the decision was taken not to amend Section 8.2 of the list by adding or deleting medicines at this time. The Committee noted that a comprehensive review of Section 8.2 would identify other effective but high-cost medicines that should be considered in the overall allocation of resources for pharmaceuticals used for management of cancer.

***Imatinib (Addition) -- Adults***

***Imatinib (Addition) -- Adults and Children***

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

The first application was by Dr Sandeep P. Kishore, Malini Aisola, Ruth Lopert and Nii Koney from the Weill Cornell Medical College for adult patients. The second application was by Dr Lawrence N. Shulman, Deputy CEO, Senior VP for Medical Affairs Director, Center for Global Cancer Medicine, Dana-Farber Cancer Institute, Boston, MA 02215 and Julie Torode, Deputy CEO, Union for International Cancer Control, 1207, Geneva; this application was for both adult and paediatric patients.

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



The Committee noted that chronic myelogenous leukemia constitutes 15% of all adult leukemia cases and 5% of all childhood leukemias with an estimated incidence of 1 to 1.5 per 100,000 people globally. In high income countries, the estimated 5-year survival rate of patients diagnosed between 2001 and 2007 was 57%, prior to the introduction of imatinib. There are no reliable data from resource poor countries but an extrapolation from existing data suggests an overall global incidence of chronic myeloid leukaemia of 100,000 patients per year.

Imatinib has been in use from 2001 and has become the first line treatment for Philadelphia chromosome positive chronic myeloid leukaemia.(141-143). It is now generally considered as the treatment of choice for CML in chronic phase, for disease control. The large RCT that compared imatinib to interferon plus cytarabine (144) showed that at 19 months, major cytogenetic remissions were seen in 87.1% of the imatinib treated group compared with 34.7% in the comparator group. At 6 years, the overall survival in the imatinib treated group was 88% (comparative data not available due to crossover of subjects) and the remission rate in the imatinib treated group was also much higher (145). Data comparing survival before and after the introduction of imatinib show a large absolute improvement in survival rates at 8 years from 45% (in the years 1991-2000) to 75% in the imatinib-treated cohorts (146).

The Committee noted that the application described use of imatinib in low and middle-income countries, with a variety of results but generally in line with the results from treatment in high income countries (147-151). Access to imatinib in low- and middle-income settings has been highly variable and to some extent has depended on the original manufacturer supplying product through compassionate access programs.

The cost of imatinib has been very high. Generic preparations may become available - Europe has already granted approval for one generic imatinib preparation and there are multiple applications for generic preparations in the US awaiting expiry of the patent period (152). The price of imatinib is therefore expected to decrease.

The Committee considered that the evidence showed that imatinib is a highly effective treatment for Philadelphia chromosome positive CML, which is a relatively uncommon form of leukemia. While noting the limited population for which the drug might be useful, the Committee considered that imatinib meets the criteria for inclusion as an essential medicine. The Committee considered that the cost-effectiveness of imatinib would be mainly dependent on the price that countries could negotiate with suppliers, but also noted that long term supply and use of the product is necessary to maintain the therapeutic effect. Therefore it would be important for countries to consider total cost in making decision to include on essential medicines list or reimbursement programs.

Given the need for the List of medicines in Section 8.2 to be reviewed, as noted above, the Committee decided that final specification of imatinib in the List of Essential Medicines should be done by the Committee once that review is completed.

#### **Trastuzumab (Addition) -- Adults**

There were 2 applications for the addition of trastuzumab for breast cancer. The first was by Dr Lawrence N. Shulman, Deputy CEO, Senior VP for Medical Affairs Director, Center for Global Cancer Medicine, Dana-Farber Cancer Institute, Boston, MA 02215 and Julie Torode,

Deputy CEO, Union for International Cancer Control, 1207, Geneva. The second application was by Knowledge Ecology International, Washington, DC 20009, University of California, San Francisco, Department of Medicine, San Francisco, CA 94143 and Universities Allied for Essential Medicines (UAEM) & Young, Professionals Chronic Disease Network (YP-CDN), Weill Cornell Medical New York, NY 10065, United States of America.

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

The importance of breast cancer as a public health priority is recognised by the fact that many of the antineoplastics necessary for its treatment are available in Section 8 of the List. HER2 positive breast cancer is estimated to account for about 20% of patients with the disease.

The Committee noted that for adjuvant therapy, the systematic review (based on 8 trials) cited in the application showed that in early HER2-positive breast cancer, the use of trastuzumab in combination with standard treatment (surgery, radiotherapy and chemotherapy) has been found to increase the likelihood of survival. The estimated relative effect (hazard ratio) from the review for overall survival (OS) and disease-free survival (DFS), were 0.66 (95% CI 0.57, 0.77) and 0.60 (95% CI 0.50, 0.71) respectively (153-155). Viani et al (2007) found that the absolute effect on survival was a mortality of 6.0% (217/4555) in the group treated with trastuzumab compared to 8.5% (392/4562) (156). The review notes that there is some risk of bias in the trials due to inadequate allocation concealment, and also notes that some of the trials were stopped early for benefit. The sensitivity analyses conducted in the review to examine these factors did not find changes in the relative effect size. The review also notes that there are two trials that have not been published, including approximately 2800 patients. A Cochrane review in 2012 found a survival benefit of 3.3%, 9.0% and 13.3% in women with low, moderate and high risk of death at 36 months (153).

In metastatic breast cancer the addition of trastuzumab to standard chemotherapy may be associated with prolonged survival. The Committee noted that the main evidence of benefit in this population is based on the trial published in 2001 (157) which found an increase of 5 months in overall survival. However, other studies have shown that the effect in advanced /metastatic breast cancer has been less.

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

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

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

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

Given the need for the List of medicines in Section 8.2 to be reviewed, as noted above, the Committee decided that final specification of trastuzumab in the List of Essential Medicines should be done by the Committee once that review is completed.

#### **8.4: Medicines used in palliative care**

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

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

In 2007, in response to a request from the WHO, the IAHPC developed a List of Essential Medicines for Palliative Care based on the consensus of palliative care workers from around the world (158). This list was based on expert opinion and the Expert Committee requested that a List be developed based on scientific evidence.

“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 (159).

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

The application submitted by the IAHPC has the principles of palliative care as (160)

- provides relief from pain and other distressing symptoms;
- affirms life and regards dying as a normal process;
- intends neither to hasten or postpone death;
- integrates the psychological and spiritual aspects of patient care;
- offers a support system to help patients live as actively as possible until death;

- offers a support system to help the family cope during the patients illness and in their own bereavement;
- uses a team approach to address the needs of patients and their families, including bereavement counseling, if indicated;
- will enhance quality of life, and may also positively influence the course of illness;
- is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications.

It was noted that there was a difficulty in implementing high quality prospective studies of symptoms and associated distress in patients receiving palliative care. The data identified were mainly from retrospective case reviews, expert opinion and case reports (158, 161-164). However there is now an interest in systematically gathering evidence in the area of palliative care in adults (165, 166).

