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The Selection and Use of Essential Medicines

Report of the WHO Expert Committee, 2015
(including the 19th WHO Model List of Essential Medicines
and the 5th WHO Model List of Essential Medicines for Children)

World Health Organization

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Executive summary

The 20th meeting of the WHO Expert Committee on the Selection and Use of Essential medicines took place in Geneva, Switzerland, from 20 to 24 April 2015. The goal of the meeting was to review and update the 18th WHO Model List of Essential Medicines (EML) and the 4th WHO Model List of Essential Medicines for Children (EMLc).

In accordance with approved procedures,[1] the Expert Committee evaluated the scientific evidence on the basis of the comparative effectiveness, safety and cost–effectiveness of the medicines. Both lists went through major revisions this year, as the Committee considered 77 applications, including 29 treatment regimens for cancer, and innovative hepatitis C and tuberculosis (TB) medicines. The Expert Committee

- recommended the addition of 36 new medicines to the EML (15 to the core list and 21 to the complementary list); and
- recommended the addition of 16 new medicines to the EMLc (four to the core list and 12 to the complementary list).

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

Section 6.2.4 Antituberculosis medicines: For the treatment of multi-drug resistant tuberculosis (MDR-TB), extensively drug-resistant tuberculosis (XDR-TB) and pre-XDR-TB, the Expert Committee recommended the addition of bedaquiline, delamanid and linezolid, and of terizidone (as a specific alternative to cycloserine), to the complementary list of the EML. Similarly, linezolid was recommended for addition to the EMLc. The Expert Committee supported the use of these medicines recommended in WHO guidelines, with careful selection of patients, close monitoring to control adverse events, and active pharmacovigilance. The Committee also recommended the addition of rifapentine to the core list of EML and EMLc for the treatment of latent TB infection.

Section 6.4.2 Antiretrovirals: The Expert Committee considered applications for addition and deletion of antiretrovirals, and noted the recommendations in the *WHO Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach*, published in 2013. The Committee recommended the addition of darunavir, new formulations of efavirenz and nevirapine, and a fixed-dose combination of

[1] See: http://www.who.int/selection_medicines/committees/subcommittee/2/eeb1098%5b1%5d.pdf

abacavir + lamivudine. The Committee did not recommend listing of the fixed-dose combinations of cobicistat + elvitegravir + emtricitabine + tenofovir and emtricitabine + rilpivirine + tenofovir. The Committee recommended deletion of 30 antiretroviral formulations from the EML and EMLc, as these are no longer recommended by WHO guidelines.

Section 6.4.4 Antihepatitis medicines: The Expert Committee recommended that a new section be inserted in the core EML to include medicines for the treatment of viral hepatitis infections, with subsections for hepatitis B and hepatitis C. The Committee recommended the addition of entecavir and tenofovir for the treatment of hepatitis B, and the addition of six oral direct-acting antiviral agents, including daclatasvir, dasabuvir, ledipasvir + sofosbuvir, ombitasvir + paritaprevir + ritonavir, simeprevir, and sofosbuvir, for the treatment of hepatitis C. The recommendations for inclusions were based on the comparative efficacy, increased tolerability, and potential public health impact of these medicines. The very high cost of hepatitis C medicines was considered and the Committee recommended that WHO take action at global level to make these medicines more accessible and affordable.

Section 8.2 Cytotoxic and adjuvant medicines: Following a review requested by the previous Expert Committee in 2013, the Committee recommended the addition of 16 new medicines and endorsed the use of 30 medicines listed currently as part of clinically proven effective treatment regimens. These medicines will be included in the complementary lists of the EML and EMLc for the treatment of specific cancers. The Committee recommended that the Model Lists should specify the cancers for which use of each medicine is recommended. Among the medicines recommended are some high-cost medicines, including imatinib, trastuzumab and rituximab. The Committee also recommended, among others, the addition of aromatase inhibitors, bendamustine, capecitabine, cisplatin, oxaliplatin and all-trans-retinoic acid.

Section 10.2 Medicines affecting coagulation: The Expert Committee recommended addition of enoxaparin to the core list of the EML with a square box symbol representative of the pharmacological class of low-molecular-weight heparins (with alternatives to be limited to nadroparin and dalteparin) for the prophylaxis and treatment of venous thromboembolism and the treatment of acute coronary syndromes. The Committee did not recommend addition of the novel oral anticoagulants (NOACs), including dabigatran, rivaroxaban and apixaban for use in stroke prevention in patients with non-valvular atrial fibrillation. The Committee found that NOACs provide no overall clinically relevant advantage compared with warfarin for patients who are established and stable on warfarin therapy. The Committee emphasized the need for further

research to define unmet needs for anticoagulation in patients who cannot be stabilized with warfarin and for use in clinical settings where access to warfarin monitoring is not reliable or available.

Section 12 Cardiovascular medicines: The Expert Committee did not recommend addition of fixed-dose combination therapy for secondary prevention of cardiovascular disease. This decision was based on the lack of evidence on clinical outcomes, the higher number of adverse events reported with the use of combinations, and the difficulties associated with dose titration of the components as proposed in the various fixed-dose combinations.

Section 18 Hormones, other endocrine medicines and contraceptives: The Expert Committee recommended addition of three new contraceptive products to the EML: the etonogestrel-releasing implant, the levonorgestrel-releasing intrauterine system, and the progesterone contraceptive vaginal ring.

Section 21.6 Anti-vascular endothelial growth factor (anti-VEGF) preparations: The Expert Committee did not recommend the addition of ranibizumab to the EML for the treatment of neovascular (proliferative) eye diseases. The Committee concluded that the available evidence shows ranibizumab and bevacizumab to have similar effectiveness and safety. In analyses of cost–effectiveness, bevacizumab is the preferred option as ranibizumab is more expensive and offers no additional clinical benefits. The Expert Committee was concerned that the inclusion of ranibizumab for the treatment of these eye diseases might divert relevant resources from other interventions.

22.1 Oxytocics: Two applications in relation to misoprostol were considered by the Expert Committee. The Committee recommended listing misoprostol for the additional indication of treatment of postpartum haemorrhage when oxytocin is unavailable or cannot safely be used; it did not recommend deletion of misoprostol for prevention of postpartum haemorrhage, noting that no new clinical trial data to support deletion have been presented since the same application was made in 2013.

Additional recommendations: The Expert Committee recommended the addition of valganciclovir, desmopressin, clopidogrel, omeprazole IV formulation, and alcohol-based hand rub. The Committee did not recommend the addition of dopamine agonists for Parkinson disease, of a new strength formulation of ferrous salt + folic acid, or of gadolinium-based radiocontrast media.

All applications and documents reviewed by the Expert Committee are available on the WHO website at: http://www.who.int/selection_medicines/committees/expert/20/en/.

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The Committee wishes to acknowledge Ms Maike Nellestijn, WHO Intern, Policy, Access and Use, for her technical and administrative assistance in the preparation and organization of the meeting.

Declaration of interests

Declarations of interests of Expert Committee Members, Temporary Advisers and WHO Secretariat

The competing interests that may occur in health care result in the potential for conflicts of interest and may lead to biased generation or assessment of evidence and to misinformed health-care policies. WHO has stringent policies for avoiding, or at least limiting, conflict of interest, particularly in the development of official guidance documents that affect health care. As declaration of conflict of interests is insufficient to neutralize potentially harmful effects, the Organization has accurate mechanisms for identifying relevant conflicts of interest and approaches for managing such conflicts (e.g. exclusion of members, recusal from participation in meeting sessions, restricting participation), thus ensuring the validity and transparency of the decision-making process and the credibility of the Expert Committee's decisions.

In reviewing and assessing the declarations of interest of the Members of the 20th Expert Committee on the Selection and Use of Essential Medicines, the WHO Essential Medicines and Health Products department sought the advice of the Office of Compliance, Risk Management and Ethics. The following conclusions were reached.

Financial and intellectual conflicts of interest

All Members and Temporary Advisers of the 20th Expert Committee on the Selection and Use of Essential Medicines submitted written disclosures of competing interests that may cause a conflict of interest when making decisions related to the Essential Medicines List. These included employment by a commercial entity, consultancy, board or advisory board membership, lecture fees, expert witness income, industry-sponsored grants including contracted research, patents received or pending, royalties, stock ownership or options, other personal financial interests; whether the institution or employer has a financial relationship with a commercial entity that has an interest in medicines evaluated by the Expert Committee. Committee Members and Temporary Advisers were also asked to disclose academic or scientific activities that created the potential for an attachment to a specific point of view that could unduly affect an individual's judgement about a specific decision. These included authorship of original studies or grant applications, directly bearing on a decision about a medicine.

Members who did not declare financial conflicts of interests above the acceptable WHO monetary threshold were: Hany Abdel-Aleem Aly, Gitanjali Batmanabane, Lisa Bero, Vittorio Bertelé, Franco Cavalli, Graham Cooke, Margareth Dalcolmo, Paul Garner, Mohammed Hassar, Kalle Hoppu, Youping Li, Michael Link, Thamizhanban Pillay, Shalini Sri Ranaganathan, Robyn Ward, Carla Coffin, Robert Mvungi, Francis Ofei and Edith Okeke.

Members who did not declare any relevant intellectual conflict of interests were: Hany Abdel-Aleem Aly, Gitanjali Batamanabane, Lisa Bero, Vittorio Bertelé, Franco Cavalli,

Graham Cooke, Margareth Dalcolmo, Paul Garner, Mohammed Hassar, Kalle Hoppu, Youping Li, Michael Link, Thamizhanban Pillay, Shalini Sri Ranaganathan, Robyn Ward, Carla Coffin, Robert Mvungi, Francis Ofei, and Edith Okeke. Several Expert Committee Members and Temporary Advisers had participated in previous guideline panels, other expert committees, narrative or systematic reviews that provided reviews or recommendations about a medicine under evaluation.

Vittorio Bertelé declared that he had co-authored a Cochrane systematic review about the safety of ranibizumab and bevacizumab for neovascular macular degeneration. The systematic review pooled together the results of all previous randomized controlled trials (RCTs) that compared bevacizumab and ranibizumab. All RCTs and the systematic review had been funded through public money (non-industry-sponsored). This was not considered a conflict of interest with respect to the evaluation of ranibizumab. Lorenzo Moja, now a WHO staff member, was the first author on this systematic review.

Lisa Bero declared that she co-authored an editorial accompanying the above-mentioned Cochrane systematic review in collaboration with Nicola Magrini, now a WHO staff member and Secretary of the Expert Committee. This was not considered a conflict of interest with respect to the evaluation of ranibizumab.

All the above-mentioned disclosures were considered to not reach the statutorily-set thresholds for direct intellectual conflicts of interests or material effect. It was determined that all Expert Committee Members and Temporary Advisers should have the opportunity to engage in the discussion on the evaluation of all medicines.

Expert Committee Members were apprised of the declarations of interests of all other participants.

Declarations of interest of each Expert Committee Member and Temporary Adviser, along with decisions and reasons why a participant might be excluded from a topic discussion, were acknowledged and fully disclosed before the deliberations of the Expert Committee meeting began.

No additional conflicts were declared at the meeting.

None of the Expert Committee Members and Temporary Advisers reported having been approached by any of the applicants.

Declarations of interest for the WHO Secretariat

Declarations of interest of the WHO Secretariat of the Essential Medicines List were also reviewed (although this was not mandatory) and guidance was sought from the Office of Compliance, Risk Management and Ethics with respect to potential conflicts.

Bernadette Cappello, Suzanne Hill, Nicola Magrini, Lorenzo Moja and Jane Robertson had no financial or relevant intellectual conflicts of interest. Lorenzo Moja had authored several systematic reviews and meta-analyses about medicines under evaluation (ranibizumab, trastuzumab, anti-thrombotic agents). Nicola Magrini had authored an

editorial accompanying the above-mentioned Cochrane systematic review and was also called to testify by the Italian Antitrust Authority in a case against Roche and Novartis for anticompetitive activities in respect of one medicine (ranibizumab) under evaluation. In this respect, it is noted that Nicola Magrini had conducted detailed discussions with the Office of Compliance, Risk Management and Ethics on this matter and, while it was determined that he did not have any direct conflict of interest with respect to the evaluation of ranibizumab, he was advised he might consider, of his own volition, recusing himself from this part of the evaluation in order to avoid a perceived conflict of interest. Nicola Magrini did decide to recuse himself from participating in the discussions and formulation of the recommendation on ranibizumab.

1. Introduction

The 20th meeting of the World Health Organization (WHO) Expert Committee on the Selection and Use of Essential Medicines was held from 20 to 24 April 2015, in Geneva, Switzerland.

The meeting was opened on behalf of the Director-General of WHO by Kees de Joncheere, Director, Essential Medicines and Health Products, Health Systems and Innovation. Mr de Joncheere welcomed all participants and explained that the purpose of the meeting was to consider applications received requesting addition, deletion, amendment and review of medicines with a view to updating the 19th Model List of Essential Medicines and the 5th Model List of Essential Medicines for Children. The applications received included, but were not limited to, an extensive review of antineoplastic medicines for the treatment of specific cancers, applications for inclusion of direct-acting antiviral agents for the treatment of hepatitis C virus infection, and applications for inclusion of new medicines for the treatment of multidrug-resistant tuberculosis.

Mr de Joncheere thanked Committee Members and Temporary Advisers for their preparation for and participation in the meeting, and reminded them that they were expected to provide advice to WHO in their individual capacities as experts and not as representatives of their governments of organizations. He reminded Committee Members and Temporary Advisers of their responsibility to prepare and approve a report of the meeting.

2. Open session

The open session of the meeting was chaired by Mr Kees de Joncheere, Director, Essential Medicines and Health Products, on behalf of the Director-General, and was attended by a variety of interested parties, including representatives of nongovernmental organizations and of WHO Member States.

Dr Gilles Forte, Coordinator, Medicines Policy, Access and Use (PAU), welcomed participants and provided an update on recent, current and upcoming activities relating to the EML. He highlighted some of the progress made and strategies employed since the previous Expert Committee meeting to improve the quality of applications and the relevance of the EML and to reposition the EML, i.e. to improve aspects of the listing process to ensure that the EML is complete and more relevant to countries' public health needs and to explore and emphasize roles that the EML could play in improving global access to and selection and use of medicines.

The Secretary of the Expert Committee, Dr Nicola Magrini, provided background and described processes and methodology for Expert Committee decision-making. He identified the Committee's main criteria for inclusion of medicines on the EML as public health relevance, the magnitude of clinical benefit and a favourable risk–benefit profile, determined through systematic evidence synthesis and appraisal. However, decision-making must also be influenced by considerations of costs and budget impact, the feasibility of its use in various clinical settings, and the need for monitoring. Dr Magrini drew attention to the issue of enabling access to cost-effective, yet potentially unaffordable, therapies, which would require particular consideration by the Expert Committee and innovative and better-coordinated actions at a global level.

Dr Suzanne Hill, PAU Senior Adviser, spoke about the issue of high medicine prices and the need for precision in the language used when discussing price versus cost. With regard to listing of these medicines on the EML and other national lists for procurement/reimbursement, careful consideration was needed both of the limitations of cost–effectiveness assessments as a basis for decision-making and of opportunity costs and affordability issues during the actual decision-making process.

Presentations and/or statements of relevance to the agenda of the Expert Committee were made by the following participants:

- Mr Murray L. Aitken, IMS Institute for Healthcare Informatics, Danbury, CT, USA
- Mr Thirukumaran Balasuramanian, Knowledge Ecology International, Geneva, Switzerland
- Ms Julie Torode, Union for International Cancer Control, Geneva, Switzerland

- Dr Manica Balasegaram, Médecins Sans Frontières, Paris, France
- Ms Melissa Barber, Youth Commission on Essential Medicines Policies.

Copies of the presentations and statements are available on the WHO website at http://www.who.int/selection_medicines/committees/expert/20/en/.

3. General items

3.1 High-priced medicines

At this meeting the Expert Committee considered a number of applications for medicines that are currently very highly priced. Examples are the direct-acting antivirals for hepatitis C, some of the medicines proposed for management of cancer, the novel oral anticoagulants (NOACs) and some of the medicines for tuberculosis (TB).

While noting that high price is not necessarily a barrier to inclusion of a medicine on the Essential Medicines List, the Committee discussed the following matters in relation to consideration of high-priced medicines in general.

Firstly, it is important to distinguish between high-priced medicines and high-cost medicines. "Cost" in this context refers to the production or manufacturing cost of the medicines, whereas "price" is the amount paid by the purchaser, whether a patient, an insurance or a government. Prices can be subject to negotiation and controls. Countries considering whether to make high-priced medicines available may need to manage expenditure by adopting price control policies, which may include generic substitution; controls on the ex-manufacturer price charged; controls on supply chain mark-ups; and price-setting, using internal or external reference pricing, or cost–effectiveness evaluation to set affordable ceiling prices.