To develop the list of proposed medicines, a working group was constituted by IAHP. They identified the most common causes of death through WHO global mortality data, and the most common and distressing symptoms in palliative care through a literature search. The final step was identification of the medicines recommended for the treatment of symptoms. The following table lists the most common and distressful symptoms occurring in palliative care and the medications included in the application:

<b><u>Anorexia (appetite loss)</u></b>	<b>Dexamethasone</b> Injection: 4 mg/mL in 1-mL ampoule (as disodium phosphate salt) Oral liquid: 2 mg/5 mL and tablet 4mg (not listed in the EML)
<b><u>Anxiety</u></b>	<b>Diazepam:</b> Injection: 5 mg/mL Oral liquid: 2 mg/5 mL Rectal solution: 2.5 mg; 5 mg; 10 mg. Tablet: 5 mg; 10 mg <b>Lorazepam:</b> Parenteral formulation: 2mg/mL in 1-mL ampoule Lorazepam: tablets 1mg and 2.5mg (not specifically listed in the EML)
<b><u>Constipation</u></b>	<b>Docusate sodium:</b> Capsule: 100 mg; Oral liquid: 50 mg/5 mL <b>Senna:</b> Oral liquid: 7.5 mg/5 mL Sodium Picosulfate oral liquid 7.5 mg/mL (not listed in the EML)
<b><u>Delirium (Confusion)</u></b>	<b>Haloperidol</b> Injection: 5 mg in 1-mL ampoule. Oral liquid: 2 mg/mL Solid oral dosage form: 0.5 mg; 2mg; 5 mg
<b><u>Depression</u></b>	<b>Amitriptyline:</b> Tablet: 10 mg; 25 mg Fluoxetine: solid oral dosage form 20 mg (as hydrochloride)
<b><u>Diarrhoea</u></b>	<b>Loperamide</b> Loperamide 2mg tablet or capsule
<b><u>Dyspnoea (breathlessness)</u></b>	<b>Morphine</b> <b>Recommended formulations for inclusion:</b> Granules (modified release) (to mix with water): 20 mg; 30 mg; 60 mg; 100 mg; 200 mg. Injection: 10 mg/mL Oral liquid: 10 mg/5 mL Tablet (immediate release): 10 mg. Tablet (controlled release): 10 mg; 30 mg; 60 mg.

<b><u>Fatigue</u></b>	<b>Dexamethasone</b> Injection: 4 mg/mL in 1-mL ampoule (as disodium phosphate salt) Oral liquid: 2 mg/5 mL Tablet 4mg (not listed in the EML)
<b><u>Nausea and Vomiting</u></b>	<b>Metoclopramide</b> Injection: 5 mg (hydrochloride)/mL in 2-mL ampoule. Oral liquid: 5 mg/5 mL Tablet: 10 mg (hydrochloride)
<b><u>Pain</u></b>	<b>Ibuprofen and Morphine</b> <b><u>Ibuprofen:</u></b> Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg. <b><u>Morphine:</u></b> Granules (modified release) (to mix with water): 20 mg; 30 mg; 60 mg; 100 mg; 200 mg. Injection: 10 mg/mL Oral liquid: 10 mg/5 mL Tablet (controlled release): 10 mg; 30 mg; 60 mg. Tablet (immediate release): 10 mg.
<b><u>Respiratory Tract Secretions</u></b>	<b>Hyoscine butylbromide</b> 10 mg/mL injectable (not listed in the EML)

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

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

Lorazepam was not considered necessary as diazepam and midazolam were already available. The evidence for sodium picosulphate was insufficient to justify inclusion and there were already two other laxatives (docusate and senna) on the list. Although the evidence for the benefit to the patient of the use of antimuscarinic agents in prevention of accumulation of respiratory tract secretions during the dying phase was acknowledged as

weak, the inclusion of hyoscine butylbromide (which, in contrast to the hydrobromide included for children, does not cross the blood-brain barrier) was supported. The inclusion of loperamide in accordance with the existing WHO Treatment of HIV Guidelines was supported.

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

<b>Medicines for common symptoms other than pain in palliative care</b>	
amitriptyline	<b>Tablet:</b> 10 mg; 25 mg; 75 mg.
dexamethasone	<b>Injection:</b> 4 mg/ml in 1-ml ampoule (as disodium phosphate salt). <b>Oral liquid:</b> 2 mg/5 ml. <b>Tablet:</b> 4 mg.
diazepam	<b>Injection:</b> 5 mg/ml. <b>Oral liquid:</b> 2 mg/5 ml. <b>Rectal solution:</b> 2.5 mg; 5 mg; 10 mg. <b>Tablet:</b> 5 mg; 10 mg.
docusate sodium	<b>Capsule:</b> 100 mg. <b>Oral liquid:</b> 50 mg/5 ml.
fluoxetine <sup>a</sup>	<b>Solid oral dosage form:</b> 20 mg (as hydrochloride). <sup>a</sup> >8 years.
haloperidol	<b>Injection:</b> 5 mg in 1-ml ampoule. <b>Oral liquid:</b> 2 mg/ml. <b>Solid oral dosage form:</b> 0.5 mg; 2mg; 5 mg.
hyoscine butylbromide	<b>Injection:</b> 20 mg/ml.
loperamide	<b>Solid oral dosage form:</b> 2 mg.
metoclopramide	<b>Injection:</b> 5 mg (hydrochloride)/ml in 2-ml ampoule. <b>Oral liquid:</b> 5 mg/5 ml. <b>Solid oral dosage form:</b> 10 mg (hydrochloride)
midazolam	<b>Injection:</b> 1 mg/ml; 5 mg/ml. <b>Solid oral dosage form:</b> 7.5 mg; 15 mg.
senna	<b>Oral liquid:</b> 7.5 mg/5 ml.

## Section 9: Antiparkinsonism medicines

### [Antiparkinsonism medicines \(Review\) -- Adults](#)

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

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

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

The current EML lists levodopa/carbidopa as 250/25, 100/10 and biperiden, an anticholinergic. Evidence shows that the risk of death was significantly reduced following initiation of Levodopa, regardless of pre-levodopa duration of illness in PD and this reduction persisted over 17 years (167). Levodopa/carbidopa is the mainstay in therapy. The 10:1 ratio of levodopa: carbidopa listed is too high to prevent the levodopa-induced nausea for many patients. The 100/25 tablet, with its 4:1 ratio is the preferable tablet to be used for titration to effective dose. Many guidelines and use data from UK (presented as an example) support this statement. Patients are usually started on 50/12.5 dose twice daily and gradually increased to 100/25 three times daily. The application reports that the current WHO listing is affecting availability of the correct formulation especially in some African countries.

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

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

Based on the data presented, the Committee decided to add the levodopa/carbidopa 100mg/25mg dosage form, but decided to retain the 100mg/10mg and 250mg/25mg dosage forms as they were commonly used, and to add a square box symbol for biperiden to allow



for the option of procuring trihexphenidyl. The Committee called for a detailed application for the addition of a dopamine agonist.

## Section 10: Medicines affecting the blood

### **10.1: Antianaemia medicines**

#### **Ferrous salt + folic acid (New formulation) -- Adults**

An application was submitted by the WHO Department of Nutrition for Health and Development Evidence and Programme Guidance Unit for inclusion of a new formulation of ferrous salt and folic acid (60 mg elemental iron in a ferrous form plus folic acid 2.8 mg tablet/capsule) for the prevention of anaemia in menstruating women and adolescent girls through an intermittent treatment regimen.

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

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

The most common side effects of iron supplementation include nausea, constipation, dark stools, and metallic taste. There is no significant difference in adverse side-effects between once weekly, intermittent iron supplementation versus no intervention or placebo (RR 1.98; 95% CI 0.31 to 12.72) and between once weekly, intermittent iron supplementation versus daily iron supplementation (RR 0.36; 95% CI 0.10 to 1.31)(168).

The EML currently lists the FDC 'ferrous salt + folic acid tablet equivalent to 60 mg iron + 400 micrograms folic acid'. Ferrous salt and folic acid are also listed separately. There is no data on efficacy comparing the "ferrous 60 mg + folic acid 400 micrograms" to "ferrous 60 mg plus folic acid 2.8 mg" in preventing anaemia. The difference in folic acid dose (400 micrograms to be replaced with 2.8 mg) is based on minimal evidence. The Cochrane review (168) and WHO guidelines (169) state the recommendation of 2.8mg is based only on the rationale of providing seven times the recommended daily dose to prevent neural tube defects and experimental evidence that high weekly doses can improve red blood cell folate concentrations to levels that have been associated with a reduced risk of NTDs.