The Committee noted that health technology assessment and cost–effectiveness analysis are associated with a number of technical and process issues that will have resource implications for countries; this has been addressed in the World Health Assembly resolution on health intervention and technology assessment (WHA76.23). These issues include the capacity required to conduct independent economic evaluations of pharmaceuticals and medical technologies, how to structure the process of assessment, how to make it transparent, and considering whether or not to set an explicit "threshold'" value for incremental effectiveness for clinically meaningful differences. A global threshold value for a decision-maker's willingness to pay for a unit of a health effect is an unresolved issue.

In the case of the cancer medicines, the Committee noted that countries would have to consider many of these policy options to manage the likely increase in total cost to the health system. The current prices of some of the monoclonal antibodies, for example, increase the cost of a basic cancer treatment regimen by a factor of at least 10. As biosimilars are developed, prices are expected to fall, as has been the experience with the prices of small-molecule drugs with the growing availability of generics. However, the extent to which the prices of biosimilars might fall is not yet fully known: anecdotal data from some European countries suggest a reduction in price of around 70%.

For small molecule drugs for cancer treatment, such as imatinib, the cost of production has been estimated, generics are now available in some settings, and price reductions of the order of 90% are considered possible (*1*).

The Committee also noted, however, that in settings where tight controls on supply chain mark-ups are implemented, there have been instances of shortages of the older, less expensive cancer medicines because of preferential supplying or prescribing of high-priced products (*2*). Strategies to ensure supply of essential medicines such as methotrexate for cancer or the penicillins for bacterial infections need to be developed at the global level.

Other policy options, such as risk-share agreements, or paying for an agreed episode of care, have been adopted in many high-income countries (*3*, *4*). The impact that these agreements have on total expenditure on the medicine, or on use, is still to be determined, and the feasibility of these arrangements in low- and middle-income countries has not been evaluated. These types of contractual arrangement usually require accurate utilization data for each medicine, either through claims databases or other mechanisms, as the basis for agreed payments to suppliers.

Where the total cost of a new medicine is high, countries will need to consider the affordability for the health system as a whole. There is an "opportunity cost" of investing in some of these medicines: expenditure may lead to a reduction in the funds available for other interventions. For example, the prices of novel oral anticoagulants (NOACs) in most countries are still several times higher than those of older oral anticoagulants such as warfarin, even taking into account of the cost of monitoring warfarin dose and response (*5*). Despite some cost–effectiveness analyses suggesting that the NOACs are "cost–effective" (*5*), replacing warfarin with an NOAC will require significant investment of a country's health-care funds, which might be better spent on alternative treatments for other diseases or health-care facilities. In making judgments regarding health-system expenditure on high-price medicines, countries will therefore need to have methods in place for estimating likely utilization of new medicines and for monitoring their use in practice.

Alternative policy approaches, such as voluntary or compulsory licenses, or government use, may be considered. Voluntary licenses have increased the availability of generic versions of several HIV treatments and are starting to be used for the new hepatitis C treatments. A number of countries have gained experience of implementing compulsory licenses for both HIV and cancer treatments. Requirements include an appropriate national legislative framework and availability of a local or foreign manufacturer that can supply a good quality generic product, as well as the political will to implement a compulsory licence. Some countries have tightened up the criteria for granting pharmaceutical patents as an alternative approach to promoting competition and improving access.

Pooled procurement and bulk purchasing can reduce prices if properly implemented. The Expert Committee noted two current examples of country groupings that are using this strategy: the Strategic Fund for Pan American Health Organization (PAHO), supporting some Latin American countries in purchasing high-price medicines, and the Nordic countries, which are discussing the options for bulk procurement. The role of tendering, including through international agencies, could be explored.

Finally, it was the view of the Expert Committee that a more global approach to dealing with high-priced medicines is needed, particularly those medicines that meet high public health need, such as the new treatments for hepatitis C. Both the development costs and the production costs of these medicines have been described (*6*, *7*). There is significant international concern about the difference (*8*, *9*) and the resulting profit margins for the manufacturers (*10*). The tiered pricing approach proposed still results in unaffordable opportunity cost in most countries, whether high- or low-income. The Committee noted that the prices are likely to be major barriers to access to these medicines.

In summary, at its meeting in April 2015, the 20th WHO Expert Committee approved inclusion of several new medicines on the EML in spite of their high price. These decisions were made on the basis of the public health need and evidence that the medicines are both highly effective and safe. It is expected that their addition to the EML will support efforts to reduce the prices. However, the Committee recognized that merely adding these medicines to the List may not be sufficient to achieve the price reductions that are needed and therefore recommended that WHO collaborate with countries in taking measures to ensure that this objective is achieved. Such measures include (but are not being limited to) the following:

- leading discussion on high-priced medicines from the perspective of public health;
- facilitating research on the effectiveness of implementation of policies on medicine prices, including pricing and intellectual property considerations, opportunity costs and access to medicines;
- updating the WHO guideline on pricing policies;
- gathering data on country experience with different price-setting mechanisms for medicines, including the use of cost–effectiveness thresholds;
- collecting country-level data on use of the medicines added to the list; and
- working with countries to develop strategies and capacity to manage high-price medicines and increase access to them.

3.2 Note on evaluation of "off-label" medicines

The Expert Committee noted that several medicines that it considered were evaluated for indications described as "off-label". With respect to this issue, the Committee noted that:

- "Label" is a national regulatory authority responsibility and there may consequently be many different labels for the same product in different countries. There is thus no global standard for what is "off-label".
- Updating the approved labels for old products is a commercial decision in each national jurisdiction and there are many examples of old products whose labels are inconsistent with current clinical evidence and thus with clinical practice.

In making its decisions, the Expert Committee therefore evaluated the current clinical evidence for products that were submitted; national labelling decisions were not considered.

3.3 Structure and function of the EML Committee and application process

The Expert Committee meets for five days every two years to review applications for the EMLs. The Committee notes that the number of applications has been increasing steadily. Misalignment between timing of receipt of applications for Expert Committee consideration and planned update or development of WHO guidelines is also an issue for further consideration. The Committee therefore recommended that WHO explore options for changing the timing or structure of Expert Committee meetings. These options could include:

- accepting applications on a rolling basis and having applications reviewed by working groups, with specific terms of reference;
- having working groups of the Expert Committee to regularly and comprehensively review chapters of the Lists;
- meeting more frequently and/or using technology to facilitate decisions;
- improved presentation of available evidence also using new technologies, and more active dissemination of the list, in a more usable format.

The Committee noted that, although WHO has introduced requirements for applications to the EML, the content and quality of the applications vary.

The Committee encouraged WHO to accept only applications that are complete and of an appropriate standard for the Committee to review.

3.4 Essential Medicines List for children

The Committee noted that, in the previous two meetings, it has proved increasingly challenging to effectively assist WHO in fulfilling the main requirements of World Health Assembly Resolution 60.20 "Better Medicines for Children". The revision and updating of the Model List of Essential Medicines requires evaluation and inclusion of medicines that are essential for the treatment of children. However, not all applications received contained a proposal to add a medicine to the EMLc, even though the medicine was relevant for children. In addition, applications proposing addition to both EML and EMLc submitted little or no evaluable paediatric data, even when such data existed.

As was noted by the WHO Secretariat in the proposal for establishment of the paediatric subcommittee in 2007, reviewing applications for essential medicines for children requires skills and technical expertise additional to those needed for a review of adult medicines. Such review needs to take account not only of paediatric clinical medicines but also of factors such as the different pharmacokinetics and pharmacodynamics (including adverse effect profiles) of medicines in children of different ages. When data are not available from paediatric clinical trials, there is still an imperative to make decisions based on the available information, as it is unethical to deprive children of access to necessary treatment.

The Expert Committee found that the review of the applications for medicines for children was particularly challenging. The application form and review template do not currently include specific items relevant to medicines for children.

In addition to the points noted above about applications in general, the Expert Committee therefore recommended that WHO:

- make consideration of paediatric needs and relevant data obligatory for all medicines proposed;
- work with relevant nongovernmental organizations to ensure support to applicants for the paediatric aspects of their applications;
- in the light of the proposal for standing working groups, establish a paediatric medicines working group with relevant expertise to ensure high-quality expert reviews of proposals for the EMLc, thereby enabling development of an EMLc that will meet the needs of the world's children.

4. Summary of recommendations

Additions to Model Lists

Section 5: Midazolam ampoule for buccal administration, and midazolam solution for oromucosal administration were added to the core list of the EML and EMLc for emergency management of convulsive seizures when an intravenous line is not available. Sodium valproate IV injection was added to the complementary list of the EML and EMLc for use in established status epilepticus.

Section 6.2.4: Rifapentine was added to the core list of the EML and EMLc for the treatment of latent tuberculosis infection. Bedaquiline, delamanid and linezolid were added to the complementary list of the EML for the treatment of multi-drug resistant tuberculosis (MDR-TB). Terizidone was added to the complementary list of the EML as an alternative to cycloserine. Linezolid was also added to the complementary list of the EMLc for treatment of MDR-TB.

Section 6.4.2: Abacavir + lamivudine fixed-dose combination was added to the core list of the EML and EMLc for treatment of HIV in children aged 6 weeks or more.

Section 6.4.2.3: Darunavir was added to the core list of the EML and EMLc for treatment of HIV, to be used as an alternative to other listed ritonavir-boosted protease inhibitors.

Section 6.4.3: Valganciclovir was added to the core list of the EML and the complementary list of the EMLc for the treatment of cytomegalovirus retinitis.

Section 6.4.4 (new section): A new section (with subsections), Antihepatitis medicines, was created. Entecavir and tenofovir disoproxil fumarate were added to the core list of the EML under subsection 6.4.4.1, Medicines for hepatitis B, for the treatment of chronic hepatitis B infection. Entecavir was also added to the core list of the EMLc for this indication. Daclatasvir, simeprevir, sofosbuvir, dasabuvir, and the fixed-dose combinations of ledipasvir + sofosbuvir and ombitasvir + paritaprevir + ritonavir were added to the core list of the EML by pharmacological classes under subsection 6.4.4.2 for the treatment of chronic hepatitis C infection.

Sections 8.2 and 8.3: The following medicines for the treatment of various cancers were added to the complementary list of the EML: all-trans retinoic acid (ATRA), bendamustine, capecitabine, cisplatin, fludarabine, filgrastim, gemcitabine, imatinib, irinotecan, oxaliplatin, rituximab, trastuzumab, vinorelbine (Section 8.2); anastrozole, bicalutamide and leuprorelin (Section 8.3).

The following medicines for the treatment of various paediatric cancers were added to the complementary list of the EMLc: bleomycin, calcium folinate, carboplatin, cisplatin, dacarbazine, etoposide, filgrastim, ifosfamide, paclitaxel and vinblastine.

A further 30 medicines currently listed on the EML and 16 listed on the EMLc were endorsed as part of proven clinically effective treatment regimens for specific cancers.

Section 10.1: An additional strength of folic acid tablets (400 µg) was added to the core list of the EML for periconceptional use in women of childbearing age for the prevention of first occurrence of neural tube defects (NTDs). The Expert Committee considered use of periconceptional daily supplementation with folic acid in women of childbearing age was an effective and clinically important public health intervention.

Section 10.2: Desmopressin was added to the complementary list of the EML and EMLc for the treatment of select patients with type I von Willebrand disease, haemophilia A and other rare bleeding disorders taking into consideration the ease of administration (particularly the intranasal formulation), the low cost and the potential for avoidance of blood derivatives.

Enoxaparin was added to the core list of the EML as the representative of the pharmacological class of low-molecular-weight heparins (with alternatives limited to nadroparin and dalteparin) for prophylaxis and treatment of venous thromboembolism, and in the treatment of acute coronary syndromes. Evidence presented showed low-molecular-weight heparins to be safe and effective, more convenient to use than IV heparin and without the requirement for routine monitoring.

Section 12.5: Clopidogrel was added to the core list of the EML for use in addition to aspirin for the treatment of acute coronary syndromes and for ischaemic heart disease following percutaneous coronary intervention.

Section 15.2: Alcohol-based hand rub was added to the core list of the EML and EMLc because of the public health need and the potential to promote its availability globally.

Section 18: Three new contraceptive medicines were added to the core list of the EML: levonorgestrel-releasing intrauterine system (18.3.3), etonogestrel implant (18.3.5) and progesterone vaginal ring (in a new subsection, 18.3.6, Intravaginal contraceptives).

Section 22.1: The indications for misoprostol on the EML were extended to include treatment of postpartum haemorrhage (PPH) in circumstances where

oxytocin is not available or cannot be safely used, on the basis of data identified during the evaluation process that supported the use of misoprostol as a treatment option for PPH.

Deletions from Model Lists

Section 6.4.2: Formulations and strengths of the following antiretroviral medicines were deleted from the EML: didanosine, emtricitabine, efavirenz, nevirapine, indinavir, lopinavir + ritonavir, ritonavir and lamivudine + nevirapine + stavudine. Formulations and strengths of the following antiretroviral medicines were deleted from the EMLc: didanosine, emtricitabine, zidovudine, efavirenz, atazanavir, lopinavir + ritonavir, saquinavir, lamivudine + nevirapine + stavudine, lamivudine + nevirapine + zidovudine and lamivudine + zidovudine.

Changes to sections

Section 11.2.1: The Expert Committee recommended that immunoglobulins of human origin currently listed in Section 19.2, Sera and immunoglobulins, of the EML and EMLc should be relocated to Section 11.2.1, Human immunoglobulins.

Section 19.3: The vaccine section was amended in the EML and EMLc to include those vaccines for which a WHO position paper exists, with reference to the WHO immunization website for up-to-date recommendations at any point in time. It was also agreed by the Committee that the EMLs should identify those vaccines for which conditional use (e.g. only in certain regions or populations, or in other specified circumstances) is recommended, with reference to relevant WHO vaccine position papers for detail.

Amended dosage strength and form

Section 5: Amendments to the description of dosage and strength of magnesium sulfate injection on the EML were recommended to provide greater clarity for providers.

Section 6.4.2.2: New dose forms of efavirenz and nevirapine were added to the core list of the EML and EMLc for the treatment of children with HIV-1 infection. The scored and dispersible tablet formulations were considered to be likely to aid compliance and paediatric dosing.

Section 17.1: A parenteral formulation of omeprazole for IV administration was added to the core list of the EML for the treatment of adults with suspected peptic ulcer bleeding for whom endoscopy is unavailable or is expected to be delayed, and for patients with confirmed peptic ulcer bleeding with high risk for

detrimental outcomes, regardless of the application of endoscopic haemostatic techniques. The Expert Committee considered that it was appropriate for parenteral omeprazole to be listed with the square box symbol, indicative of similar within-class performance of proton-pump inhibitors and for consistency with the listed omeprazole oral dose forms.

Reinstatement

Section 12.3: Based on the evidence presented, the Expert Committee recommended that atenolol should be included on the EML as an alternative beta-blocker (to bisoprolol, metoprolol and carvedilol) for use in hypertension, with a note to state that it should not be used as first-line treatment for uncomplicated hypertension in patients aged over 60 years.

Rejected applications

Section 2.2: The application to amend the listing for morphine to allow alternative opioids to hydromorphone and oxycodone was rejected because no new evidence was presented to support the inclusion of additional opioids as alternatives to morphine on the EML and EMLc. No changes were made to the current morphine listing.

Section 6.3: The application for the addition of itraconazole to the EML and EMLc was rejected because itraconazole, while of similar efficacy to fluconazole for many indications, has been shown to be inferior to other antifungal agents in other settings.

Section 6.4.2: Applications for addition to the EML of fixed-dose combinations of cobicistat + elvitegravir + emtricitabine + tenofovir and emtricitabine + rilpivirine + tenofovir were rejected because there was insufficient evidence of a relevant clinical advantage in terms of efficacy of these combinations over currently recommended first-line treatments for HIV infection available on the EML.

Section 8.1: The application to extend the listing on the EML for azathioprine to include the additional indication of multiple sclerosis was rejected. Instead, the Expert Committee recommended a comprehensive review be undertaken of all medicines used for the management of multiple sclerosis, given the public health importance of the condition.

Section 9: The application for addition of dopamine agonists to the EML was rejected on the basis that there was insufficient evidence to show that the medicines offered any efficacy or safety advantages over the existing antiparkinsonism medicines included in the EML.

Section 10.1: The application to list a new formulation and strength of ferrous salt + folic acid on the core list of the EML for use in menstruating women and adolescent girls was rejected as the evidence presented for efficacy of intermittent supplementation was insufficient to support a recommendation for listing.

Section 10.2: The application for addition of novel oral anticoagulants (dabigatran, rivaroxaban and apixaban) to the EML was rejected on the basis that, overall, there was no relevant clinical advantage of these anticoagulants over warfarin in patients established and stable within the therapeutic range with warfarin therapy. The Expert Committee also noted that, unlike bleeds related to warfarin, there are currently no specific antidotes for reversing the effects of the novel oral anticoagulants in case of emergencies.