After careful consideration, the Committee decided not to include this combination, even though the programmatic needs for appropriate supplementation in pregnancy were recognised. Data to show the intermittent regimen to be at least equivalent over existing

options (not placebo) for the prevention of anaemia and/or neural tube defects would be needed. It was also noted that no commercial preparation of this fixed-dose combination yet exists.

## Section 11: Blood products and Plasma Substitutes

### **11.2: Plasma fractions for specific use**

#### **Human normal immunoglobulin (Additional dosage) -- Adults and Children**

An application was submitted by CSL Behring AG, Bern Switzerland for inclusion of SCIG 20% in the complementary list of WHO Model List of Essential Medicines.

Expert reviews were provided by Dr Abdol Majid Cheraghali, Dr Youping Li and Dr Johannes Löwer. Comments were received from International Patient Organisation for Primary Immunodeficiencies, African Society for Immunodeficiencies, Latin American Society for Immunodeficiencies and Dr Ana Padilla, QSM/EMP.

Human normal immunoglobulin is included in the WHO Model List of Essential Medicines (section 11.2 – Plasma fractions for specific use) in concentrations from 5% - 16%, for intramuscular, intravenous and subcutaneous administration). This application is for a 20% concentration to be used subcutaneously with no change in indications. The schedules and doses of SCIG 20% would be the same as with the 15-16% concentrations but the infusion volumes would be smaller (170).

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

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

#### **Whole blood and red blood cells (Addition) -- Adults and Children**

An application was submitted by AABB (formerly the American Association of Blood Banks), the American Red Cross and Canadian Blood Services for inclusion of Whole Blood and Red Blood Cells in the WHO EML.

Extensive comments were received from Ministries of Health, medicines and blood regulatory authorities, multilateral agencies, experts in transfusion medicine and their professional associations, Red Cross National Societies and associations of Voluntary Blood donors. All comments remain available on the WHO EML website  
[http://www.who.int/selection\\_medicines/committees/expert/19/applications/blood/en/index.html](http://www.who.int/selection_medicines/committees/expert/19/applications/blood/en/index.html).

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

The application states that the inclusion of Whole Blood and Red Blood Cells on the WHO Model List of Essential Medicines will accomplish a number of critical objectives in furtherance of WHA Resolution 63.12., This would include among others,

- heightened awareness of the need for blood in every country and of the role of blood in protecting the public health,
- the government's responsibility for ensuring financially sustainable funding and support for a safe and adequate supply of blood that is accessible to patients in need,
- create a favorable environment for governments to support a National Regulatory Authority specifically pertinent to blood,
- invest in infrastructure, systems and governance for blood establishments,
- underscore the need for effective and efficient procurement systems to provide equipment, supplies and reagents to collect, process, test, store and transport blood,
- the need to ensure that blood is cost-effective, affordable and available and
- underscore the importance of, and enable appropriate regulatory oversight of, blood collection, processing, testing, storage and distribution to ensure the safety and quality of blood and the safety of blood transfusion.

The Committee noted the discussion in the Open session which reflected the many comments published in the meeting website, both supporting and opposing the inclusion of Whole Blood and Red Blood Cells. The Committee considered the fact that the application raises many issues that span technical, clinical, ethical and regulatory aspects.

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

The Committee agreed that there was no need to debate whether blood and RBCs were essential as they were necessary for the treatment and management of many clinical conditions such as anaemia and diseases of the blood (where the haemoglobin levels requiring transfusion are well defined), gastrointestinal bleeding, injuries, during surgery, obstetrics conditions such as postpartum haemorrhage and in neonatal conditions such as exchange transfusions (171-176).

The Committee then considered the issue of safety of blood. Based on the application and the comments, the safety issues in relation to use of blood are well defined, and the importance of appropriate quality standards for its production is clear. Global application of these standards will improve the safety of blood for use in transfusion. The risk of transfusion-mediated viral infections remains a constant concern.

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

The Committee considered the concerns raised by some Member States and organisations in relation to payment for donors, commercialisation and commodification, including the arguments in relation to Factor VIII and factor IX complex currently on the WHO Model List of Essential Medicines. Factor VIII and IX are supplied as commercial products, used for a very limited number of conditions affecting a small population, and requires sophisticated manufacturing technology and therefore cannot be seen as an example of commodification for Whole Blood or Red Cells which have limited life span/ shelf life and are used in very different clinical situations that affect a much larger population. The Committee noted that neither the applicant, nor any of the comments provided data to support the claims that listing blood and red blood cells would lead to their commodification.

It was noted that medicines regulatory authorities, through the ICDRA resolution, had expressed a strong preference for listing blood and red blood cells, as an essential medicine, in order to advance access to safe blood products that are appropriately regulated and traceable. Listing as an essential medicine would not be a sufficient solution, but would enable the beginning of a systematic approach to improving access to safe blood products. The Committee noted that the WHA resolution called upon Member States “ to enhance the quality of evaluation and regulatory actions in the area of blood products and associated medical devices, including in vitro diagnostic devices.”

The Committee completely concurred that listing Whole Blood and Red Cells in the WHO Model List of Essential Medicines would not be contradictory to the principles of voluntary, non-remunerated blood donations as stated in WHA Resolution 63.12. Such a listing would strongly support these principles.

Having considered all the above arguments, the Committee decided to change the heading of Section 11 to “Blood products and plasma substitutes of human origin” and restructure the section to specify blood products clearly. The note under sub-section 11.2 would be moved to sub-section 11.1 and updated to reflect World Health Assembly Resolution 63.12. Sub-section 11.1 would be relabelled as “Blood and blood components”, listing fresh frozen plasma, red blood cell concentrates, platelets and whole blood. The balance of the section would be re-numbered. Sub-section 11.2 would be labelled as “Plasma-derived medicinal products”, with a sub-section of 11.2.1 labelled as “Human immunoglobulins”. Sub-section 11.2.2 would be labelled as “Blood coagulation factors”, listing factor VIII and factor IX. Sub-section 11.3 would be labelled as “Plasma substitutes”. A note would also be inserted to indicate that a review of this last sub-section would be needed at the next meeting of the Expert Committee as it contains dextran, and also consider a possible move of the three immunoglobulins (anti-D, anti-tetanus and anti-rabies) from section 19.2 to the new sub-section 11.2.1.

Section 12: Cardiovascular medicines

***Fixed-dose combination for secondary prevention of cardiovascular disease (Addition) -- Adults***

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

Expert reviews were provided by Mr Andrew Gray and Dr Lisa Bero.

The three preparations mentioned in the application are:

(a) Indian Polycap in two strengths

low dose: aspirin 100 mg, simvastatin 20 mg, ramipril 5 mg, atenolol 50 mg, hydrochlorothiazide 12.5 mg;

high-dose: aspirin 200 mg, simvastatin 40 mg, ramipril 10 mg, atenolol 100 mg, and hydrochlorothiazide 25 mg),

(b) Trinomia/Sincronium:

aspirin 100 mg, simvastatin 40 mg, and ramipril (2.5 mg, 5 mg, or 10 mg)

(c) Red Heart Pill in two strengths and combinations, not yet commercially available

aspirin 75mg, simvastatin (20 or 40mg), lisinopril 10mg, atenolol 50mg and

aspirin 75mg, simvastatin (20 or 40mg), lisinopril 10 mg, hydrochlorothiazide 12.5 mg

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

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

The clinical trials cited in the proposal were mostly in primary prevention, were of short duration and relied on surrogate endpoints (177, 178). There is as yet no trial with any of the FDC powered to show a difference in morbidity and mortality. While the medicines in the proposed FDC have been individually tested, there have been no adequate trials of the FDCs in secondary prophylaxis.