Section 11.2.3 (proposed new section): The application for addition of plasma-derived C1-esterase inhibitor to the EML and EMLc for the treatment of hereditary angioedema was rejected as the Expert Committee considered that the public health relevance required for inclusion of an essential medicine was unclear given the rarity of the condition.

Section 12.7 (proposed new section): Based on the evidence presented in the application for various fixed-dose combinations of cardiovascular medicines for the secondary prevention of cardiovascular disease, the Expert Committee did not recommend addition of any of the proposed "polypill" preparations to the EML. The Committee was concerned about the lack of evidence on clinical outcomes and the higher rates of adverse events and discontinuations reported. The Committee also had reservations related to the difficulty of titrating the doses and/or cessation of the individual ingredients.

Section 14.2: The two applications for addition to the EML and EMLc of gadolinium-based radiocontrast media for use with MRI were rejected. The Expert Committee concluded that the applications did not provide adequate evidence linking improved diagnostic efficacy with improvements in patient management and clinical benefits for the indications described. The Committee considered whether these medicines actually met the definition of an essential medicine in terms of public health need. In addition, there were safety concerns.

Section 21.6: The application for the addition of ranibizumab to the EML for the treatment of neovascular eye diseases was rejected. While recognizing the importance of effective management strategies for these conditions, and the fact that ranibizumab is registered in many countries for these conditions while bevacizumab (currently listed on the EML) is used off-label, the overall evidence showed similar effectiveness between the two medicines, and bevacizumab is the preferred option in terms of cost–effectiveness.

Section 22.1: The application for deletion of misoprostol for prevention of postpartum haemorrhage was rejected as no new trials were presented comparing the use of misoprostol and oxytocin for this indication. The Expert Committee concluded that the existing listing for misoprostol for the prevention of PPH on the EML should remain unchanged.

A summary of the medicines and formulations added to and deleted from the Model Lists is presented in Table 1.

Table 1
Summary of changes to the EML and EMLc

EML	
New medicine added	**Indication**
Alcohol-based hand rub	Hand hygiene
All-trans retinoic acid	Cancer
Anastrozole	Cancer
Bedaquiline	MDR-TB
Bendamustine	Cancer
Bicalutamide	Cancer
Capecitabine	Cancer
Cisplatin	Cancer
Clopidogrel	ACS
Daclatasvir	Chronic hepatitis C
Darunavir	HIV
Dasabuvir	Chronic hepatitis C
Delamanid	MDR-TB
Desmopressin	Bleeding disorders
Entecavir	Hepatitis B
Enoxaparin	VTE and ACS
Etonogestrel implant	Contraception
Filgrastim	Cancer
Fludarabine	Cancer

Table 1 *continued*

EML	
New medicine added	**Indication**
Gemcitabine	Cancer
Imatinib	Cancer
Irinotecan	Cancer
Ledipasvir+sofosbuvir	Chronic hepatitis C
Leuprorelin	Cancer
Linezolid	MDR-TB
Ombitasvir+paritaprevir+ritonavir	Chronic hepatitis C
Oxaliplatin	Cancer
Progesterone vaginal ring	Contraception
Rifapentine	LTBI
Rituximab	Cancer
Simeprevir	Chronic hepatitis C
Sofosbuvir	Chronic hepatitis C
Terizidone	MDR-TB
Trastuzumab	Cancer
Valganciclovir	CMV retinitis
Vinorelbine	Cancer
EMLc	
New medicine added	**Indication**
Alcohol-based hand rub	Hand hygiene
Bleomycin	Cancer
Calcium folinate	Cancer
Carboplatin	Cancer
Cisplatin	Cancer
Dacarbazine	Cancer
Darunavir	HIV
Desmopressin	Bleeding disorders

Table 1 *continued*

EMLc	
New medicine added	**Indication**
Entecavir	Hepatitis B
Etoposide	Cancer
Filgrastim	Cancer
Ifosfamide	Cancer
Paclitaxel	Cancer
Rifapentine	LTBI
Valganciclovir	CMV retinitis
Vinblastine	Cancer
New indications for medicines on the EML	
Medicine	**Indication**
Misoprostol	Treatment of PPH
Tenofovir disoproxil fumarate	Hepatitis B
New formulations added to the EML	
Medicine	**Indication**
Abacavir+lamivudine	FDC tablet
Efavirenz	Scored tablet 200 mg
Folic acid	400 mcg tablet
Levonorgestrel	Intrauterine system
Midazolam	Oromucosal solution
Nevirapine	Dispersible tablet
Omeprazole	Powder for injection
Valproic acid	Injection
New formulations added to the EMLc	
Medicine	**Indication**
Abacavir+lamivudine	FDC tablet
Efavirenz	Scored tablet 200 mg
Midazolam	Oromucosal solution

Table 1 *continued*

New formulations added to the EMLc	
Medicine	**Indication**
Nevirapine	Dispersible tablet 50 mg
Valproic acid	Injection
Medicines / formulations deleted from the EML & EMLc	
Refer to Table 3, pages 43–44.	

Abbreviations: ACS – acute coronary syndrome; CMV – cytomegalovirus; FDC – fixed-dose combination; LTBI – latent tuberculosis infection; MDR-TB – multi-drug resistant tuberculosis; PPH – postpartum haemorrhage; VTE – venous thromboembolism

5. Applications for the 19th Model List of Essential Medicines and the 5th Model List of Essential Medicines for Children

Section 2: Medicines for pain and palliative care

2.2: Opioid analgesics

Morphine – (hydromorphone and oxycodone) (Review) – EML and EMLc

An application was submitted by Dr Willem Scholten (until October 2012, team leader, Access to Controlled Medicines, WHO), requesting modification of the wording of the EML and EMLc listings for certain opioid analgesics – morphine, hydromorphone and oxycodone.

Expert reviews of the application were prepared by two members of the Expert Committee. No public comments on the application were received.

In applications to the 19th Expert Committee in 2013, Dr Scholten proposed the addition of hydromorphone and oxycodone as examples of the opioid class, requesting that this be expressed in the Model Lists with a footnote to the square box listing of morphine stating "two or more alternatives to morphine should be available". Following consideration of these applications, the 19th Expert Committee recommended the addition of a square box symbol to the listings for morphine, with a note that alternatives be limited to hydromorphone and oxycodone. The rationale for this recommendation is documented in the report of the 2013 Expert Committee meeting (*11*).

The current application provided copies of the 2013 applications for hydromorphone and oxycodone, which had not named any alternative opioids or provided any new data to support the request to modify the wording of the current listing. The Committee noted that the proposed modification to the current wording would, in effect, allow any opioid to be available as an alternative to morphine on the WHO Model Lists and, if adopted by countries, on national lists.

The Committee considered that, within the same pharmacological class, individual opioids can differ considerably in terms of characteristics that include (but are not limited to) pharmacology, potency, formulation, and suitability for paediatric use. The Committee considered that all opioids could not be thought of as simply interchangeable within class. The Committee advised that changing the current listing to allow additional alternatives to morphine would require submission of appropriate data demonstrating similar clinical performance. In the absence of any new evidence to support the inclusion of additional opioids as alternatives to morphine on the EML and EMLc, the Committee did not recommend any changes to the listing for morphine (and, by extension, hydromorphone and oxycodone) at this time.

Section 5: Anticonvulsants/antiepileptics

Magnesium sulfate (review) – EML

An application was submitted by the Availability of Quality Maternal Health Products (AQMHP) Working Group, Maternal Health Technical Resources Team, UN Commission on Life Saving Commodities for Women and Children, requesting a revision of the language used to describe magnesium sulfate on the EML.

An expert review of the application was prepared by one member of the Expert Committee. No public comments on the application were received.

Magnesium sulfate is currently included on the 18th Model List as: *Injection: 500 mg/ml in 2-ml ampoule; 500 mg/ml in 10-ml ampoule*. The application proposed revising the description of the listed formulations to include additional information as follows: *Injection: 0.5 g/ml in 2-ml ampoule (1 g in 2 ml; 50% w/v); 0.5 g/ml in 10-ml ampoule (5 g in 10 ml; 50% w/v)*. No other changes were requested.

The rationale given for the suggested changes was that, in many international and national clinical guidelines, the concentration of magnesium sulfate solutions required for treatment is specified as a percentage. It is claimed that some providers have difficulty understanding how much magnesium sulfate this represents in a specific volume of water and there is concern that this confusion may lead to dosing errors, especially in emergency situations. It was asserted in the application that the proposed additional information in the magnesium sulfate entry in the EML will provide improved clarity and understanding in relation to the contents of magnesium ampoules produced commercially.

The Expert Committee noted that dosing schedules in WHO's *Managing complications of pregnancy and childbirth: a guide for midwives and doctors* (*12*) include the recommended dose of magnesium sulfate both in grams (g) and as a percentage strength of magnesium sulfate solution.

The Expert Committee also noted that WHO guidelines recommend magnesium sulfate for the prevention of eclampsia in women with severe pre-eclampsia and for treatment of women with eclampsia, in preference to other anticonvulsants (*13*). Magnesium sulfate has been included on the EML for use in eclampsia and severe pre-eclampsia since 1995.

The Expert Committee considered that the requested amendments to the description of magnesium sulfate on the EML were reasonable and may serve to provide greater clarity for providers. The Committee considered further clarity could be achieved with the addition of the words "equivalent to" and by disambiguation of "w/v" to "weight/volume" and therefore recommended that the listing for magnesium sulfate be amended to read as follows:

magnesium sulfate*	**Injection:** 0.5 g/mL in 2-mL ampoule (*equivalent to* 1 g in 2 mL; 50% weight/volume); 0.5 g/mL in 10 mL ampoule (*equivalent to* 5 g in 10 mL; 50% weight/volume) * For use in eclampsia and severe pre-eclampsia and not for other convulsant disorders.

Midazolam (new indication) – EML and EMLc

An application was submitted by Drs Satinder Aneja and Suvasini Sharma, Department of Pediatrics, Lady Hardinge Medical College and Kalawati Saran Children's Hospital, New Delhi, for the inclusion of parenteral midazolam on the EML for buccal administration for the treatment of acute repetitive convulsive seizures and of prolonged convulsive seizures, including status epilepticus, in adults and children when intravenous access is unavailable. The EML already contains intravenous and oral preparations of midazolam as a preoperative/sedative medication and as a medicine for use in palliative care.

Expert reviews of the application were prepared by two members of the Expert Committee. Comments on the application were received from Dr Myriam Henkens, International Medical Coordinator, Médecins Sans Frontières.

The Expert Committee noted that correspondence received from the WHO Department of Mental Health and Substance Abuse advised that WHO has included a scoping question on use of buccal midazolam in its latest revision of Emergency Triage Assessment and Treatment (ETAT) guidelines and Mental Health Gap Action Programme (mhGAP) for children and adults respectively. The Guideline Development Group, on review of synthesised evidence following GRADE methodology, has suggested a strong recommendation for use of buccal midazolam. Both sets of guidelines are being finalized for submission to WHO Guidelines Review Committee GRC for approval.

The incidence of acute symptomatic seizures (isolated or recurrent) is 29–39 per 100 000 per year (*14*). The median pooled incidence of epilepsy from published studies is 45.0 (interquartile range (IQR) 30.3–66.7) per 100 000 per year for high-income countries and 81.7 (IQR 28.0–239.5) for low- and middle-income countries (*15*). Acute symptomatic seizures are more common in the neonatal period than at any other time of life, particularly in premature infants. The second highest incidence and prevalence occur in patients over 65 years of age: reported incidence is 2–13 per 1000 individuals per year over 65 and may be higher as seizures in older patients are frequently underdiagnosed (*16–19*). Traumatic brain injury, cerebrovascular disease, drug withdrawal, infection and metabolic insults are the commonest causes.

Seizures are a common presentation in emergency room settings. Some 12–30% of adults with a new diagnosis of epilepsy present in status epilepticus, a potentially life-threatening condition (*20*). Treatment for acute convulsive seizures is aimed at halting seizures as rapidly as possible in order to prevent

progression to status epilepticus, cardiorespiratory compromise and cerebral damage. Absence of timely intervention may lead to a protracted seizure episode that is more difficult to control plus significant subsequent neurological morbidity and mortality.

Many drugs have been studied in the management of this condition. Intravenous lorazepam, diazepam or phenytoin is often used for immediate control of status epilepticus. Rectally administered diazepam gel is effective in controlling serially occurring seizures. Buccal midazolam, however, is more effective than rectal diazepam in control of both seizures and frequency of hospitalization or intensive care admissions for community, pre-hospital or ambulatory treatment when intravenous access is not immediately available (*21–23*). The number needed to treat (NNT) for achieving seizure cessation largely favours buccal midazolam (NNT = 4–6) (*23*). Moreover, buccal midazolam is significantly more acceptable than rectal diazepam to health professionals and patients (*24*, *25*). The superior efficacy of midazolam compared with diazepam probably reflects more favourable pharmacokinetics of midazolam and erratic absorption of rectal diazepam (*26*).

Evidence suggests that midazolam is as safe as diazepam with regard to respiratory complications, although small differences cannot be excluded. Only very limited differences in the number of patients who experience respiratory depression with rectal diazepam and buccal midazolam, requiring intubation and ventilation, have been reported (*21–25*, *27*).

Cost–effectiveness analyses showed that buccal midazolam use in the community setting is more cost–effective than rectal diazepam. It offers health-related benefits for patients and health-care systems, including health-related quality of life and reduced need for ambulance call-out and stays in hospital (*28*, *29*). According to the International Drug Price Indicator Guide 2013, the median price of midazolam 5 mg/mL is US$ 0.26/mL.

WHO's *Guidelines on the management of acute convulsive seizures in adults and children (when no intravenous access is available)* recommend administration of rectal diazepam for control of acute convulsive seizures (*30*). The evidence profiles include the comparative effectiveness of buccal midazolam, reporting the same efficacy and safety data cited in the sections above but underlining the fact that the buccal formulation is generally not readily available and is not licensed. Midazolam injection, however, is widely available and various human studies have used the intravenous preparation for buccal use. The onset of benzodiazepine effect is faster with IV injection; absorption of buccal midazolam requires more time. Treatment initiation time, however, is shorter with buccal midazolam: IV injection involves transfer of the solution into the syringe, starting an IV line, and pushing the drug slowly and carefully. In some cases establishing an IV line can be challenging, especially in infants and in the emergency management of convulsive seizures when an IV line is not available.

The EML already contains intravenous preparations of midazolam for preoperative/sedative medication and for use in palliative care. Buccal midazolam is suitable for administration by non-medical personnel. Although adverse effects may occur, including respiratory depression, the safety of buccal midazolam is adequate for use in community settings to control acute convulsions (generalized tonic, tonic–clonic and complex partial) within a short time, irrespective of their duration or their diverse etiology. Buccal midazolam is considered to be more acceptable, and is easier to administer, than rectal diazepam.

The Expert Committee acknowledged that:

- The fastest route for administering antiepileptic drugs is intravenously; however, peripheral venous access may be difficult to achieve in convulsing patients, especially children.
- The situation is made more difficult in pre-hospital settings and by resource constraints and a lack of trained personnel, resulting in the frequent first-line use of non-IV routes for administration of anticonvulsant medications in resource-limited settings.
- IV access is not possible in home settings when treatment is to be administered by parents/caregivers.
- Treatment for prolonged seizures usually involves giving one dose of diazepam gel into the rectum.

The Expert Committee decided that there is sufficient evidence to prioritize buccal midazolam (both the oromucosal solution and the parenteral formulation for buccal administration) as it is more effective and more acceptable than rectal diazepam, the most appropriate comparator included in the EML. The Expert Committee therefore recommended addition to the core list of the EML and EMLc of the oromucosal formulation of midazolam and also the parenteral formulation for buccal administration for the emergency management of convulsive seizures when an intravenous line is not available. It is expected that inclusion of buccal midazolam in the Model List will increase the availability of the commercial product for buccal administration.

Valproic acid (sodium valproate) (new formulation) – EML and EMLc

An application was submitted by Drs Satinder Aneja and Suvasini Sharma, Department of Pediatrics, Lady Hardinge Medical College and Kalawati Saran Children's Hospital, New Delhi, for the addition of an intravenous formulation of valproic acid (sodium valproate) to the complementary list of the EML and EMLc for the treatment of established status epilepticus in adults and children.

Expert reviews of the application were prepared by two members of the Expert Committee. Comments on the application were received from Dr Myriam Henkens, International Medical Coordinator, Médecins Sans Frontières.

Status epilepticus (SE) is considered as a medical emergency. Based on recent understanding of the pathophysiology, it is now considered that any seizure that lasts more than 5 minutes needs to be treated as SE (*31*). First-line treatment for SE is a benzodiazepine (lorazepam, diazepam, midazolam or clonazepam) given rectally, orally, IM or IV depending on the situation and the drug type (*20*). However, approximately one third of SE patients fail to respond to initial treatment with benzodiazepines and are considered to have established SE (ESE) (*32*).

Some 12–30% of adults with a new diagnosis of epilepsy present in SE (*20*). The annual incidence of SE in Europe is estimated at between 9.9 and 17.1 per 100 000 people, and in the United States at between 18.1 and 41 per 100 000 people (*33-36*). The incidence of SE varies with age, showing a bimodal distribution with peaks in early childhood and in elderly individuals (*35-37*). The condition is associated with an overall mortality of 8% in children and 30% in adults. An additional 5–10% of people suffering from SE have permanent sequelae, such as permanent vegetative state or cognitive difficulties (*20*). The standardized mortality ratio (SMR), the relative risk of mortality compared with the general population, for patients with long-term mortality associated with SE is 2.8 (95% CI: 2.1–3.5). In those aged more than 65 years SMR is 2.2 (95% CI: 1.6–2.9) and in those aged less than 65 years it is 5.1 (95% CI: 2.8–8.0) (*38*).

While benzodiazepines mainly potentiate GABA-induced chloride influx, sodium valproate is associated with multiple mechanisms of action: frequency-dependent prolongation of sodium channel inactivation, attenuation of calcium-mediated transient currents and augmentation of GABA (*39*). In addition, benzodiazepines have a relatively short duration of action. It is therefore proposed that for the maintenance of action, and thus the treatment of established SE, IV sodium valproate might be added to benzodiazepines.

Limited evidence is available to guide the treatment of benzodiazepine-refractory status epilepticus. Currently, the first phase III clinical trial of ESE, the Established Status Epilepticus Treatment Trial (ESETT) is being carried out in children and adults to determine which of fosphenytoin, levetiracetam and sodium valproate is the most effective in terminating ESE (*32*).

The following studies presented effectiveness and safety results of use of IV sodium valproate in the treatment of established SE:

- Yasiry & Shorvon, 2014 (*40*). Meta-analysis yielded a mean effect size for the efficacy of sodium valproate in benzodiazepine-resistant convulsive status epilepticus of 75.7% (95% CI: 63.7–84.8%). Efficacy of phenytoin was 50.2% (95% CI: 34.2–66.1%) and that of phenobarbital 73.6% (95% CI: 58.3–84.8%).
- Malamiri, Ghaempanah, Khosroshahi, Nikkhah, Bavarian & Ashrafi, 2012 (*41*). This randomized, double-blind study compared the efficacy and safety of IV sodium valproate with IV phenobarbital

in children with status epilepticus not responding to IV diazepam. No difference in efficacy in terms of seizure cessation was found (27/30 in the sodium valproate group versus 23/30 in the phenobarbital group). Seizure recurrence rates within 24 hours were higher in the phenobarbital (12/23) group compared with the sodium valproate group (4/27) (Fisher exact test, $P = 0.004$). The overall occurrence of clinical adverse effects was higher in the phenobarbital group (22/30) than in the valproate group (7/30) (Fisher exact test, $P < 0.001$).

- Agarwal, Kumar, Chandra, Gupta, Antony & Garg, 2007 (*42*). In a randomized, open-label trial of sodium valproate versus phenytoin in patients (adults and children) with status epilepticus who did not respond to first-line IV diazepam, there was a statistically non-significant difference for reducing risk of non-cessation of seizures between IV valproate and IV phenytoin (6/50 versus 8/50; RR 0.75; 95% CI: 0.28–2.00). The overall occurrence of clinical adverse effects was higher in the phenytoin (8/50) group than in the valproate (5/50) group.

The incidence of adverse events for IV sodium valproate in SE overall is limited (10–20%) and includes dizziness, thrombocytopenia, and mild hypotension, which was independent of infusion rates. Cardiovascular and respiratory tolerability is good even for high doses and fast infusion rates (up to 30 mg/kg at 10 mg/kg per minute) (*43*). Mild hyperammonaemia and mild thrombocytopenia have been reported in a few patients. Overall, the efficacy–safety profile could be considered favourable.

In January 2015, the Medicines and Healthcare Products Regulatory Agency (MHRA) strengthened its warnings on the use of valproate in women of childbearing potential, based on the information that children exposed to valproate in the womb are at an approximately 11% risk of malformations at birth compared with a 2–3% risk for children in the general population (*44–46*).

Hepatic failure resulting in fatalities has occurred in patients receiving sodium valproate (*47*). Patients with a hepatic disease or hepatic dysfunction should not be given IV sodium valproate.

There are no data on cost–effectiveness, and no systematic cost comparison data available. The cost of IV sodium valproate differs from country to country. In Australia sodium valproate IV is around 60 Australian dollars per 400 mg vial, phenobarbital $A4 per vial and phenytoin $A3 per vial. In India, by contrast, sodium valproate for injection is around Rs6 per 100 mg (Rs24 or US$ 0.4 for 400 mg), IV phenytoin Rs5 per 100 mg, and IV phenobarbital Rs12 per 100 mg (US$ 1 is about Rs60). For a 10-kg child, at the standard 20 mg/kg dose, the cost would be Rs12 for IV sodium valproate, Rs10 for IV phenytoin and Rs24 for IV phenobarbital.

Patients with status epilepticus who receive IV sodium valproate will need monitoring of vital signs, oxygenation and respiratory efforts. Liver function tests and complete blood counts are also needed.

The Expert Committee acknowledged that there is limited evidence available in favour of IV sodium valproate for the treatment of benzodiazepine-refractory status epilepticus. While recognizing the importance of effective management strategies for benzodiazepine-refractory status epilepticus and emphasizing the need for high-quality head-to-head randomized controlled trials to compare the effectiveness and safety of antiepileptic medicines in SE, the Expert Committee recognizes the difficulty of ascertaining whether some antiepileptic medicines are more effective than others.

Randomized controlled trials comparing antiepileptic medicines (phenytoin, carbamazepine, valproic acid) in children and adults with convulsive epilepsy provide indirect evidence of the role of valproic acid in the treatment of SE (*48*, *49*). It is unlikely that there is a clinically relevant difference between valproic acid and the other antiepileptic medicines. All antiepileptic medicines are associated with important adverse effects. Sodium valproate is associated with a higher risk of fetal malformations if taken in pregnancy. Rarely, sodium valproate has been associated with fulminant hepatic failure and hyperammonemia, particularly in young children (*43*).

The Committee noted advice from the WHO Mental Health and Substance Abuse Department which stated that the Guideline Development Group, on review of synthesized evidence following GRADE methodology, has suggested a conditional recommendation for IV sodium valproate to be preferred to IV phenobarbital or IV phenytoin, despite similar efficacy, because of its superior risk–benefit profile. The Expert Committee therefore considered it was reasonable to recommend addition of IV valproic acid (sodium valproate) to the complementary list of the EML and EMLc for the treatment of benzodiazepine-refractory status epilepticus.

Section 6: Anti-infective medicines

6.2: Antibacterials

6.2.4: Antituberculosis medicines

Bedaquiline (addition) – EML

Delamanid (addition) – EML

Linezolid (addition) – EML and EMLc

Terizidone (addition) – EML and EMLc

Applications for inclusion of bedaquiline (EML), delamanid (EML), linezolid (EML and EMLc) and terizidone (EML and EMLc) in the complementary lists as second or subsequent-line medicines for treatment of multidrug-resistant tuberculosis (MDR-TB) were submitted by the Laboratories, Diagnostics and Drug Resistance unit of the WHO Global TB Programme. A separate application for bedaquiline (EML) was submitted by Janssen Research & Development LLC.

Expert reviews of each application were prepared by two members of the Expert Committee. Numerous public comments on the applications were received and are available on the WHO website. A memorandum was received from Dr Mario Raviglione, Director of the Global Tuberculosis Programme at WHO.

WHO's *Guidelines for the programmatic management of drug-resistant tuberculosis – 2011 update* (*50*) recommends use of a treatment regimen with at least four to five active drugs from the following groups: second-line parenteral agents (e.g. kanamycin, amikacin); fluoroquinolones (e.g. levofloxacin, moxifloxacin); oral bacteriostatic second-line drugs (e.g. ethionamide, cycloserine); and Group 5 drugs (e.g. clofazimine, linezolid).

An application to add bedaquiline to the EML was first made in 2013. The application was rejected on the grounds of limited safety evidence and limited availability (at that time bedaquiline was registered only in the USA). The same year, an application was also made to review second-line antituberculosis medicines; linezolid and terizidone were not included as efficacy and safety data were limited (*11*).

The overall incidence of drug-susceptible tuberculosis that can be treated with first-line drugs has been decreasing over the past two decades. However, it is estimated that half a million new MDR-TB cases emerge each year, accounting for 5% of all tuberculosis cases in the world, and more than 200 000 MDR-TB patients die (*51*). Notification rates and overall prevalence might be considerably lower than actual estimations. Globally, 3.5% of all new tuberculosis cases and 20.5% of previously treated cases are estimated to be MDR-TB (*51*). The burden of MDR-TB varies greatly by region; eastern Europe and central Asian regions have been identified as having the highest burden of MDR-TB. Many MDR-TB cases go undetected and patients are not placed on appropriate treatment,

increasing the risk that they die and/or transmit drug-resistant strains to others. In 2013, countries reported that about 100 000 patients worldwide started MDR-TB treatment (*51*). Outcome reporting in recent years, however, has shown that only about half the MDR-TB patients complete their treatment successfully (*52*). This is particularly true of about one third of MDR-TB cases who have lost susceptibility to fluoroquinolones or to second-line injectable agents or to both (extensively-drug resistant tuberculosis, XDR-TB). XDR-TB represents about 9% of MDR-TB cases, is highest in patients with HIV, is more difficult to diagnose, requires complex treatment with drugs that have higher levels of toxicity, is characterized by poor treatment outcomes, and is associated with a higher risk of mortality (*51*). The transmissibility of XDR-TB strains has been documented in outbreaks and in regular reports of cases with no previous history of tuberculosis treatment (*53–58*); this represents a formidable, additional public health concern and makes the proper treatment of MDR- and XDR-TB patients all the more important. Bedaquiline, delamanid, linezolid and terizidone are proposed as treatment options in MDR-TB regimens.

In consideration of the applications, the Expert Committee acknowledged the following:

- Evaluation of the efficacy of antituberculosis drugs has generally relied on microbiological, rather than clinical, end-points (i.e. sputum conversion).
- Death from untreated pulmonary tuberculosis is considerable; 10-year case-fatality among sputum smear-positive and HIV-negative cases of pulmonary tuberculosis is around 70%; among culture-positive (but smear-negative) cases it is around 20% (*51*).
- Evidence to inform the selection of agents for treating MDR-TB is essentially limited to outcome data from treatment cohorts; these data – in addition to in vitro studies in both animals and humans – confirm the efficacy of the second-line anti-TB medicines referred to in the WHO guidelines.
- Efficacy against MDR-TB of some second-line anti-TB medicines referred to in the WHO guidelines has been evaluated by previous Expert Committees. Consideration was given to support for and facilitation of access to regimens that are more acceptable for patients and providers, phase IIb clinical evidence and the alternatives already in the EML.

Bedaquiline (addition) – EML

Bedaquiline is a diarylquinoline compound with a novel mode of action. It demonstrates in vitro activity against MDR-TB, including pre-XDR-TB and XDR-TB.

A phase IIb, placebo-controlled, randomized trial suggested that bedaquiline is effective in MDR pulmonary tuberculosis in adults (*59*). The primary efficacy analysis of time to sputum culture conversion was based on a modified intention-to-treat (mITT) population, which excluded subjects who had drug-susceptible tuberculosis, XDR-TB or unconfirmed MDR-TB (based on susceptibility tests taken before randomization), for a total of 132 subjects (66 in each of the bedaquiline and placebo groups). Compared with placebo, bedaquiline was shown to reduce the median time to culture conversion from 125 to 83 days. The hazard ratio for conversion in the bedaquiline group versus the placebo group was 2.44 (95% CI: 1.57–3.80; $P < 0.001$) (*59*). Based on the WHO definition of cure (*60*), after 120 weeks more patients in the bedaquiline group than in the placebo group were cured (38 of 66 patients (58%) and 21 of 66 patients (32%), respectively; $P = 0.003$) (*59*). A second phase IIb, uncontrolled, open-label trial evaluated bedaquiline as part of an individualized MDR-TB treatment regimen in patients with sputum smear-positive pulmonary MDR-TB (data on file, Janssen Research and Development). Efficacy results in this trial were generally consistent. Median time to sputum culture conversion was 57 days. According to the WHO definition of cure, 61% subjects were considered cured at the end of the study (120 weeks), a result that could be counted as a significant success given the magnitude of benefit (in comparison with baseline MDR-TB cure rates of 32%).

During the 120 weeks in the intention-to-treat (ITT) population of the randomized controlled trial, rates of adverse events, treatment-related adverse events and adverse events leading to study discontinuation were similar in the two study groups. The most frequent adverse events were nausea, arthralgia and vomiting; severity was limited. Of most concern, 10/79 patients (13%) in the bedaquiline group and 2/81 patients (2%) in the placebo group died ($P = 0.02$). There was no discernible relationship between death and culture conversion, relapse, microbiological response, susceptibility to drugs used in the MDR-TB background medication regimen, HIV status or severity of disease. The reasons for the imbalance between the two groups were not clear, particularly in terms of relationship between causes of deaths and drug use. The use of bedaquiline was associated with moderate prolongation in the QT interval (mean 15.4 ms at study week 24) (*59*, *61*). Prescribing information for bedaquiline suggests that the risk of QT-interval prolongation might be increased when bedaquiline is used in combination with other medicines that prolong the QT-interval, such as fluoroquinolones and 4-aminoquinoline antimalarial drugs. Monitoring – regular ECGs, liver enzymes, electrolyte levels – is recommended. An uncontrolled, phase IIb, open-label study showed similar patterns of adverse events, and 16/233 (7%) of patients died. Tuberculosis was the most common cause of death (nine patients) (data on file, Janssen Research and Development).

Janssen Therapeutics has proposed a tiered pricing strategy for access to bedaquiline. Costs per 6-month patient course are about US$ 900 in low-income countries, US$ 3000 in middle-income countries and US$ 30 000 in high-income countries. Studies assessing the cost–effectiveness of bedaquiline, based on the assumptions of the translation of trial results to current practice, showed favourable cost–effectiveness ratio and cost-savings (*62*, *63*).

The WHO guideline, *The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance*, recommends addition of bedaquiline to a WHO-recommended regimen for adult patients with MDR-TB (conditional recommendation/very low quality of evidence) when an effective treatment regimen containing four second-line drugs in addition to pyrazinamide according to WHO recommendations cannot be designed, and/or when there is documented evidence of resistance to any fluoroquinolone in addition to multidrug resistance (*64*).

Marketing authorization has been obtained for bedaquiline in the Philippines, the Republic of Korea, the Russian Federation, South Africa and USA, as well as in countries of the European Union. For most patients with MDR-TB, WHO guidelines suggest an intensive phase of 8 months and total treatment duration of 20 months. Bedaquiline is indicated in adults (≥18 years) as part of combination therapy. The total duration of treatment with bedaquiline is 24 weeks. Bedaquiline is currently available through the Global Drug Facility of the Stop TB Partnership at a cost of US$ 900–3000 for 188 x 100 mg tablets.

Countries are advised to implement use of bedaquiline using a phased approach and under the five conditions recommended by WHO: careful selection of patients; close monitoring of patients; use in a regimen that follows WHO recommendations; informed patient consent; and active pharmacovigilance (*65*, *66*). This is because of the limited experience with use of bedaquiline in the variety of circumstances that might be expected in treatment programmes, and uncertainty about the overall value of bedaquiline in MDR-TB treatment regimens.

Taking into consideration the significant public health need for new and effective treatments for MDR-TB and XDR-TB, the available data on effectiveness and safety and WHO interim policy guidance, the Expert Committee recommended the addition of bedaquiline to the complementary list of the EML for the treatment of adult patients with MDR-TB, pre-XDR-TB and XDR-TB.

The Committee recommended that bedaquiline be reserved for use as part of a WHO-recommended MDR/XDR-TB regimen in patients for whom there are few or no other treatment alternatives. In addition, the Expert Committee considered that bedaquiline should be introduced only in settings where close monitoring of patients and active pharmacovigilance can be ensured.

The Committee recognized that there is an urgent and unmet public health need in the case of MDR-TB, that the evaluation of new drugs for this

disease is a fast-moving field, and that current data related to toxicity are limited. The Expert Committee therefore recommended that bedaquiline be reviewed on an ongoing basis and considered at its next meeting as part of a review of the antituberculosis medicines section.

The Committee also noted that there have been concerns about the quality of some bedaquiline products and recommended that WHO explore options for addressing these concerns.

Delamanid (addition) – EML

Delamanid is a nitro-dihydro-imidazooxazole with high in vitro activity against MDR-TB (*66*).