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

The Committee noted that there are serious gaps in the data on the proposed FDC formulations. Only one of the three dosage forms listed has undergone a bioavailability study comparing the individual components with the FDC (179). The application states “Other fixed dose combination therapies demonstrate similar degrees of bioequivalence with the individual components” but does not provide data to support this claim.

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

#### **12.4: Medicines used in heart failure**

##### **Spironolactone (New indication) -- Adults**

An application was submitted by Evan Blank, Claire Hutchinson, Alexander Peters and Rajesh Vedanthan (Mount Sinai School of Medicine), Mark Huffman, Amisha Patel (Northwestern Feinberg School of Medicine) and Sandeep Kishore (Weill Cornell Medical College) for aldosterone antagonists be added as a therapeutic class (with spironolactone as the representative) to Section 12.4 of the WHO Model List Of Essential Medicines.

Expert reviews were provided by Dr Kuruvilla Prasad Mathews and Dr Suzanne Hill. Comments were received from the Dr Shanthi Mendis, Coordinator, CPM/WHO, Dr Valentin Fuster, Director, Sinai Heart, New York, Dr Prabhakaran, Public Health Foundation of India, and Dr Myriam Henkens, International Medical Coordinator, MSF.

Spironolactone has been in the WHO Model List of Essential Medicines since 1983, as a potassium-sparing diuretic.

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

The trial was stopped early after a mean follow-up period of 24 months, due to an interim analysis showing that spironolactone was superior to placebo. The trial found a 30% reduction in overall mortality (HR=0.70; 95% CI 0.60 to 0.82), a 35% reduction in hospitalization (HR=0.65; 95% CI 0.54 to 0.77), and significant improvement in heart failure symptoms based on the NYHA functional class ( $P<0.001$ ) in the treatment group. The number needed to treat (NNT) to prevent one death over 24 months was 8.8 (180).

The second clinical trial was the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), which evaluated the effectiveness of eplerenone (25 mg initial dose, titrated to a maximum of 50 mg) in patients with post-MI left ventricular systolic dysfunction ( $LVEF\leq 40\%$ ) in a randomized, double-blinded, placebo-controlled trial. Eplerenone reduced overall mortality by 15% (HR=0.85, 95% CI, 0.75 to 0.96) and cardiovascular disease-specific mortality by 17% (HR = 0.83, 95% CI, 0.72 to 0.94) when compared to placebo over a mean follow-up of 16 months(181).

The third trial was the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) a randomized, double-blinded, placebo controlled study that also showed that eplerenone was effective in patients with left ventricular systolic dysfunction ( $EF < 35\%$ ) and mild symptoms (NYHA class II). The trial was also stopped early due to a significant decrease in death from cardiovascular causes (HR= 0.76, 95% CI, 0.61 to 0.94) and decrease in hospitalization from heart failure (HR= 0.58, 95% CI, 0.47 to 0.70)in the eplerenone treatment group (182).

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

The most recent systematic review concluded that eplerenone was similar to older, less expensive aldosterone antagonists but hyperkalemia may be more frequent with eplerenone whereas gynaecomastia was more frequent with the older aldosterone antagonists (183). Other systematic reviews have confirmed the decrease in mortality with aldosterone antagonists (184).

There are no direct comparative studies between spironolactone and eplerenone.

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

The Heart Failure Society of America Guidelines Committee recommends “Until such time as the effectiveness of these two drugs (spironolactone and eplerenone) in several different patient groups are compared in a well-designed clinical trial, it seems most reasonable for the clinical use of these agents to be consistent with their use in clinical trials. If cost or insurance reimbursement is an issue, as it will be for many, a reasonable choice is to substitute spironolactone” (185).

The Committee recommended the expansion of the indication for spironolactone for heart failure (by listing in section 12.4, as part of the Core List), without a square box because of the current price differential between spironolactone and eplerenone as the other main aldosterone antagonist and possible significant differences in safety profile with respect to hyperkalemia. No change was made to the EMLc, as additional data would be needed to justify inclusion for this patient group, in which the aetiology of heart failure is very different.

### Section 13: Dermatological medicines (topical)

#### **13.4: Medicines affecting skin differentiation and proliferation**

##### **Benzoyl peroxide (Review) -- Adults and Children**

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

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

Acne is one of the common skin conditions mostly affecting the younger age group. Benzoyl peroxide has been in use in different formulations for over 50 years and is available worldwide. It remains the first line choice of treatment for mild to moderate acne, being effective and inexpensive and is mentioned in a large number of national treatment guidelines, such as in the USA and the UK (186-188).

Systematic reviews have evaluated the efficacy and safety of benzoyl peroxide across a range of age groups and presentations and two reviews in 1999 (189) and 2004 (190) rated benzoyl peroxide treatment effect favorably to placebo. Side effects were erythema, peeling and occasionally burning. A recent systematic review using GRADE methodology on the management of acne compared benzoyl peroxide to other contemporary treatments and concluded it should be considered as the first line choice for mild acne (191). The adverse events mentioned, seldom severe, may be linked to the higher concentrations available, including the 10% formulation.

The Committee recommended that benzoyl peroxide should be retained on the WHO list of essential medicines for both adults and children.

##### **Coal tar (Review) -- Adults**

The 18<sup>th</sup> Expert Committee requested a review of whether adults and children with psoriasis be treated with coal tar solution compared to other topical preparations for psoriasis. The review was prepared by the ILDS.

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

Although coal tar preparations, have been used for over 100 years in psoriasis their mechanism of action is still unclear. It is available for the treatment of psoriasis in a variety of different formulations for lesions on the trunk and limbs, and shampoos for scalp lesions.



A Cochrane systematic review of topical treatments for psoriasis included 131 RCTs where some investigated coal tar versus placebo or alternative medicines, notably vitamin D analogues and topical corticosteroids (192). Both vitamin D analogues (e.g. calcipotriol) and corticosteroids perform better than placebo, but no better than each other. Combined vitamin D and corticosteroids performed significantly better than either treatment alone.

There have been concerns expressed over potential carcinogenicity of coal tar preparations. Reviews of the literature have however been unable to uncover evidence of increased risk of cancer in those treated with medical formulations of coal tar (193, 194).

One study has estimated the relative costs of coal tar and calcipotriol using contemporary measures of psoriasis area and severity. The coal tar treatment produced greater improvement in severity and at less cost (\$0.92 per 1% improvement in scoring) than calcipotriol treatment (\$35.42 per 1%) after 12 weeks of treatment. After treatment and 6 weeks of follow-up (at week 18), the relative costs were \$1.01 in the coal tar group and \$58.11 in the calcipotriol group because the coal tar group maintained the improvement while the calcipotriol group significantly worsened (195). Although there are other medications available, coal tar is an effective and safe treatment for psoriasis, is affordable and widely available.

The Committee therefore recommended retention of coal tar on the EML.

#### [Dithranol \(Deletion\) -- Adults](#)

The 18<sup>th</sup> Expert Committee requested a review of dithranol for possible deletion from the EML. The review was submitted by the International League of Dermatology Societies (ILDS).