A phase II, three-arm, placebo-controlled, double-blind, randomized trial conducted in nine countries suggested that delamanid has short-term efficacy (i.e. two months) against MDR pulmonary tuberculosis in adults. The primary efficacy analysis was based on the proportion of patients with sputum culture conversion (defined as a series of at least five consecutive weekly cultures negative for *M. tuberculosis*, without subsequent positive cultures) at two months (*67*). Overall, 434 patients completed the trial and 402 were analysed, based on a modified intention-to-treat (mITT) population. More patients in the delamanid groups than in the placebo group achieved sputum culture conversion (64/141 patients (45%) delamanid 100 mg; 57/136 patients (42%) delamanid 200 mg; and 37/125 patients (30%) placebo; respectively $P = 0.008$ and $P = 0.04$).

Two open-label extension studies based on the follow-up of the RCT cohort evaluated the long-term efficacy of delamanid. Although limited by their observational nature, the studies show that treatment with delamanid for an additional six months produced favourable treatment outcomes (WHO-defined treatment outcomes of "cured" or "treatment completed") in 75% of patients (*68*).

The number of patients exposed to delamanid in all trials (887 individuals) is limited. About one fifth had a cumulative exposure longer than six months. The only clinically relevant adverse event with a difference in incidence between the delamanid treatment groups and the placebo group was prolongation of QT interval. Most frequent adverse events were nausea, vomiting and dizziness and were present in similar proportions in the delamanid and placebo groups (*67*, *68*).

Information regarding the published price of delamanid is limited, but it is expected that the price will be comparable to that of bedaquiline. The WHO Expert Group that developed the WHO guideline, *The use of delamanid in the treatment of multidrug-resistant tuberculosis: interim policy guidance* (*69*) considered delamanid to be cost–effective in most settings, but the quality of this evidence was considered "very low".

The WHO guideline recommends that delamanid may be added to a WHO-recommended regimen for treatment of MDR-TB in adult patients (conditional recommendation/very low quality of evidence). It also recommends that use of delamanid as part of MDR-TB treatment regimens should be subject to: careful selection of patients; close monitoring of patients; use in a regimen that follows WHO recommendations; informed patient consent; and active pharmacovigilance (*69*). This is because of the limited experience with use of delamanid in the variety of circumstances that might be expected in treatment programmes and uncertainty about the overall value of delamanid in MDR-TB treatment regimens.

The Expert Committee noted that there may be significant challenges in obtaining this medication, and access to its use for compassionate use programmes has been restricted. Delamanid is approved in the European Union and is indicated for treatment of MDR pulmonary TB in adults (≥ 18 years) as part of combination therapy. The total duration of treatment with delamanid is 24 weeks.

Taking into consideration the significant public health need for new and effective treatments for MDR/XDR-TB, the available data on effectiveness and safety and WHO interim policy guidance, the Expert Committee recommended the addition of delamanid to the complementary list of the EML for the treatment of adult patients with MDR-TB, pre-XDR-TB and XDR-TB.

The Committee also recommended that delamanid be reserved for use as part of a WHO-recommended MDR/XDR-TB regimen in patients for whom there are few or no other treatment alternatives. In addition, the Committee considered that delamanid should be introduced only in settings where close monitoring of patients and active pharmacovigilance can be ensured.

The Committee recognized that there is an urgent and unmet public health need in the case of MDR-TB, that the evaluation of new drugs for this disease is a fast-moving field, and that current data related to toxicity are limited. The Expert Committee therefore recommended that delamanid be reviewed on an ongoing basis and considered at its next meeting as part of a review of the antituberculosis medicines section.

Linezolid (addition) – EML and EMLc

Linezolid is an oxazolidinone antibiotic indicated in adults and children for treatment of infections caused by susceptible Gram-positive bacteria e.g. hospital- and community-acquired pneumonia, skin and soft tissue infections and vancomycin-resistant *Enterococcus faecium* infections. It is classified as a Group 5 second-line antituberculosis medicine in WHO's guidelines for programmatic management of drug-resistant tuberculosis (*50*). WHO guidelines also recommend linezolid as an option for treatment of MDR/XDR-TB when

adequate treatment regimens cannot be constructed with medications from other groups (*65*). Linezolid is used "off label" for the treatment of MDR/XDR-TB.

Data regarding the effectiveness of linezolid for the treatment of MDR/XDR-TB are limited. However, on the basis of its documented activity against *M. tuberculosis*, both in vitro and in animal studies, linezolid has been used in salvage cases, to treat patients with extensive drug resistance or intolerance (*70–72*). Linezolid has been studied in RCTs (*72–74*) and in several retrospective and prospective case series (*75–77*) and further evaluated in meta-analyses of MDR-TB and XDR-TB patients (*78*, *79*). In several countries linezolid has proved effective in achieving culture conversion in refractory XDR-TB. The overall percentage of patients with treatment success varied between 68% and 100% depending on the study and the outcome (sputum or culture conversion).

Published data on children are limited; they derive from case reports and small cohort studies and relate to fewer than 20 children. Most children on linezolid had culture conversion, generally within 1–3 months, and successful long-term outcome. One was lost to follow-up and there was one death (respiratory failure, culture-negative at the time of death). While some pharmacokinetic data are available, additional data are needed with regard to paediatric dosing of linezolid in MDR-TB, particularly for linezolid used in combination with medications that have similar adverse effects.

Adverse events attributable to linezolid occurred in approximately two thirds of patients (*73*, *79*). In some cases adverse events resolved quickly while in others (15–25% of patients) they required reduction of the linezolid dosage or interruption of treatment. The main adverse events – occurring in more than 10% of cases – were anaemia, peripheral neuropathy, gastrointestinal disorders, optic neuritis and thrombocytopenia (*79*). The risk of adverse events increases as linezolid dose increases (*78*, *79*). Acquired drug resistance to linezolid has also been observed (*73*).

Overall, the Expert Committee agreed that use of linezolid in the treatment of MDR/XDR-TB is associated with benefit but that benefit needs to be balanced with the toxicity associated with long-term use of the drug and further amplification of drug resistance.

The Committee discussed the "off label" use of linezolid for the treatment of MDR/XDR-TB. The Committee considered that the available evidence supporting this use of linezolid, while limited, was adequate, particularly considering the urgent public health need for effective later-line treatments for MDR/XDR-TB. The Committee also noted that, in some settings, it is recommended that use of linezolid for its licensed indications be reserved because of its potential for use in XDR-TB (*80*). To date, inclusion of linezolid on the EML/EMLc for its licensed indications has not been considered by the Expert Committee.

With regard to price, the Expert Committee noted that, in 2012, in countries where linezolid is patent-protected it was priced at approximately US$ 2500 per month of treatment (at a dose of 600 mg daily) (*78*). In India, where linezolid is not patented, the generic product is priced at US$ 50–70 per month. Linezolid is currently available through the Global Drug Facility of the Stop TB Partnership at a cost of US$ 107.00–109.60 for 20 x 600 mg tablets.

Taking into consideration the significant public health need for new and effective treatments for MDR-TB, pre-XDR-TB and XDR-TB, the available data on effectiveness and safety for linezolid, and WHO guidelines for the programmatic management of drug-resistant tuberculosis, the Expert Committee recommended that linezolid be added to the complementary list of the EML and EMLc for the treatment of MDR/XDR-TB. The Committee considered that inclusion of linezolid on the EML and EMLc had the potential to promote availability of effective treatment combinations in countries with a heavy MDR/XDR-TB burden.

The Committee recommended that linezolid should be reserved for use as part of a WHO-recommended MDR/XDR-TB regimen in patients for whom there are few or no other treatment alternatives. In addition, the Committee considered that linezolid should be introduced only in settings where close monitoring of patients and active pharmacovigilance can be ensured.

The Committee recognized there is an urgent and unmet public health need in the case of MDR-TB, that the evaluation of new drugs for this disease is a fast-moving field, and that current data related to toxicity are limited. The Expert Committee therefore recommended that linezolid be reviewed on an ongoing basis and considered at its next meeting as part of a review of the antituberculosis medicines section.

Terizidone (addition) – EML and EMLc

Terizidone is an antibiotic and a structural analogue of cycloserine, with a similar mode of action. It is used in place of cycloserine in some tuberculosis centres. Cycloserine is currently included in the complementary list of the EML and EMLc. Both cycloserine and terizidone are classified as oral bacteriostatic second-line anti-TB drugs in WHO guidelines for the programmatic management of drug-resistant tuberculosis (*50*).

There is scant evidence concerning terizidone in treatment of MDR-TB or XDR-TB. All studies are observational; most use a retrospective cohort design and describe use of multiple different drugs together in individualized treatment. Because treatment was individualized, one drug may have contributed more than others to bacteriological improvement and to final treatment outcomes. The percentage of included patients with MDR-TB varied: one study included no MDR-TB patients and one included only XDR patients. Very few of these

studies provided data that allow comparison of treatment outcomes in those who received or did not receive one or another of the drugs of interest. A large meta-analysis of individual data for more than 9000 patients, assessing the role of individual drugs, is of only limited value since terizidone was given to just 12 patients at a single centre (*81*). It does show, however, that the use of cycloserine, as part of multidrug regimens, was significantly associated with treatment success (compared with failure, relapse or death). Given that terizidone is a structural analogue of cycloserine, the Expert Committee considered it was reasonable to assume that the two medicines have similar effects.

The assessment and reporting of adverse events in studies were limited. The data collection was not standardized, and validated systems to grade events were not used. Adverse events were common but were not attributed to a specific drug; estimates of toxicity due to specific drugs are thus extremely uncertain. A recent systematic review analysed the occurrence of adverse events with cycloserine and terizidone. Serious adverse events, mostly psychiatric and neurological, were similar in frequency and type for the two drugs (*82*).

Data supporting use of terizidone in children were also limited, particularly with regard to adverse events. The Expert Committee also noted that no child-friendly formulation of terizidone is available.

Terizidone is currently available through the Global Drug Facility of the Stop TB Partnership at a cost of US$ 79.40–83.30 for 50 x 250 mg capsules.

Taking into consideration the significant public health need for new and effective treatments for MDR-TB, pre-XDR-TB and XDR-TB, the available data on effectiveness and safety of terizidone and cycloserine, and WHO guidelines for the programmatic management of drug-resistant tuberculosis, the Expert Committee recommended that terizidone should be included on the complementary list of the EML as an alternative to cycloserine for the treatment of MDR/XDR-TB. The Committee recommended that this be indicated as a note alongside the current cycloserine listing.

The Expert Committee recommended that terizidone be reserved for use as part of a WHO-recommended M/XDR-TB regimen in patients for whom there are few or no other treatment alternatives. In addition, the Committee considered that terizidone should be introduced only in settings where close monitoring of patients and active pharmacovigilance can be ensured.

The Committee did not recommend inclusion of terizidone on the EMLc at this time, recognizing that there are limited data on the use of terizidone in children and on how it compares with cycloserine, particularly in relation to adverse effects. The lack of a child-friendly dose form of terizidone was also noted. The Expert Committee recommended that evidence on the use and effects of terizidone in paediatric patients be reviewed at its next meeting.

The Committee recognized there is an urgent and unmet public health need in the case of MDR-TB, that the evaluation of new drugs in this disease

is a fast-moving field, and that current data related to toxicity are limited. The Expert Committee therefore recommended that terizidone be reviewed on an ongoing basis and considered at its next meeting as part of a review of the antituberculosis medicines section.

Rifapentine (addition) – EML and EMLc

An application was submitted by Dr Alberto Matteelli of the WHO TB/HIV and Community Engagement unit for inclusion of rifapentine (RPT) as an individual medicine, to be used in combination with isoniazid (INH), for the treatment of latent tuberculosis infection (LTBI).

Expert reviews of the application were prepared by two members of the Expert Committee. The Global TB Community Advisory Board, Treatment Action Group, and TB Proof supported the application, as did the Community Research Advisory Group (CRAG).

It is estimated that about one third of the world's population is infected with *M. tuberculosis* (*83*). Most infected individuals demonstrate no signs or symptoms of active disease, nor are they infectious; they are, however, at risk of developing active disease and becoming infectious in the future. In general, people infected with *M. tuberculosis* have a 10% lifetime risk of falling ill with tuberculosis. The risk is much higher, however, for immunocompromised individuals (e.g. people living with HIV, malnutrition or diabetes) or people who use tobacco (*84*).

In May 2014 the World Health Assembly passed a resolution approving the post-2015 Global TB Strategy (subsequently renamed as the END-TB Strategy) with its ambitious vision of a world free of tuberculosis and targets for 2035 that include a 90% reduction in tuberculosis incidence (compared with 2015) (*85*). The application to include rifapentine on the EML and EMLc was made as a means of contributing to achievement of the targets of the END-TB Strategy.

The application presented a systematic review and meta-analysis, assessing which treatment is effective in preventing development of active tuberculosis disease in individuals identified with LTBI and at high risk of progression to active disease (*86*). Fifty-three randomized controlled trials evaluated LTBI treatment and recorded at least one of the two pre-specified end-points (prevention of active tuberculosis, and/or hepatotoxicity of grade III or above). The results of clinical trials demonstrated the effectiveness of the 12-week regimen of rifapentine and isoniazid (3RPT/INH), administered once weekly for the treatment of LTBI in adults, compared with the 6- or 9-month INH regimen (6INH, 9INH), considered as standard for this indication.

Randomized controlled trials explored the effectiveness of RPT/INH in children aged 2 years or more (*87*), HIV-infected (*88*) and non-HIV-infected

(*87*) patients. Non-inferiority in terms of efficacy, and significantly better treatment adherence and completion of the 3RPT/INH regimen compared with INH were observed, although higher treatment completion rates could have been biased in favour of 3RPT/INH.

Table 2 compares the RPT/INH regimen with the current standard of care: 9 months of INH treatment. Data on efficacy, safety and completion rates are derived from the TBTC-S26 study: an open-label, randomized, non-inferiority trial comparing 3 months of directly observed once-weekly therapy with rifapentine (900 mg) plus isoniazid (900 mg) (combination-therapy group) with 9 months of self-administered daily isoniazid (300 mg) (isoniazid-only group) in subjects at high risk for tuberculosis (*87*).

Table 2
Comparison of 3 months RPT/INH versus 9 months INH in patients at high risk for tuberculosis

	INH	RPT/INH	Comment
Efficacy	TB incidence in treated subjects 0.40% (15/3745)	TB incidence in treated subjects 0.18% (7/3986)	The odds ratio of 0.44 (0.18–1.07) shows a trend towards higher efficacy of RPT/INH
Safety	Incidence of severe hepatotoxicity in treated subjects 2.75% (103 / 3745)	Incidence of severe hepatotoxicity in treated subjects 0.45% (18 / 3986)	The odds ratio of 0.16 (0.10–0.27) shows that RPT/INH is significantly safer in treated subjects
Completion rate	69%	82%	The proportion of individuals completing treatment is significantly higher for RPT/INH
Duration of treatment	9 months	12 weeks	The shorter duration of RPT/INH treatment is considered to translate into better adherence
Dosing	Daily	Weekly	The simpler weekly dosing is expected to make RPT/INH more acceptable than INH to both programme and patients

Table 2 *continued*

	INH	RPT/INH	Comment
Total number of tablets[a]	180 or 270	108	The smaller number of pills is expected to make RPT/INH more acceptable than INH to patients

[a] Isoniazid 300 mg tablets.

The results of a recent network meta-analysis of published data (*86*) and the TBTC-S26 study (*87*) show that 3RPT/INH is well tolerated when used for the treatment of LTBI, including by children (2–17 years old) and by HIV-infected and HIV-non-infected adults. The 3RPT/INH regimen is associated with less hepatotoxicity and more possible hypersensitivity reactions than the standard 6INH or 9INH therapy. A total of five toxicity-attributable deaths were reported, mostly from a single trial. All were due to severe hepatitis in INH treatment groups, and at least four occurred in patients who were on INH for 12 months or longer (*86*).

In the TBTC-S26 main study, the overall incidence of serious adverse events (SAEs) was low; SAEs were reported in 2.7% of patients in the INH arm and 1.5% of patients in the RPT/INH arm (*87*). In the paediatric sub-study of TBTC-S26, SAEs were reported in six children (1.2%), all of whom were in the INH arm. In the HIV sub-study of TBTC-S26, SAEs were reported in 10.8% of INH patients and 3.9% of RPT/INH patients.

Based on market prices in the USA, a full course of preventive therapy with RPT for an adult will cost US$ 273. Sanofi has proposed a reduced pricing strategy, such that a full course of RPT treatment would cost US$ 72. Costs outside USA are difficult to predict. A recent study based on assumptions of the translation of trial results to current practice yielded favourable cost–effectiveness and cost-savings results for RPT (*89*).

In 2014, WHO published *Guidelines on the management of latent tuberculosis infection*, which recommends systematic testing and treatment of LTBI in several at-risk populations. Five regimens are recommended by WHO for the treatment of LTBI: 6-month isoniazid; 9-month isoniazid; 3 months of weekly rifapentine plus isoniazid; 3–4 months of isoniazid plus rifampicin; and 3–4 months of rifampicin alone (strong recommendation, moderate to high quality of evidence) (*90*).