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

Dithranol has been used topically for many years for the treatment of psoriasis. It is available in various formulations such as creams, ointments or pastes in strengths of between 0.1 to 2%. However, clinical use has decreased in most parts of the world and it is seldom available in resource-poor areas. The main reason for its decreased use has been the known risk of severe irritant reactions when the preparation is applied to psoriatic plaques and, in particular, in extra-lesional skin (192).

There is little evidence of the efficacy of dithranol, as this is an old medication that has not been subject to substantive clinical trials. However data collected in a Cochrane review of the treatment of plaque type psoriasis with topical medications found that it was more effective than placebo (196). Burning and itching are very common adverse events that occur on skin lesions and normal skin in contact with it. In a systematic review of adverse events with topical treatments in psoriasis, dithranol performed worst with 72% patients having adverse events (197).

The Expert Committee decided to delete this medicine due to concerns about the balance between benefits and risks and the low utilisation of this medicine (192, 197, 198)). There are other suitable alternatives for this indication in the EML.

## Section 17: Gastrointestinal medicines

### **17.1: Antiulcer medicines**

#### **Antiulcer medicines (Review) -- Adults**

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

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

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

#### **H<sub>2</sub> receptor antagonists (H<sub>2</sub>RAS) versus proton pump inhibitors (PPIs) for gastroesophageal reflux disease (GERD)**

According to the most recent American Gastroenterological Association Medical Position Statement on the management of GERD; *“for the treatment of patients with esophageal GERD syndromes (healing esophagitis and symptomatic relief) ... PPIs are more effective than H<sub>2</sub>RAs, which are more effective than placebo”* (199). All other recent consensus guidelines agree with this recommendation (200, 201).

However, H<sub>2</sub>RAs have several advantages: faster onset and longer duration of action, no need to time administration before meals, lower cost and probably safer in pregnancy. Furthermore they can be used in patients who cannot tolerate PPIs because of side effects.

#### **H<sub>2</sub>RAS versus PPIs for nonulcer dyspepsia (NUD)**

There is limited evidence on the efficacy of H<sub>2</sub>RAs and PPIs in patients with non-ulcer dyspepsia. A Cochrane systematic review and meta-analysis of RCTs on pharmacological interventions for NUD concluded both H<sub>2</sub>RAs and PPIs were more effective than placebo in symptoms of oesophagitis, and there was no evidence of a difference between H<sub>2</sub>RAs and PPIs (202, 203).

#### **PPI parenteral preparation**

The vast majority of patients that require PPI treatment can be treated with oral PPIs. However, there are some situations where intravenous (IV) PPI treatment is either preferable or is the only possible route of administration.

The most important and common indication for IV PPIs is peptic ulcer bleeding. Intravenous omeprazole has been approved for this indication in Europe, and the application is pending with the US FDA. This is based mainly on the results of a large high-quality multi-center RCT that was published in 2009 (204), but older Cochrane systematic reviews and meta-

analyses of RCTs had found that there is strong evidence supporting the efficacy of high-dose IV PPI treatment in such patients (205).

### **Comparative Costs**

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

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

18: Hormones, other endocrine medicines and contraceptives

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

#### **Glibenclamide (Review) -- Adults**

The 18th WHO Expert Committee on the Selection and Use of Essential Medicines in 2011 requested a review on the safety of sulfonylureas in the elderly, to determine if updates to the EML are needed.

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

Expert reviews were prepared by Mr Andrew Gray and Dr Kuruvilla Prasad Mathews. Comments were received from Director, MND, WHO and Dr Myriam Henkens, International Medical Coordinator, MSF.

The worldwide 2011 estimated prevalence of diabetes in the elderly population (60 years and above) is between 15% to 20% (206). The WHO EML currently lists only glibenclamide from the sulphonylurea category; elderly patients are a significant proportion of type II diabetics and the safety of sulphonylureas in this group is therefore important.

The review evaluated the comparative safety and efficacy of 4 second generation sulfonylureas (second generation SFUs) for the treatment of type 2 non-insulin dependent diabetes in elderly patients. The medications reviewed were glibenclamide (also called glyburide), gliclazide, glimepiride and glipizide. The review also analyzed the cost of the four medications as well as their availability on NEMs of 40 low and middle-income countries.

A 2007 meta-analysis of 21 studies showed that based on HbA1c results, glibenclamide compared to other SFUs, including gliclazide, glimepiride and glipizide, did not have an increased efficacy in treatment of diabetes (207).

The same meta-analysis also showed that there was an increased risk of hypoglycemia of 52% with glibenclamide when compared with other insulin secreting anti-diabetes medicines and 83% higher risk compared to other SFUs (207).

A retrospective, cohort study of more than 13,000 patients concluded that glibenclamide had the highest rate of hypoglycemia at 16.9 per 1000 person-years, compared to all other SFUs (208). The authors also concluded that the physiological changes associated with increasing age such as declining renal and hepatic function, as well as polypharmacy and concurrent illnesses additionally predispose the elderly to hypoglycemia; this predisposition is further compounded by use of glibenclamide. Another retrospective, cohort study of more than 33,000 patients in the UK showed that the risk of hypoglycemia was higher with glibenclamide when compared to other SFUs(209). The authors also concluded that patients older than 65 years, were at higher risk of hypoglycemia versus adults less than 65 years of age with a relative risk of 1.27 (CI 1.06-1.51).

In the analysis of the NEMs, the most widely available second generation sulfonylurea was glibenclamide with a overall listing on 39 of the 40 NEMs (97.5%) followed by gliclazide and glipizide, available on 50% and 27.5% of the NEMs, respectively.

The Committee discussed the fact that all 4 sulphonylureas are available as generics but there is considerable variation in price between countries, and therefore it is not possible to make a clear decision based on cost. However glibenclamide appeared to be the cheapest in most countries.

The Committee decided that glibenclamide be replaced in the Core List with gliclazide (30mg, 60mg, 80mg), with a square box symbol as the example of a second-generation sulphonylurea, and a note be added to the effect that glibenclamide should not be used in patients aged 60 years and older.

#### [Oral hypoglycemics \(Review\) – Adults](#)

The 18th WHO Expert Committee on the Selection and Use of Essential Medicines in 2011 requested a review on oral hypoglycaemics - “Should adults with type 2 diabetes be treated with 1) alpha-glucosidase inhibitors, such as acarbose; 2) amylin analogues, such as pramlintide; and 3) dipeptidyl peptidase-4 inhibitors such as sitagliptin and meglitinides such as repaglinide and mitiglinide compared with other classes of oral hypoglycaemic medicines (metformin; sulfonylureas such as glibenclamide, glimepiride, and gliclazide; thiazolidinediones such as pioglitazone and rosiglitazone)?”

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

Expert reviews were provided by Mr Andrew Gray and Dr Kuruvilla Prasad Mathew. Comments were received by Director, MND, WHO.

The review compared the four groups of oral hypoglycaemics 1) DPP-4 inhibitors 2) glitazones 3) alpha-glucosidase inhibitors, such as acarbose and 4) meglitinides, against metformin (biguanide) and sulphonylureas. The base was a systematic review in 2010 (210), which was combined with other systematic reviews of oral hypoglycaemics (211-217).

A detailed comparison using the GRADE methodology was done between metformin and each of the 4 groups, and also with sulphonylureas and each of the 4 groups. The tables are

available at

[http://www.who.int/selection\\_medicines/committees/expert/19/applications/Sulfonylurea\\_18\\_5\\_A\\_R.pdf](http://www.who.int/selection_medicines/committees/expert/19/applications/Sulfonylurea_18_5_A_R.pdf)

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

For the effect on HBA1c, none of the medicines in the 4 groups were better than either metformin or sulphonylurea; the strength of the evidence ranged from low to high. For weight loss, metformin was better than the DPP – 4 inhibitors and glitazones but there was no difference with alpha-glucosidase inhibitors and meglitinides. Sulphonylureas had a better effect on weight loss than the glitazones but there was no difference between sulphonylureas and the other 3 groups (DPP-4 inhibitors, alpha-glucosidase inhibitors and meglitinides).