Universal treatment of all individuals with LTBI is not recommended because of uncertainties concerning the balance between benefit and harm. A positive benefit/harm trade-off is certainly present in those individuals with

LTBI who are at risk for progression from LTBI to active tuberculosis disease: people living with HIV; adult and child contacts of pulmonary tuberculosis cases; patients starting treatment with an anti-tumour necrosis factor; patients receiving dialysis; patients preparing for organ or haematological transplantation; and patients with silicosis (*90*, *91*).

Drug-specific adverse reactions can occur with both RPT and INH. WHO does not have specific recommendations on standards of clinical monitoring during LTBI treatment because of the lack of evidence on the optimal monitoring strategy. However, the Organization suggests regular routine clinical monitoring of individuals receiving treatment for LBTI through a monthly visit to health-care providers (*90*).

Considering the public health need for standardized practices on LTBI management and the recommendations in the recent WHO guidelines (*90*), the Expert Committee recommended the addition of rifapentine to the core list of the EML and EMLc for the treatment of latent tuberculosis infection, with this restricted indication to be noted in the List. The Committee recommended that eligibility for treatment with rifapentine should be as stated in the WHO guidelines.

6.3: Antifungal medicines

Itraconazole (addition) – EML and EMLc

An application for the inclusion of itraconazole (oral capsules 100 mg, oral suspension 10 mg/mL and intravenous formulation 10 mg/mL) on the EML and the EMLc was submitted by the Global Action Fund for Fungal Infection, in association with the International Foundation for Dermatology, the University of Manchester and the Medical Mycology Reference Laboratory of the Instituto de Salud Carlos III, and prepared by Drs Ana Alastruey, David Denning, Sara Gago, Roderick Hay, Elizabeth Peers, and Juan Luis Rodriguez Tudela.

Expert reviews of the application were prepared by two members of the Expert Committee. Comments on the application were received from Dr Myriam Henkens, International Medical Coordinator, Médecins Sans Frontières.

The mechanism of action of azoles is to impair the synthesis of ergosterol by binding to fungal cytochrome P450 isozymes, resulting in perturbation of membrane-bound systems and leading to cell leakage and death (*92*). Currently, the WHO Model List includes only one systemic azole, fluconazole (*11*). Itraconazole has a broader spectrum of activity than fluconazole, including activity against filamentous fungi such as *Aspergillus* spp. (*93*). The application noted that no azole drug with activity against filamentous fungi is included in the Model List and requested listing of itraconazole as an individual medicine. The Expert Committee noted that fluconazole is currently included on the Model List with a square box as representative of the azole group of antifungals.

However, the application argued that fluconazole is not only inactive against filamentous fungi but is also inferior to itraconazole for many indications.

The application presented data from published meta-analyses and, where there were no data from randomized clinical trials (most indications), drew on a combination of clinical guidelines, large prospective and retrospective series, and supportive data to define the role of itraconazole in clinical practice (*94–121*).

The Committee noted the numerous approved indications for itraconazole formulations in immunocompromised and/or non-immunocompromised patients, including blastomycosis, histoplasmosis, aspergillosis, onychomycosis, and oropharyngeal and oesophageal candidiasis, and for prophylaxis of fungal infections in neutropenic patients and following haematopoietic stem cell transplantation (HSCT). The application also described a range of uses of itraconazole recommended in treatment guidelines.

The application described the effectiveness of itraconazole in the identified clinical trials in terms of response rate by infection type. Response rates in excess of 90% were reported for vulvovaginal candidiasis, oropharyngeal candidiasis, dermatophyte infections, blastomycosis, sporotrichosis, non-meningeal coccidioidomycosis, paracoccidioidomycosis and *Talaromyces marneffei* infection. Response rates of less than 50% were reported for invasive aspergillosis, chromoblastomycosis and cryptococcosis. No assessment of the quality of the evidence was included in the application.

The application made reference to recommendations for use of itraconazole in the 2014 WHO *Guidelines on the treatment of skin and oral HIV-associated conditions in children and adults* for eosinophilic folliculitis and as second-line therapy for tinea (dermatophyte infections) (*103*). For eosinophilic folliculitis, however, the WHO guidelines recommend antiretroviral therapy as primary treatment; additional symptomatic treatment is recommended for persistent or severe symptoms with addition of an oral antihistamine, then topical steroids, and then – if response is inadequate – oral itraconazole. For tinea infections, if there is inadequate response to oral griseofulvin, oral itraconazole (or oral terbinafine) may be used as second-line therapy. The application noted that itraconazole may offer particular benefit in low- and middle-income countries (LMICs) for the prophylaxis of fungal infections in neutropenia, in invasive aspergillosis, and in some HIV patients needing azole maintenance therapy after cryptococcal meningitis and living in areas endemic for *Histoplasma* or *Talaromyces*.

The application requested listing of itraconazole in the EML and the EMLc but noted that there are few data on the use of itraconazole in infants and older children. Results of pharmacokinetic studies were presented as evidence that oral itraconazole solution is effective for treatment of oropharyngeal

candidiasis in HIV-positive children (*122*) and for prevention of invasive fungal infection in children with neutropenia (*123*).

The Expert Committee noted that multiple generic forms of itraconazole capsules are available, while the oral solution and intravenous formulations are still branded products. Little is known of the pharmacokinetics of the generic formulations of itraconazole widely used in south-east Asia. The therapeutic range of itraconazole is not well defined and there is large variation in plasma itraconazole concentrations with the capsule and oral liquid forms. Therapeutic drug monitoring is often recommended (*106*).

The Committee noted that the capsule and oral liquid formulations of itraconazole are not interchangeable. Oral itraconazole suspension has better oral bioavailability and results in approximately 30% higher systemic drug exposure than itraconazole capsules (*124*).

The oral bioavailability doubles when itraconazole capsules are administered after food, and absorption is impaired by co-administration with agents that reduce gastric acidity (e.g. proton pump inhibitors) and in achlorhydria (or hypochlorhydria), which is frequently associated with critical illness (*124*). There is no food effect with the oral suspension, and oral bioavailability increases in the fasted state. Itraconazole is erratically absorbed in AIDS patients who have variable gastric pH (*125*).

Itraconazole is metabolized predominantly via the cytochrome P450 isoenzyme CYP3A4. There are numerous drug–drug interactions, occurring via several different mechanisms: in HIV-infected patients, there are important interactions with antiretrovirals, particularly non-nucleoside reverse-transcriptase inhibitors (NNRTIs). Itraconazole metabolism is accelerated by medicines that induce CYP3A4, including rifampicin, phenytoin, carbamazepine, efavirenz and nevirapine. Co-administration may result in an inability to achieve therapeutic serum concentrations of itraconazole (*126*).

Many clinically significant drug–drug interactions relate to the suppression of CYP3A4 activity by itraconazole, which leads to higher exposures of agents that are metabolized via this route, including benzodiazepines, digoxin, ciclosporin, tacrolimus, sirolimus, statins and warfarin (*126*).

Itraconazole has more gastrointestinal side-effects than fluconazole, particularly in neutropenic and HSCT patients receiving itraconazole suspension for prophylaxis (*102*). Peripheral neuropathy may be more common with itraconazole than fluconazole (*127*). Dose adjustment may be required in patients with renal impairment and monitoring is required in patients with hepatic impairment (*126*).

Taking into account the evidence presented, the Expert Committee did not recommend the specific addition of itraconazole to the EML and EMLc. The

Committee considered that itraconazole could be an alternative agent within the current square box listing of fluconazole and can therefore be selected by countries for inclusion in national EMLs.

The Expert Committee accepted that itraconazole has a role in the treatment of a wide range of fungal infections, including some conditions for which fluconazole is not effective (e.g. aspergillosis). Itraconazole has demonstrated similar efficacy to fluconazole for many indications, but is inferior to other antifungal agents in other settings (e.g. itraconazole is not used as a first-line agent for either induction or maintenance therapy for cryptococcal meningitis). The Committee noted that capsule and oral solution formulations of itraconazole are not interchangeable and that the dosing recommendations differ in relation to food. There are a large number of significant drug–drug interactions including important interactions with antiretrovirals and medicines metabolized by CYP3A4. Therapeutic drug monitoring is used in most high-income countries for those with life-threatening infection and long-term therapy.

The Expert Committee recommended that consideration be given to a comparative review of all antifungal agents at its next meeting, to include assessment of other antifungal agents for various indications for treatment of both adults and children.

6.4: Antiviral medicines

6.4.2: Antiretrovirals

Various antiretroviral medicines and/or formulations (deletion) – EML and EMLc

An application was submitted by the WHO Department of HIV/AIDS for deletion of several antiretroviral medicines and/or formulations from the EML and EMLc.

Expert reviews of the application were prepared by two members of the Expert Committee. Comments on the application were received from Dr Myriam Henkens, International Medical Coordinator, Médecins Sans Frontières (MSF). MSF did not support the deletion of ritonavir (solid oral dose form, 100 mg). However, the Expert Committee noted that an alternative formulation of ritonavir, 100 mg (heat-stable tablet), was available on both the EML and EMLc and was not being proposed for deletion.

The Committee noted that the rationale provided by the WHO Department of HIV/AIDS for the requested deletions fell into four categories, namely:

- *Category 1: Dosage* – where the listed dose is not aligned with dosing guidelines in the 2013 WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* (*128*).
- *Category 2: IATT formulary* – alignment of the EML with formulation recommendations of the Inter-Agency Task Team (IATT) on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and their Children (*129*).
- *Category 3: Exclusion of adult formulations from the EMLc* – to promote full alignment with the IATT recommendations, simplify the EMLc and avoid overlap with the EML.
- *Category 4: Other* – deletions due to availability of fixed-dose combination (FDC) formulations or exclusion from updated antiretroviral therapy (ART) guidelines.

The requested deletions, the associated rationale, and recommendation of the Expert Committee are summarized in Table 3.

Table 3
Requested deletions, rationale and Expert Committee Recommendations

Medicine	Dose form/strength/ formulation	Delete EML	Delete EMLc	Deletion category	Expert Committee recommen-dation
abacavir	Tablet: 300 mg (as sulfate)		x	3	Delete
	Oral liquid: 100 mg (as sulfate)/5 mL		x	2	Retain
atazanavir	Solid oral dosage form: 300 mg		x	3	Delete
didanosine	Buffered powder for oral liquid: 100 mg, 167 mg, 250 mg packets	x	x	1	Delete
	Capsule (unbuffered enteric-coated): 125 mg, 200 mg, 250 mg, 400 mg	x	x	1	Delete
	Tablet (buffered chewable, dispersible): 25 mg, 50 mg, 100 mg, 150 mg, 200 mg	x	x	1	Delete
efavirenz	Oral liquid: 150 mg/ 5 mL	x	x	1	Delete
	Capsule: 50 mg, 100 mg and 200 mg	x	x	2	Retain
	Tablet: 600 mg		x	3	Delete
emtricitabine	Capsule: 200 mg	x	x	1, 4	Delete
	Oral liquid: 10 mg/mL	x	x	1	Delete
indinavir	Solid oral dose form: 400 mg	x		4	Delete
lamivudine	Oral liquid: 50 mg/ 5 mL		x	2	Retain

Table 3 *continued*

Medicine	Dose form/strength/ formulation	Delete EML	Delete EMLc	Deletion category	Expert Committee recommen-dation
lamivudine + nevirapine + stavudine	Tablet (dispersible): 60 mg + 100 mg + 12 mg	x	x	1	Delete
	Tablet: 150 mg + 200 mg +30 mg		x	3	Delete
lamivudine + nevirapine + zidovudine	Tablet: 150 mg + 200 mg + 300 mg		x	3	Delete
lamivudine + zidovudine	Tablet: 150 mg + 300 mg		x	3	Delete
lopinavir + ritonavir	Capsule: 133.3 mg + 33.3 mg	x	x	1	Delete
	Tablet (heat-stable): 200 mg + 50 mg		x	3	Delete
ritonavir	Solid oral dose form: 100 mg	x	x	2	Delete
saquinavir	Solid oral dosage form: 20 mg (as mesilate)		x	1	Delete
stavudine	Capsule: 15 mg, 20 mg, 30 mg	x	x	2	Retain
	Powder for oral liquid: 5 mg/mL	x	x	2	Retain
zidovudine	Capsule: 250 mg		x	1	Delete
	Capsule: 100 mg	x	x	2	Retain
	Solution for IV infusion injection: 10 mg/mL in 20-mL vial		x	1	Delete
	Tablet: 300 mg		x	3	Delete

For medicines and formulations proposed for deletion under categories 1, 3 and 4, the Committee considered the rationale justifying deletion was reasonable for all medicines proposed. The Committee therefore recommended deletion of these medicines and formulations as summarized in the table.

The Committee recommended that medicines and formulations proposed for deletion under category 2 (with the exception of ritonavir, solid oral dose form, 100 mg), be retained on the EML and EMLc. The Committee considered that deletion of medicines and formulations from the lists in order to align them with IATT recommendations, while rational, could be premature, as the availability and acceptability of alternative "preferred" formulations (e.g. scored, dispersible dose forms, FDCs) is not yet fully known. The Expert Committee therefore considered that it would be appropriate to retain abacavir oral liquid 100 mg/5 mL, efavirenz capsule 50 mg, 100 mg and 200 mg, lamivudine oral liquid 5 mg/5 mL, stavudine capsule 15 mg, 20 mg and 30 mg, stavudine powder for oral liquid 5 mg/ mL and zidovudine capsule 100 mg on the EML and EMLc for now, but recommended their deletion from the Lists without further consideration at the next Expert Committee meeting unless an application was received in support of their retention.

In the case of ritonavir, solid oral dose form, 100 mg, the Committee recommended deletion, noting the current listing of a heat-stable tablet formulation on the EML and EMLc.

6.4.2: Antiretrovirals – fixed-dose combinations

Abavacir + lamivudine (addition) – EML and EMLc

An application was submitted by Clinton Health Access Initiative Inc. for inclusion of abacavir (as sulfate) + lamivudine 60 mg/30 mg fixed-dose combination dispersible, scored tablet formulation on the EML and EMLc for the treatment of children aged 6 weeks or more with HIV infection.

Expert reviews of the application were prepared by two members of the Expert Committee. Comments on the application were received from Dr Myriam Henkens, International Medical Coordinator, Médecins Sans Frontières.

An application to include abacavir (as sulfate)/lamivudine 60 mg/30 mg dispersible tablets on the EML and EMLc was considered by the Expert Committee in 2013. A decision was deferred at that time, as the Committee noted that the proposals originally submitted in the application were subsequently amended by the WHO Department of HIV/AIDS, reflecting work that was in progress on guidelines for the use of antiretroviral drugs. The guidelines had not been completed or approved by WHO's Guidelines Review Committee at the time of the Expert Committee meeting in 2013 (*11*).

The Committee acknowledged the public health need for suitable antiretroviral therapy for paediatric patients, noting that – despite progress in

scaling-up prevention of mother-to-child-transmission – an estimated 240 000 children were infected with HIV in utero or during breastfeeding in 2013 (*130*). *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*, published by WHO later in 2013, included some notable changes, such as the recommendation that all HIV-positive infants and children under 5 years of age start ART immediately upon diagnosis (*128*).

The 2013 guidelines recommend abacavir (ABC) + lamivudine (3TC) (or zidovudine (AZT) + 3TC) as the nucleoside reverse transcriptase inhibitor (NRTI) backbone for first-line ART in infants and children under 3 years of age. The ABC + 3TC combination is also the preferred NRTI backbone for children aged 3–10 years (and adolescents weighing less than 35 kg) and – though not the first choice – is a recommended NRTI backbone for first-line ART in adolescents aged 10–19 years and weighing 35 kg or more (*128*).

The use of dispersible fixed-dose combination (FDC) tablets is an alternative to single syrups or tablets in the treatment of very young children and/or infants. The 2013 WHO guidelines also state that it is preferable to use an age-appropriate FDC of any ART regimen, if such a formulation is available, and recommend avoidance of oral liquid or syrup formulations wherever possible. The guidelines describe dispersible tablets as the preferred solid oral dosage forms, since each tablet can be made into liquid at the point of use (*128*). In addition, the dispersible, scored tablet formulation of abacavir + lamivudine is classified as an "optimal" paediatric ART formulation by the WHO Interagency Task Team (IATT) on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and their Children (*129*).

Individually, both abacavir and lamivudine are included on the current EML and EMLc. Evidence for effectiveness and safety was evaluated at the time listing was recommended (2002).

The Expert Committee noted that preliminary, unpublished 2011 pricing data presented in the application indicated that the price of the dispersible tablet formulation was about 30% less than that of the separate syrup formulations (based on average price per patient per year). In addition to the lower cost of the product itself, the application claimed likely freight savings associated with using pills and capsules rather than syrups, which are significantly heavier and bulkier. Moreover, wastage at the patient level is typically presumed to be significantly higher with syrups than tablets.