In the effect on high-density glycoprotein, triglycerides, hypoglycaemia and gastrointestinal adverse events, again none of the medicines in the 4 groups had a consistently favourable effect or even a trend compared to metformin and sulphonylureas.

For comparison of cost, all medicines in the 4 groups were more expensive than metformin and sulphonylureas.

None of the medicines in the 4 groups were shown to be better than metformin and sulphonylureas and at the most were equivalent in only some aspects. There were safety concerns with some medicines of the groups and none of them offered any safety advantages over biguanides and sulphonylureas. Rosiglitazone had been withdrawn from European markets and pioglitazone was also withdrawn in France and Germany. The most recent concern about safety has been on a potential increased risk of pancreatitis and pancreatic duct metaplasia in patients with type II diabetes treated with GLP-1 agonists and DPP-4 inhibitors (218).

The convenience sample of the NEMLs of 15 low and middle-income countries showed that only 5 countries had products from this group (rosiglitazone, pioglitazone, acarbose and repaglinide).

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

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

## Section 21: Ophthalmological preparations

*Azithromycin (Addition) -- Adults and Children*

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

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

Trachoma, a chronic keratoconjunctivitis caused by recurrent infection from *C. trachomatis*, is the leading cause of infectious blindness worldwide (219). The current WHO guidelines recommend a single oral dose of azithromycin as the treatment. It was noted that oral azithromycin is not included in section 21.1.

Two studies were submitted in support of the application.

A randomised, controlled, double-masked, double-dummy, non-inferiority study including 670 children from Guinea Conakry and Pakistan was conducted. Three groups received one of three treatments: azithromycin 1.5% eye drops twice daily for 2 days, for 3 days or azithromycin single 20 mg/kg oral dose.

The cure rate at day 60 in the per protocol analysis was 93.0%, 96.3% and 96.6% in 2-day group, 3-day group, and oral treatment group respectively. The azithromycin 1.5% eye drops groups were non-inferior to oral azithromycin. There were no significant differences between the groups with respect to trachoma re-emergence ( $p > 0.545$ ).

All three treatments markedly reduced the trachomatous grading on days 30 and 60. There were no significant differences between the treatment groups with respect to trachomatous grading ( $p > 0.170$ ) (220).

The second study was a mass treatment programme with no comparator; in February 2008, a program was undertaken to treat the entire population of the Kolofata Health District in Cameroon (115,274 residents) with azithromycin 1.5% eye drops twice/day for 3 days. A total of 51 659 adults and 59 681 children <15 years old were treated.

"One year after two rounds of topical treatment, prevalence dropped to 3.1% (95%CI 2.0–4.9) ( $p < 0.0001$ ), a decrease of 90%. The prevalence of Trachomatous Inflammation decreased significantly ( $p = 0.0001$ ) to 3.1% one year after the second round of treatment. The prevalence of intense trachomatous inflammation disappeared after two annual treatments (0% after second treatment ( $p = 0.0005$ ))" (221, 222).

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

The WHO Prevention of Blindness and Deafness Unit (PBD) Unit supported the application and mentioned future activities (revision of the WHO Trachoma Control Manual) that would support azithromycin eye drops.



In summary, azithromycin eye drops were similar to the single oral dose treatment but required three days of topical application. There appears to be better safety with azithromycin eye drops. Donation programmes with suitable presentations of the ophthalmic solution are planned. The oral preparation is not recommended for pregnant women or children under 1 year of age, and for these patient groups, the ophthalmic solution offers an important option. The use of oral azithromycin and its limitations are given in the WHO guidelines (223). The only alternative for such patients is topical tetracycline, which requires a protracted course (6 weeks or 6 months, depending on the dose regimen used).

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

#### Bevacizumab (Addition) -- Adults

An application was submitted by the International Council of Ophthalmology for the inclusion of bevacizumab for the treatment of proliferative (neovascular) eye diseases. Expert reviews were provided by Dr Gitanjali Batmanabane, Dr Abdol Majid Cheraghali and Dr Nicola Magrini. The application was supported by the WHO Department of Prevention of Blindness Deafness.

Age-related macular degeneration is the leading cause of blindness in persons over 50 in developed countries and it is estimated that by 2020, as many as 7.5 million people worldwide over age 65 may have vision loss attributable to this disease (224). Ten to twenty percent of patients with AMD are expected to have the neovascular form of the disease, that is responsible for 90% of all cases of severe vision loss. The Committee therefore accepted that there is a clear public health need for the treatment of the neovascular form of age-related Macular degeneration (nAMD).

The application for bevacizumab was based on a large randomized controlled trial funded by the National Institutes of Health, USA (Comparison of AMD Treatments Trials (CATT) which compared bevacizumab with ranibizumab (225, 226). The trial randomized 1200 patients to one of four treatments; either bevacizumab or ranibizumab and either monthly or 'as needed' treatment regimens. For the primary outcome, change in visual acuity at 1 and 2 years of follow up, bevacizumab and ranibizumab were equivalent. Bevacizumab administered monthly was equivalent to ranibizumab administered monthly, with 8.0 and 8.5 letters gained on the visual acuity scores, respectively. Bevacizumab administered as needed was equivalent to ranibizumab as needed, with 5.9 and 6.8 letters gained, respectively.

The analysis of adverse outcomes showed that rates of death, myocardial infarction, and stroke were similar for patients receiving either bevacizumab or ranibizumab. The Committee also considered the hospitalization events with bevacizumab compared to ranibizumab (24.1% vs. 19.0%; risk ratio, 1.29; 95% CI, 1.01 to 1.66), and noted that the excess events were broadly distributed in disease categories not identified in previous studies. The Committee accepted the explanation given in the study that the differences in

hospitalization rates were probably due to baseline imbalances. The Committee also noted that in the trial, the higher doses of bevacizumab (monthly regimen) were associated with a lower hospitalization rate than the lower dose (as needed regimen), which might be explained by chance or baseline imbalances in the groups for comorbidities or other patient characteristics.

The Committee considered the results from a second trial, not mentioned in the application. This British study (IVAN) with 300 patients per arm was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) program (227). The results of this trial showed that the two treatments had similar efficacy and safety, including comparisons of monthly versus 'as needed' treatment regimens. In the IVAN trial the frequency of systemic arteriothrombotic events and heart failure were lower for bevacizumab than ranibizumab (0.7% vs. 2.9%, OR 0.23; 95% CI, 0.05 – 1.07; P = 0.03).

The Committee considered the observational studies evaluating the safety of bevacizumab, or comparing bevacizumab and ranibizumab. These data were mostly from record-linkage studies or large pharmacoepidemiology databases. A recent EMA report (July 2012) reviewing all these safety studies of bevacizumab concluded that: "... the CHMP agreed that detailed safety information provided from the CATT and IVAN studies is reassuring and no evidence can be provided that bevacizumab is systemically more unsafe than ranibizumab and vice-versa. The CATT study was not powered to detect rare adverse events or to show differences in the number of events with a relatively high background incidence in elderly people with AMD" (228).