The Committee recommended addition of the FDC abacavir (as sulfate) + lamivudine 60 mg/30 mg dispersible, scored tablet formulation to the EML and to the EMLc for the treatment of children aged 6 weeks or more with HIV infection. The Committee considered that the proposed FDC formulation of abacavir + lamivudine represented a rational treatment option for paediatric HIV patients and noted that use of age-appropriate FDC formulations is encouraged

in the WHO guidelines. For this application the Committee was not provided with pharmacokinetic or dosing information for children under 1 year of age.

In making this recommendation, the Committee noted that both abacavir and lamivudine are currently included on the EML and EMLc as single agents and that this FDC formulation is included in the most recent WHO guidelines for the use of antiretroviral drugs for treatment of HIV. The FDC formulation is also categorized as an "optimal" paediatric ARV formulation by the IATT and is likely to aid compliance and dosing of children.

Cobicistat + elvitegravir + emtricitabine + tenofovir disoproxil fumarate (addition) – EML
Emtricitabine + rilpivirine + tenofovir disoproxil fumarate (addition) – EML

Applications were submitted by Gilead Sciences Inc. for inclusion of the fixed-dose combination formulations of:

- cobicistat + elvitegravir + emtricitabine + tenofovir disoproxil fumarate (COBI+EVG+FTC+TDF); and
- emtricitabine + rilpivirine + tenofovir disoproxil fumarate (FTC+RPV+TDF)

on the Model List for treatment of HIV-1 infection in treatment-naive adult patients.

In the case of FTC+RPV+TDF, listing was sought for patients with HIV-1 RNA less than or equal to 100 000 copies/mL at the start of therapy and for virologically suppressed patients (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen at the start of therapy.

Expert reviews of the application were prepared by two members of the Expert Committee. No public comments on the application were received.

WHO's *Global update on the health sector response to HIV, 2014* reported that, at the end of 2013, there were approximately 12.9 million people receiving ART globally, 11.7 million of whom were in low- and middle-income countries (*130*).

Recommended ART regimens require the use of three or more drugs in combination, and this represents a large pill burden for patients. Fixed-dose combination formulations are recommended and confer multiple benefits, including a reduced pill burden and better adherence to treatment (*131*).

The 2013 WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* currently recommend that first-line ART in adult patients should consist of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI). The guidelines recommend use of integrase inhibitors (INI), second-generation NNRTIs and protease inhibitors (PIs) as part of third-line regimens (*128*).

The Committee noted advice from the WHO Department of HIV/AIDS that current recommendations on preferred antiretroviral drugs and regimens would be revised in June 2015 (for publication in November 2015).

The Expert Committee noted that other recent international treatment guidelines recommend first-line ART with two NRTIs and a ritonavir-boosted protease inhibitor (PI/r), an NNRTI or an INI. Specifically, the British HIV Association guidelines, updated in November 2013, recommend that therapy-naive patients start combination ART containing TDF and FTC as the NRTI backbone, and atazanavir (ATV)/r, darunavir (DRV)/r, efavirenz (EFV), raltegravir (RAL) or EVG+COBI as the third agent (*132*). The guidelines of the European AIDS Clinical Society, updated in November 2014, include co-formulated COBI+EVG+FTC+TDF as a recommended first-line regimen for ART-naive adult HIV-positive persons, but state that it should not be initiated in persons with estimated glomerular filtration rate (eGFR) less than 70 mL/min or, unless it is the preferred treatment, in persons with eGFR less than 90 mL/min (*133*). The US Department of Health and Human Services guidelines (last updated May 2014) recommend COBI+EVG+FTC+TDF as first-line therapy only for ART-naive patients with pre-ART creatinine clearance greater than 70 mL/min (*134*).

Emtricitabine and tenofovir are NRTIs, rilpivirine is a second-generation NNRTI, elvitegravir is an integrase inhibitor, and cobicistat is a pharmacokinetic enhancer (of elvitegravir).

Cobicistat + elvitegravir + emtricitabine + tenofovir disoproxil fumarate (addition) – EML

Two randomized, double-blind, active-controlled phase III trials (Study 102 and Study 103) were presented in the application as evidence for efficacy of COBI+EVG+FTC+TDF in ART-naive patients (*135*, *136*).

Study 102 compared treatment with COBI+EVG+FTC+TDF with treatment with EFV+FTC+TDF. In Study 103, treatment with COBI+EVG+FTC+TDF was compared with treatment with ATV/r plus FTC+TDF. Both studies assessed non-inferiority of COBI+EVG+FTC+TDF versus the comparator in terms of the proportion of the intention-to-treat population with a viral load less than 50 copies/mL at week 48, with 95% confidence intervals and a pre-specified non-inferiority margin of 12%.

The Committee noted that the primary efficacy end-point analyses supported the non-inferiority of COBI+EVG+FTC+TDF to the comparator treatment in terms of virological response at week 48 in treatment-naive HIV-1 infected patients in both studies. Virological suppression was maintained through to week 96.

The application also presented data from three switching studies in treatment-experienced patients, which demonstrated maintenance of virological

suppression following a switch to COBI+EVG+FTC+TDF from ritonavir-boosted PI-based regimens (*137*), NNRTI-based regimens (*138*) and a regimen of raltegrevir and emtricitabine + tenofovir (*139*). No evidence was presented in the application to support the efficacy of COBI+EVG+FTC+TDF as second- or later-line ART in patients in whom first- or second-line ART had failed.

The Committee noted that the results of an integrated analysis of data from Studies 102 and 103 support COBI+EVG+FTC+TDF as being generally well tolerated with a frequency of treatment-emergent adverse effects similar to the comparator regimens.

Emtricitabine + rilpivirine + tenofovir (addition) –EML

Two randomized, double-blind, active-controlled phase III trials (ECHO and THRIVE) were presented in the application as evidence for the efficacy of FTC/RPV/TDF in ARV-naive patients with viral load greater than 5000 copies/mL (*140*, *141*). Patients were randomized to 96 weeks' treatment with RPV 25 mg daily or EFV 600 mg daily, plus a fixed-dose background regimen of two NRTIs.

The Committee noted that, at 96 weeks, the response rate in pooled analyses of ECHO and THRIVE was 78% in both groups. For patients with HIV-RNA less than or equal to 100 000 copies/mL at baseline, the response rate was 84% with RPV and 80% with EFV (*140*). Further analysis showed a lower response among RPV-treated patients compared with EFV-treated patients when baseline viral load was greater than 500 000 copies/mL (60% vs 75%; 95% CI: -31.0, 1.8) (*142*).

Safety of FTC/RPV/TDF was assessed in ECHO and THRIVE, and results showed it to be associated with a lower incidence of treatment-related grade 2–4 adverse events compared with EFV + FTC/TDF (*142*).

Expert Committee recommendations

Overall, the Expert Committee considered that the fixed-dose combination of COBI+EVG+FTC+TDF demonstrated non-inferiority in terms of efficacy and safety compared with TDF+3TC/FTC+EFV, the currently recommended first-line regimen in the WHO guidelines. The Committee acknowledged that a fixed-dose combination formulation offers advantages in terms of reducing pill burden and possibly improving adherence, but noted that no clinical advantage in terms of efficacy and/or safety of COBI+EVG+FTC+TDF over current recommended regimens has been demonstrated.

The Committee noted that RPV has been shown to be inferior to EFV in patients with higher viral load and is therefore indicated only for patients with a low viral load (< 100 000 copies/mL). The Committee considered that triaging patients according to baseline viral load or switching from one regimen to another following the attainment of virological suppression is not consistent with

a public health approach and may not be feasible in resource-limited settings. Moreover, in consideration of patients co-infected with tuberculosis, RPV cannot be co-administered with rifampicin.

The Committee noted that both the proposed fixed-dose combination products have wide regulatory approval and marketing authorization in Europe and other high-income countries (including Australia, Japan, the United Kingdom, and USA). The licensing status of these products is under review in numerous low- and middle-income countries. In its application, Gilead advised that it has licensing agreements in place with other manufacturers to produce Gilead HIV medicines at lower cost for low- and middle-income countries.

While it acknowledged that the data presented in the applications were supportive of the efficacy of the relevant FDCs being non-inferior to that of the studied comparators, and despite the benefits associated with FDC formulations in treating HIV, the Expert Committee did not recommend the addition of COBI/EVG/FTC/TDF and FTC/RPV/TDF to the Model List of Essential Medicines. The Committee noted that the proposed formulations contain medicines not currently recommended for first-line treatment of HIV infection in WHO guidelines, and considered that there was insufficient evidence of a relevant clinical advantage in terms of efficacy of these FDC combinations over currently recommended first-line treatments that are included on the EML. The Committee noted that the WHO guidelines will be updated later in 2015.

6.4.2.2: Non-nucleoside reverse transcriptase inhibitors

Efavirenz (EFV or EFZ) (new formulation) – EML and EMLc

Nevirapine (NVP) (new formulation) – EML and EMLc

Applications were submitted by Clinton Health Access Initiative Inc., supported by WHO's Department of HIV/AIDS, for inclusion of new formulations of efavirenz (200 mg scored tablet) and nevirapine (50 mg dispersible tablet) on the EML and EMLc for the treatment of children and adolescents with HIV infection.

Expert reviews of the applications were prepared by two members of the Expert Committee. Comments on each application were received from Dr Myriam Henkens, International Medical Coordinator, Médecins Sans Frontières.

Applications to include these formulations on the EML and EMLc were considered by the Expert Committee in 2013. A decision was deferred at that time, as the Committee noted that the proposals originally submitted were subsequently amended by the WHO Department of HIV/AIDS, reflecting work that was in progress on the 2013 guidelines. The guidelines had not been completed or approved by WHO's Guidelines Review Committee at the time of the Expert Committee consideration in 2013 (*11*).

WHO's 2014 *Global update on the health sector response to HIV* reported that, at the end of 2013, approximately 12.9 million people were receiving ART globally, 11.7 million of whom were in low- and middle-income countries (LMICs). At the same time, moreover, only 23% of the estimated 3.2 million children in LMICs living with HIV were receiving ART, compared with 37% of adults (*130*). The Committee acknowledged the challenges associated with the scaling-up of treatment of paediatric patients with HIV, including that of access to suitable paediatric formulations.

The Expert Committee noted the recommendations in the 2013 WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*, which included some notable changes such as the recommendation that all HIV-positive infants and children less than 5 years start ART immediately after diagnosis (*128*).

Current WHO guidelines recommend efavirenz as part of first- and second-line ART regimens in children aged 3 years of more and weighing 10 kg or more as follows:

- For children infected with HIV and aged 3 years or more (including adolescents), EFV is the preferred non-nucleoside reverse transcriptase inhibitor (NNRTI) for first-line treatment and NVP is the alternative.
- After failure of a first-line ritonavir-boosted lopinavir (LPV/r)-based regimen, children aged 3 years or more should switch to a second-line regimen containing an NNRTI plus two NRTIs; EFV is the preferred NNRTI (*128*).

Use of nevirapine is recommended in current WHO guidelines as follows:

- An LPV/r-based regimen should be used as first-line ART for all HIV-infected children younger than 3 years (36 months), regardless of NNRTI exposure. If LPV/r is not feasible, treatment should be initiated with an NVP-based regimen.
- For HIV-infected children 3 years of age and older (including adolescents), EFV is the preferred NNRTI for first-line treatment and NVP is the alternative (*128*).

The Committee noted that efavirenz 200 mg scored tablets and nevirapine 50 mg dispersible tablets are both classified as "optimal" paediatric ARV formulations by the WHO Interagency Task Team (IATT) on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and their Children (*129*).

Efavirenz is currently included on the EML and EMLc as capsules (50 mg, 100 mg, 200 mg), oral liquid (150 mg/5 mL) and tablets (600 mg). Nevirapine is currently included on the EML and EMLc as oral liquid (50 mg/5 mL) and tablets (200 mg). Evidence for effectiveness and safety was evaluated at the time listing was recommended (2002).

A summary of the available data on the comparative cost of efavirenz presented in the application showed that average price per patient per year of the 200 mg scored tablets was lower than that of the 100 mg and 50 mg tablets/capsules. Similarly, the average price per patient per year of nevirapine 50 mg dispersible tablets was lower than that of nevirapine syrup. Other claimed advantages included freight savings, reduced wastage and simpler supply chain management.

The Expert Committee agreed on the public health need for paediatric formulations of ART medicines and considered that the proposed formulations of efavirenz and nevirapine represented rational treatment options for paediatric HIV patients. The Committee noted that these formulations are included in the 2013 WHO guidelines and are categorized by the IATT as "optimal" paediatric formulations. It considered that scored and dispersible tablet formulations are likely to aid compliance and paediatric dosing.

The Expert Committee therefore recommended addition of both efavirenz 200 mg scored tablet and nevirapine 50 mg dispersible tablet to the core list of the EML and EMLc for the treatment of children and adolescents with HIV-1 infection.

6.4.2.3: Protease inhibitors

Darunavir (addition) – EML and EMLc

An application was submitted by Dr Marco Vitoria, WHO Department of HIV/AIDS, for addition of darunavir to the EML and EMLc for the treatment of HIV infection, in anticipation of improvements in formulation and price reduction that will place ritonavir-boosted darunavir (DRV/r) on a comparable level to existing recommended ritonavir-boosted protease inhibitors lopinavir (LPV/r) and atazanavir (ATZ/r).

Expert reviews of the application were prepared by two members of the Expert Committee. Comments on the application were received from Dr Myriam Henkens, International Medical Coordinator, Médecins Sans Frontières, and from Janssen-Cilag Ltd.

The Committee noted that use of a boosted protease inhibitor in combination with two nucleoside/nucleotide reverse-transcriptase inhibitors (NRTIs) is recommended in WHO's 2013 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* as second-line ART for adults and adolescents. It is also recommended as second-line ART for children who received first-line ART with non-nucleoside reverse transcriptase

inhibitor (NNRTI)-based regimens. According to the 2013 guidelines, heat-stable fixed-dose combinations (FDCs) of ATV/r or LPV/r are the preferred boosted protease inhibitor (PI) options for second-line ART. DRV/r can be used as an alternative (*128*).

The application describes the main limitation of DRV/r: unlike the alternative ritonavir-boosted PIs, it is not currently available in a heat-stable FDC, although one is in development.

The application presented results from a 2012 WHO-commissioned systematic review of data from trials that compared drugs used in second-line ART (ATV/r, LPV/r and DRV/r) to support the comparative effectiveness and safety of DRV/r when used as part of ART (*143*). Evidence assessment using GRADE methodology showed low- or very-low-quality evidence for using ATV/r or DRV/r (once daily) over LPV/r (twice daily) or vice versa as the preferred boosted PI options. The Expert Committee considered that the systematic review of data suggests that DRV/r is an acceptable treatment option to ATV/r and/or LPV/r as second-line ART, as it has similar (or greater) efficacy and a similar safety profile to ATV/r and LPV/r. DRV/r is not currently a "preferred" treatment option in WHO ART guidelines because of its greater cost and unavailability as a heat-stable FDC.

The Committee noted correspondence received from Janssen Sciences Ireland (sponsor of Prezista® brand of darunavir) indicating their support for inclusion of darunavir on the EML and EMLc for the treatment of HIV infection because of the growing need for second-line HIV medicines in resource-limited settings. Janssen advised that the ex-factory price for the 1200 mg and 800 mg daily doses of darunavir are US$ 1.80 and US$ 1.20 respectively in sub-Saharan Africa and least-developed countries.

No information was provided regarding the price and timeline for development of the heat-stable FDC.

The Committee noted that the 2013 *Update to the optimal list of paediatric ARV formulations. IATT Meeting Report* (*129*) does not include any darunavir formulations in the "optimal" list of paediatric ARV formulations. Darunavir tablets 75 mg are included in the "limited-use" list for third-line use in special circumstances where appropriate, when boosting with separate ritonavir is available. Darunavir oral liquid (500 mg/5 mL) and 150 mg tablets are included in the "non-essential" list. The 75 mg tablet was considered a more suitable option for inclusion than the oral liquid on the limited-use list, as darunavir is not approved for use in children under 3 years of age and the 75 mg tablet provides dosing for all body weights above 15 kg.

In consideration of the public health need for second-line treatment alternatives for HIV infection, the Expert Committee recommended addition of darunavir to the EML and EMLc as an alternative to the other listed ritonavir-boosted PIs, in anticipation of a reduction in price and of market availability

of the heat-stable FDC formulation, said to be in development. The Committee advised that it would welcome an application for inclusion of the FDC when it becomes available.

With regard to the formulations and strengths proposed for inclusion, the Expert Committee recommended addition to the EML of darunavir 75 mg, 400 mg, 600 mg and 800 mg tablets, and addition of darunavir 75 mg tablets to the EMLc. It was noted that darunavir is not approved for use in children under 3 years of age and that the 75 mg tablet would provide dosing for all body weights above 15 kg. The Committee did not recommend addition to either list of darunavir oral liquid 100 mg/mL or 150 mg tablets on the basis that these formulations are classified as "non-essential" for paediatric use in the IATT Meeting Report, and that more suitable dosage forms and strengths are available for adult patients.