The Committee noted that currently available formulations of bevacizumab are not specifically formulated for intravitreal injections. Bevacizumab comes in a sterile solution 25 mg/mL (i.e., 1.25 mg/0.05 mL), so it does not need to be diluted, reconstituted, or altered in any way. The Committee considered that reports of adverse events (e.g. endophthalmitis) resulting from reformulation of the vial size currently available for use for multiple injections had been traced to inadequate sterility in the compounding process. The Committee noted, therefore, that safe use of bevacizumab as currently formulated requires that use may need to be restricted to a single patient per vial, notwithstanding the wastage. Any alternative approach to using a single vial for multiple patients would obviously have to comply with appropriate safe and sterile injection practices, including any requirements for storage of the product to ensure that there would be no possibility of contamination. However, even allowing for wastage, based on anecdotal cost comparisons, the cost of using currently available vials of bevacizumab for intravitreal injection may be less than 1/20<sup>th</sup> of the cost of using alternative products such as ranibizumab.

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

While noting the absence of stringent regulatory authority approval for use of bevacizumab for the indication of AMD, the Committee recommended that it be included in the List on grounds of public health need, demonstrated safety and effectiveness and favourable cost-effectiveness. The Committee again drew attention to the need for safe preparation and administration of intravitreal bevacizumab. The Committee recommended the listing of



bevacizumab 25mg/ml injection (100 mg vial) in the Complementary List in a new section 21.6 (anti-VEGF preparations).

**Ketorolac (Addition) -- Adults**

An application was submitted by the International Council of Ophthalmology proposing the addition of ketorolac eye drops.

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

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

There are no WHO guidelines for these conditions and it is unclear from the application whether NSAID eye drops are recommended as routine after the surgery for the conditions mentioned above. Ketorolac is effective in moderate to severe ocular inflammation after cataract surgery but the comparison was with the vehicle solution rather than with another medicine (229). A Cochrane review states that the role of NSAID is in the treatment of cystoid macular oedema following cataract surgery is unclear (230).

In allergic conjunctivitis, a double blind, placebo-controlled study of 148 patients evaluated treatment given four times daily over a 7-day period and showed that ketorolac was significantly better than placebo in regards to ocular itching, conjunctival inflammation, conjunctival injection, swollen eyes, foreign-body sensation, and ocular discharge (231). A second study of 93 subjects with similar design, but lacking slit-lamp observations, reported ketorolac was significantly better than placebo in reducing conjunctival inflammation and photophobia after 7 days of treatment (232). A significant placebo effect (as seen in improvement from baseline in the control group) was noted in both trials. Ketorolac appears to be used widely but the application did not contain any systematic reviews of its efficacy and safety nor any comparative trials with other NSAID eye preparations. Seasonal allergic conjunctivitis was also not considered by the Committee to be of sufficient public health relevance to require ketotifen to be added to the EML.

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

*Ketotifen (Addition) -- Adults and Children*

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

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

In the application, seasonal allergic conjunctivitis was quoted as being a common (20%), mild condition. However these are estimates and there are no surveys to validate this figure (233). The application did not have estimates of the disability caused by this condition.

The current WHO EML does not have a medicine for seasonal allergic conjunctivitis and neither are there any WHO guidelines for the treatment of this condition. There are no topical ocular antihistamines in the EML.

The application did not contain any systematic reviews of ketotifen efficacy in seasonal allergic conjunctivitis; the studies were mainly on conjunctival allergen challenge models some comparing ketotifen to placebo (234). A Cochrane Review on "Topical antihistamines for treating perennial allergic conjunctivitis" is at protocol stage (235).

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

*Latanoprost (Addition) -- Adults*

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

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

Glaucoma is the second leading cause of blindness worldwide (236) and at present there are acetazolamide tablets, and timolol and pilocarpine eye drops in the WHO Model List of Essential Medicines for glaucoma.

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

"Timolol, the leading topical beta-adrenergic antagonist, is often used as a first line therapy for the treatment of glaucoma. Dorzolamide, the first topical carbonic anhydrase inhibitor to become available on the market, is often prescribed as an add-on therapy. A review of studies comparing the efficacy of latanoprost to combined timolol and dorzolamide

suggested that the intraocular pressure lowering effect of latanoprost is equivalent to that of concomitant timolol dorzolamide therapy. In addition, data suggests that adding latanoprost to timolol and dorzolamide leads to a further 16% reduction of intraocular pressure.”(237)

A recent systematic review judged the prostaglandin agents to be superior to other monotherapies “We judged the strength of evidence from these 3 most recent trials to be low. However, with the addition of the consistent high-quality systematic reviews, the conclusion that topical glaucoma medications decrease IOP is well supported, as is the conclusion that prostaglandin agents are superior to other monotherapies with regard to decreasing IOP”(238).

A meta-analysis which evaluated trials comparing latanoprost with timolol found latanoprost to be more effective than timolol. Additionally latanoprost had the advantage of once daily administration (239).

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

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

#### **Ofloxacin (Addition) -- Adults and Children**

An application was submitted by the International Council of Ophthalmology proposing the addition of ofloxacin 0.3% for infectious keratitis in section 21.1; at present only gentamicin 0.3% is included in that section.

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

In the developing world, it has been estimated that up to 5% of all blinding conditions are directly related to ocular trauma and the subsequent infection (240). This estimate is supported by population based studies in several countries. In a blindness survey in Nepal, corneal trauma and ulceration were found to be the second leading cause of unilateral visual loss after cataract, accounting for 7.9% of all blind eyes. A study in South India found that the incidence of ulcerative keratitis was 11.3 cases per 10,000 persons, resulting in an estimate of 840,000 new ulcers on an annual basis in India alone.

The application provided one clinical trial where ofloxacin 0.3% has been compared with fortified gentamicin (1.5%) plus cefuroxime (5%) in microbial keratitis which showed similar rates of cure. The authors state that treatment with ofloxacin monotherapy was associated with less toxicity without providing data (241). Another trial was identified in the expert reviews in which ofloxacin was found to be more effective than gentamicin (242).

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

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

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

Section 22: Oxytocics and antioxytocics

### **22.1: Oxytocics**

#### **Misoprostol (Deletion) for PPH prevention -- Adults**

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

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

Misoprostol was considered by the 18th Expert Committee and added to the 17<sup>th</sup> WHO EML for prevention of postpartum haemorrhage. However there was a specific note which stated "For prevention of postpartum haemorrhage where oxytocin is not available or cannot be safely used".

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

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

An application has been submitted by Gynuity Health Projects, NY, USA for the inclusion of misoprostol for the treatment of postpartum hemorrhage (PPH) attributable to uterine atony.

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

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

This application requests that misoprostol be listed with an indication for the treatment of postpartum haemorrhage when oxytocin is unavailable. Specifically "Intravenous oxytocin

should be used when available, but misoprostol could be an effective alternative in settings in which IV oxytocin is not feasible”.

Misoprostol for treatment of PPH was considered by the 18th Expert Committee (159). The data presented in this application had been considered by the 18th Expert Committee and there were no new clinical trials. Since the 18<sup>th</sup> Committee, there has been a change in WHO treatment guidelines, with the use of misoprostol in the treatment of postpartum haemorrhage now recommended as follows (243):

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

The Committee has previously recommended misoprostol for prevention of postpartum haemorrhage where oxytocin is not available or cannot be safely used. It had however not recommended the use of misoprostol for the treatment of PPH.

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

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

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

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

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

- The following applications were received:
  - Proposal for the deletion of haloperidol and chlorpromazine from the EMLc.
  - Inclusion of clozapine as complementary medicine for treatment resistant schizophrenia in adults.

- Two applications for the inclusion of the second generation antipsychotic risperidone; one proposing inclusion in the Core EML only, the other proposing inclusion of tablets in the Core List and other formulations in the Complementary List in both EML and EMLc
- Modify the minimum age for the use of fluoxetine as complementary medication in childhood depression.

**Clozapine (Addition as complementary medicine) -- Adults**

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

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

The 17th edition of WHO Model List of Essential Medicines includes haloperidol and chlorpromazine in *24.1 Medicines used in psychotic disorders*. The evidence review and the consequent recommendations of the guideline development group (GDG) for *WHO's mental health Gap Action Programme Intervention Guide* (mhGAP-IG) identified some medicines in addition to psychosocial interventions for the treatment of psychotic disorders in 2009. The recommendations identified first-generation antipsychotics (broadly equivalent to typical antipsychotics), haloperidol or chlorpromazine as a first choice and second-generation antipsychotics (broadly equivalent to the group of atypical antipsychotics) as their alternatives if availability and cost is not a constraint (66).

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

In the pivotal trial comparing clozapine to chlorpromazine published in 1988, 30% of treatment resistant patients responded to clozapine as compared with 4% to chlorpromazine(244). Later clinical trials have shown a response rate between 30-50% (245).

NICE Guideline, 2010 suggests to “Offer clozapine to people with schizophrenia whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least two different antipsychotic drugs.....” (246).

Randomised clinical trials involving a large number of patients have been done with second-generation antipsychotics and 2 major long term studies have been conducted by the National Institute of Mental Health (247, 248). These studies have shown a broadly similar response rate but differences in their adverse effects (247, 248). Clozapine has been shown to be better than other second-generation antipsychotics in patients with an inadequate response to other antipsychotics (249).

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

The application requested the addition of clozapine for the management of cases refractory to other antipsychotics; the Committee therefore decided to recommend addition of clozapine to the Complementary List of the EML.

## **24.2: Medicines used in mood disorders 24.2.1: Medicines used in depressive disorders**

### **Fluoxetine (Change to age restriction/Deletion from EMLc) -- Adults and Children**

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

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

Depression appears to be rare in children younger than six years; the prevalence from 6 years to adolescence is less than in adolescents. In a meta-analysis of twenty-six studies including 60,000 observations on children, overall prevalence estimates for children under 13 years old was 2.8% (SE= 0.5%) and for those between 13–18 years old it was 5.6% (SE = 0.3%) which is close to adult figures (250).

The WHO's mental health Gap Action Programme Intervention Guide (mhGAP-IG) was published in 2010, based on WHO guidelines, which were in turn based on a series of evidence reviews conducted in 2009. The Guideline Development Group made the following strong recommendation:

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

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

The Subcommittee in 2007 had noted the discrepancies in the minimum age for fluoxetine approved by a number of regulatory authorities and endorsed the inclusion of fluoxetine in EMLc with an age restriction of 8 years (251).

The Committee decided to retain the minimum age for fluoxetine at 8 years as the evidence submitted to raise the age to 12 was not considered sufficient. However, the need for a thorough review of the section was noted as a priority.

### **Risperidone (Addition) – Adults**

The following two applications to include risperidone in the WHO Essential Medicines List were received from:

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



2. *Massachusetts General Hospital, The Chester M. Pierce MD Division of Global Psychiatry, Boston, MA 02114 (Young Professionals Chronic Disease Network)* proposed the **inclusion of the second generation antipsychotic risperidone in the core EML.**

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

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

It is estimated that about 41.7 million people need treatment for schizophrenia and related disorders in low- and middle-income countries (LMICs). The majority of these cases are concentrated in Asia (70%) and Africa (16%) (252). Schizophrenia is a significant contributor to the global disease burden, accounting for 1.1% of disability-adjusted life years (DALY's) lost (253)

The mhGAP published by the WHO in 2010 (254) has three antipsychotics (haloperidol, chlorpromazine, and fluphenazine), all of which are currently on the Model List. It states that if the responses to these medications are inadequate, providers may choose to treat patients with a second-generation antipsychotics, if available and affordable. An excerpt from the guide states:

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

A 2010 Cochrane review of 23 randomized controlled trials (RCTs) including nearly 4445 patients found risperidone to be more effective than typical antipsychotics in treating schizophrenia and schizoaffective disorder (255). Based on pooled data from nine RCTs, risperidone was more likely than haloperidol to cause clinical improvement in the short-and longer term. Another more recent Cochrane review found that risperidone was more efficacious than both quetiapine and ziprasidone, though less efficacious than clozapine and olanzapine. Importantly, risperidone has a safer side effect profile than both clozapine and olanzapine (256-259). Other reviews have also shown the overall efficacy of risperidone over first-generation antipsychotics (260, 261).

Whereas risperidone (and other second-generation antipsychotics) are less likely to cause extrapyramidal side effects when compared to typical antipsychotics, they are more likely to cause metabolic side effects such as weight gain, hyperlipidemia, and hyperglycemia.



The unit price of risperidone including generics had fallen substantially since 2008. A comparison of pre- and post-generic production data revealed the impact of generic production on the price. In 2002, the cost of a 2 mg tablet of risperidone ranged from 0.070 USD to 1.33 USD, with the median price being roughly 70 cents. In 2011, however, the cost of a 2 mg tablet of risperidone ranged from 0.0080 USD to 0.067 USD, with the median price being just 0.034 USD, or roughly 3 cents (262). Data was also compared in the Indian market. Amongst 12 branded generic manufacturers the price of 10 units of 1 mg tablets ranged from 7.00 rupees to 19.70 rupees (263).

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

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

## Section 27: Vitamins and minerals

### Calcium (Addition) – Adults

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

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

The Committee noted the proposed inclusion of calcium supplementation in the EML followed two recent WHO guidelines assessing the use of calcium supplements in pregnant women: *WHO recommendations for the prevention and treatment of pre-eclampsia and eclampsia*, published in 2011 and *Calcium supplementation in pregnant women*, developed in 2012 (264, 265).

In both guidelines, WHO makes a strong recommendation for supplementation for pregnant women with 1.5 g to 2 g of elemental calcium per day in areas where dietary calcium intake is low and for women at high risk of developing hypertensive disorders during pregnancy. Two recent Cochrane systematic reviews investigated whether calcium supplements consumed on a daily basis during pregnancy safely improved maternal and infant outcomes. (266, 267). Calcium supplementation during pregnancy significantly reduced the risk of pre-eclampsia and high blood pressure (with or without proteinuria).

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

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

#### Section 28: Ear, nose and throat medicines

##### *Ear, nose and throat (Review) -- Adults and Children*

A “Review of the existing recommendations for essential medicines for ear, nose and throat conditions in adults and children and suggested modifications”, was submitted by Dr Shelly Chadha and Dr Andnet Kebede, Prevention of Blindness and Deafness Unit, WHO to include medicines and dosages for adults.

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

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

**6. Summary of recommendations**

18th WHO Model List of Essential Medicines

**Additions to Model List**

**Deletions from Model List**

**Changes to sections**

**Amended dosage strength and form**

**Change to age restriction**

**Re-instatement**

**Rejected applications**

4th Essential Medicines List for Children

**Additions to EMLc**

**Deletions from EMLc**

**Changes to sections**

**Amended dosage strength and form**

**Change to age restriction**

**Rejected applications**

**Recommendations for reviews**

**Medicines marked for consideration of deletion at the next meeting**

**Annex 1**

18th WHO Model List of Essential Medicines

(Available as a separate document)

**Annex 2**

4th WHO Model List of Essential Medicines for Children

(Available as a separate document)

**Annex 3**

The Anatomical Therapeutic Chemical (ATC) Classification System

To be compiled from 18<sup>th</sup> EML + 4<sup>th</sup> EMLc

**Annex 4**

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

To be compiled from 18<sup>th</sup> EML + 4<sup>th</sup> EMLc



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