6.4.3: Other antivirals

Valganciclovir (addition) – EML

An application was submitted by Dr Nathan Ford, WHO Department of HIV/AIDS, for the addition of valganciclovir to the Model List for the treatment of cytomegalovirus retinitis (CMVr), a preventable late-stage opportunistic infection in people living with HIV/AIDS.

Reviews of the application were prepared by two members of the Expert Committee. Comments in support of the application were received from Myriam Henkens, International Medical Coordinator, Médecins Sans Frontières.

CMVr is part of a systemic infection, although in HIV/AIDS patients in low- and middle-income countries, the eye is the only end-organ where the presence of clinical infection is easy to establish. Evidence from both before and after the introduction of highly active anti-retroviral therapy (HAART) in resource-rich and resource-poor settings has shown that CMV viraemia predicts mortality and, in most reports, is the most powerful predictor of mortality (*144–147*).

Left untreated, CMVr can lead to permanent loss of vision as a result of damage to the optic nerve or macula, of retinal detachment (which can present years after CMVr has been treated) or of the development of immune recovery uveitis. Early diagnosis and treatment are crucial to preventing both vision loss and transmission of CMVr to the contralateral eye, which occurs within six months of infection in 50–61% of untreated CMVr cases (*148*).

Estimates of the incidence and prevalence of CMVr in resource-limited settings vary. CMVr incidence ranges from 0 to 19.6% in sub-Saharan Africa (*149*), while estimated prevalence ranges from less than 5% in southern Africa to more than 30% in south-east Asia (*150*). Although the introduction and scale-up of HAART in developed countries has dramatically reduced the prevalence

of CMVr in these settings, high ART accessibility does not correlate completely with reduced CMVr.

Clinical guidelines first recommend that HIV/AIDS patients at risk for or recently diagnosed with CMVr have access to HAART, which slows progression of the condition (*149*). Treatment options for CMVr include intravenous ganciclovir, foscarnet, or cidofovir; ganciclovir implant; intravitreal injections of ganciclovir, foscarnet, cidofovir or fomivirsen; and oral valganciclovir or ganciclovir (*96*). Intravenous ganciclovir has been the gold standard for treatment of CMVr; however, this requires daily infusions and indwelling catheters, with attendant risks of secondary sepsis (*149*), and this treatment is not always feasible in resource-limited settings.

Valganciclovir is an oral medication that has been shown to be therapeutically equivalent to intravenous ganciclovir in adults (*151*) and is recommended because of its lower cost, lower risk of adverse reactions, high efficacy and easy administration, and the fact that it can be used for both induction and maintenance therapy (*149*). Oral valganciclovir is the standard of care in developed countries and has shown to reduce CMVr-related mortality even in patients failing HAART (*152*, *153*). Induction treatment (900 mg twice a day for 21 days) is followed by maintenance treatment (900 mg once daily) until the following criteria are met: the retinitis has become inactive on retinal examination; the patient has been receiving ART for at least 3 months; and the CD4 count is above 100 cells/mm^3. Valganciclovir is well tolerated; the most common adverse reactions reported included diarrhoea, nausea, fever, neutropenia and oral candidiasis (*154*).

The Expert Committee acknowledged that CMV infection is an increasing concern in paediatric patients, with a high incidence of congenital CMV infections and a growing number of immunocompromised patients (*155*). The Committee considered that a clinical need exists for antiviral therapy to be available for paediatric patients with CMV infection. Data on the clinical efficacy of valganciclovir in the paediatric population are limited; however, several studies have shown that, in various paediatric dosing algorithms, combined with therapeutic drug monitoring to ensure exposure within the therapeutic window, valganciclovir might be used in anti-CMV treatment for neonates, infants and children (*155*–*157*).

Following an agreement between Roche and the Medicines Patent Pool (August 2013), the price of valganciclovir for 138 developing countries was reduced to approximately US$ 275 for 60 tablets (*157*). Based on this, courses of 12 weeks (3 weeks induction, 9 weeks maintenance therapy) and 27 weeks (3 weeks induction, 24 weeks maintenance) will cost approximately US$ 907.20 and US$ 1814.40 respectively. With generic formulations available, prices are expected to decline further.

The Expert Committee recommended addition of valganciclovir to the core list of the EML for treatment of cytomegalovirus retinitis. The Committee accepted that oral valganciclovir provides systemic effects equivalent to those of IV ganciclovir in both induction and maintenance treatment of CMVr. The Committee considered that valganciclovir, being an oral preparation, offered advantages over IV ganciclovir, particularly in resource-limited settings, in terms of price and ease of administration.

In view of the clinical need for effective antiviral treatments for children, the Expert Committee also recommended that valganciclovir be added to the complementary list of the EMLc for the treatment of paediatric patients with CMVr. Inclusion on the complementary list was considered appropriate because of the need for therapeutic drug monitoring.

6.4.4: Anti-hepatitis medicines

6.4.4.1: Medicines for hepatitis B

Entecavir (addition) – EML and EMLc

Tenofovir disoproxil fumarate (new indication) – EML

An application was submitted by Dr Philippa Easterbrook, WHO Global Hepatitis Programme, Department of HIV/AIDS, for the addition of entecavir to the EML and EMLc for the treatment of chronic hepatitis B infection.

In addition, a separate application was submitted by Gilead Sciences Inc., California, USA, for the addition of tenofovir disoproxil fumarate (TDF) to the EML for the treatment of chronic hepatitis B. TDF is currently included in the Model List as an antiretroviral agent in Section 6.4.2.1 Nucleoside/Nucleotide reverse transcriptase inhibitors.

The Committee noted that the requests for inclusion of these medicines reflect recent WHO guidelines (2015) for the treatment of chronic hepatitis B (*158*). These guidelines recommend treatment with either tenofovir or entecavir. Entecavir is the recommended agent for use in children aged 2–11 years. Tenofovir is licensed for use in those aged 12 years and above. Nucleoside/nucleotide analogues (NAs) with a low barrier to resistance (lamivudine, adefovir or telbivudine) can lead to drug resistance and are not recommended in the WHO guidelines (*158*). It is expected that inclusion of entecavir and tenofovir in the Model List will help facilitate the scale-up of hepatitis B treatment.

Expert reviews of the applications were prepared by two members of the Expert committee. Comments in support of the entecavir application were received from Dr Myriam Henkens, International Medical Coordinator, Médecins Sans Frontières. Correspondence in support of the applications was also received from the WHO Department of HIV/AIDS and Global Hepatitis Programme.

Hepatitis B infection is caused by the hepatitis B virus (HBV), an enveloped DNA virus that infects the liver, causing hepatocellular necrosis and

inflammation. Chronic hepatitis B (CHB) is defined as persistence of hepatitis B surface antigen (HBsAg) for six months or more. The disease is a major public health problem; an estimated 240 million people were chronically infected worldwide in 2005, with a disproportionally large burden of HBsAg infection in all sub-Saharan African regions and east Asia (*159*). Although most carriers will not develop hepatic complications from CHB, 15–40% will develop serious sequelae during their lifetime, including cirrhosis and hepatocellular carcinoma (HCC) (*160*).

Several interventions have the potential to dramatically reduce the burden of HBV infection. By 2011, hepatitis B immunization programmes had been introduced in 180 countries, targeting infants (first dose at birth), and have been highly effective in reducing the incidence and prevalence of hepatitis B in many endemic countries (*161*). However, the applications emphasized that, despite these advances, viral hepatitis is not being systematically addressed in most countries, and it will be several decades until the immunization programmes have an impact on HBV-related deaths.

At present, CHB cannot be cured in most people, and the goal of treatment is therefore to suppress viral replication which reduces (or reverses) progression of liver fibrosis and cirrhosis, thereby reducing the risk of liver failure, HCC and death. Long-term (potentially lifelong) therapy is required for the majority of patients (*158*).

Since the 1990s, NAs and interferon (IFN)-alpha have been widely used for the treatment of CHB. The NAs currently licensed are lamivudine, telbivudine, adefovir, tenofovir and entecavir. Development of viral resistance as a result of mutations in the viral DNA during replication is the primary limitation of most oral antiviral agents. The National Clinical Guideline Centre in the United Kingdom reports that very low rates of drug resistance are recorded for entecavir compared with adefovir, lamivudine and telbivudine (*162*). At present, no induced drug resistance mutations caused by tenofovir treatment have been clearly identified.

A series of systematic reviews and a network meta-analysis, commissioned as part of the WHO guideline development process, confirm the efficacy of entecavir. In the treatment of naive, hepatitis B e antigen-positive (HBeAg-positive) Asian CHB patients, undetectable HBV DNA levels were achieved in more entecavir-treated patients than in those treated with adefovir (RR 1.73; 95% CI: 1.38–2.17) (*163*). Compared with lamivudine, entecavir showed greater efficacy in terms of improved liver histology (RR 1.16; 95% CI 1.07–1.26), normalization of serum alanine aminotransferase (ALT) (RR 1.15; 95% CI: 1.11–1.2) and HBV DNA loss (RR 1.65; 95% CI: 1.37 to 1.98) (*164*). After three and five years of treatment with entecavir there were low cumulative rates of mortality (3% and 3.8%) and HCC (3.9% and 6.6%). The cumulative probability of developing genotypic resistance to entecavir was low at three years (1.2–3.3%)

and five years of treatment (0.8–1.2%) (*165–169*). Similar effectiveness of entecavir compared with lamivudine and lamivudine plus adefovir was apparent in adult treatment-naive patients with decompensated cirrhosis (*170*, *171*). Although data on use in children are more limited, there is evidence of high virological response to tenofovir in adolescents, with normalization of serum ALT at 72 weeks treatment and no observed viral resistance (*172*) and an ongoing placebo-controlled trial of entecavir in children (AI463189) which showed entecavir to be superior to placebo at reducing HBV DNA to less than 50 IU/mL, HBeAg seroconversion and normalization of serum ALT levels at 48 weeks of treatment (*173*).

Two double-blind, phase III studies compared tenofovir with adefovir in patients with HBeAg-negative or HBeAg-positive CHB (*174*). The studies concluded that tenofovir had greater antiviral efficacy than adefovir and a similar safety profile. In the trial on patients with HBeAg-positive CHB, treatment with tenofovir resulted in a significantly higher proportion of patients with undetectable serum HBV (76% versus 13%), ALT normalization (68% versus 54%) and HBsAg loss (3% versus 0%). In the trial on patients with HBeAg-negative CHB, 48 weeks of treatment with tenofovir resulted in significantly more patients with undetectable serum HBV-DNA than treatment with adefovir (93% versus 63%). Tenofovir resistance was not detected in any of the patients after up to 96 weeks of treatment; it should be noted, however, that patients at the greatest risk of drug resistance received additional therapy with emtricitabine.

Based on the available evidence, a network meta-analysis, including a total of 21 pair-wise comparison randomized controlled trials (RCTs) comprising 5 073 HBeAg-positive nucleoside-naive persons and 16 trials comprising 2 604 HBeAg-negative nucleoside-naive persons, showed that individuals treated with tenofovir monotherapy had the highest probability of achieving undetectable HBV DNA at the end of 1 year of treatment. This result was observed in both HBeAg-positive (94.1%; 95% CI: 74.7–98.9%) and HBeAg-negative (97.6%; 95% CI: 56.7–99.9%) persons (*158*). For entecavir treatment, the result was 64.5% (95% CI: 49.1–80.5%) in HBeAg-positive and 91.9% (95% CI: 87.3–95.1%) in HBeAg-negative individuals.

With regard to safety, both entecavir and tenofovir seem to be well-tolerated drugs with minimal side-effects. The National Clinical Guideline Centre does note that further research should be undertaken to determine the long-term safety of tenofovir, including the risk of clinically significant hypophosphataemia and related bone toxicity in people with CHB (*162*). No significant differences in tolerability and renal parameters are reported between treatment with entecavir and tenofovir (*175*). It is recommended that baseline renal function be measured and baseline risk for renal dysfunction assessed in all individuals before initiation of antiviral therapy. Renal function should be monitored annually in persons

on long-term tenofovir and entecavir therapy and growth should be monitored carefully in children when entecavir is administered.

The Committee noted that, compared with lamivudine and other NAs with a low barrier to resistance, entecavir and tenofovir have a high genetic barrier to resistance and very low observed rates of drug resistance over long-term follow-up. It was also noted, however, that resistance to entecavir occurs frequently in individuals with lamivudine resistance (*158*).

The Expert Committee noted that, according to the WHO Global Price Reporting Mechanism, the minimum treatment cost per year for tenofovir is US$ 36, with a median of US$ 46. The Committee also noted advice from the applicant of their pricing strategies and licensing agreements in low- and middle-income countries. Although studies presented in the application showed entecavir to be either cost–effective or the preferred strategy (*176–180*), the Committee noted that the production cost of entecavir has been estimated to be far below the price currently charged (*181*).

Taking into consideration the significant public health need, the clear evidence from RCTs supporting the role of both medicines in various CHB treatment regimens , and the inclusion of these medicines in the recently released WHO guidelines for the prevention, care and treatment of chronic hepatitis B infection, the Expert Committee therefore recommended the addition of tenofovir and entecavir to the core list of the EML and the addition of entecavir to the core list of the EMLc for the treatment of chronic hepatitis B under a new section (Antihepatitis medicines) and subsection (Medicines for hepatitis B).

6.4.4.2: Medicines for hepatitis C

Sofosbuvir (addition) – EML

Daclatasvir (addition) – EML

Simeprevir (addition) – EML

Ledipasvir + sofosbuvir (addition) – EML

Ombitasvir + paritaprevir + ritonavir with or without dasabuvir (addition) – EML

Five applications for direct-acting antiviral (DAA) regimens were submitted for addition to the Model List for the treatment of chronic hepatitis C virus (HCV) infection: sofosbuvir (Gilead Scien ces), daclatasvir (Médecins Sans Frontières – Access Campaign), simeprevir (Janssen Pharmaceutica), ledipasvir + sofosbuvir (fixed-dose combination (FDC)) (Gilead Sciences), and ombitasvir + paritaprevir + ritonavir (FDC), with or without dasabuvir (Dr Andrew Hill, University of Liverpool). A summary of key information for the DAAs and combination regimens proposed for inclusion on the EML is shown in Table 4.

During the 19th meeting of the WHO Expert Committee in 2013, the Committee stressed the need to follow the development of DAAs and to consider applications for all-oral treatment options for hepatitis C (*11*).

Expert reviews of each application were prepared by two members of the Expert Committee. Public comments in support of the sofosbuvir, daclatasvir and the ledipasvir and sofosbuvir FDC applications were received.

An overview of HCV medicines that are currently available, or that are in advanced clinical development, was received from the Treatment Action Group (TAG) (*182*). The Expert Committee discussed the available and forthcoming DAA regimens and considered the research gaps in the treatment for HCV on the basis of the TAG report. The Expert Committee acknowledged the importance of approved new DAAs for hepatitis C, the promising pipeline of drugs in development, and determination of optimal DAA regimens with best-in-class drugs as an area in need of a public health research agenda.

The global burden of chronic hepatitis C is enormous with an estimated 185 million infected worldwide and 350,000 HCV-related deaths per year (*183*). The worldwide prevalence of hepatitis C infection varies substantially. Egypt has the highest prevalence with more than 15% of the population infected and Africa has an estimated HCV seroprevalence of 3%. Further, due to shared routes of transmission, co-infection with HIV and HCV is common, with approximately 4–5 million persons co-infected with HCV/HIV worldwide (*184*).

Table 4
DAA and DAA combination regimens discussed by the 2015 Expert Committee[a]

DAA/regimen Pharmaco-logical class	Genotype(s)	Data in HIV/HCV	Hepatic impairment	Renal impairment	Propensity for DDIs	Dosing, duration, combination
Sofosbuvir Nucleotide polymerase inhibitor (NS5B)	Pan-genotypic	SVR comparable	No dose adjustment for mild, moderate or severe hepatic impairment	No dose adjustment for mild or moderate renal impairment; no data or dose for severe renal impairment	Low	Once daily dosing Used with PEG-IFN/RBV or RBV alone in G1, G4, G5 and G6. Used with RBV in G2 and G3. Duration 12 or 24 weeks depending on genotype and regimen Used with daclatasvir, with or without RBV, for 12 or 24 weeks (depending on genotype, cirrhosis) Used with simeprevir for 12 or 24 weeks (depending on cirrhosis) Very limited in vivo data for G5 and G6

Table 4 *continued*

DAA/regimen Pharmaco-logical class	Genotype(s)	Data in HIV/HCV	Hepatic impairment	Renal impairment	Propensity for DDIs	Dosing, duration, combination
Simeprevir Protease inhibitor (NS3)	G1 and G4	SVR with PEG-IFN/RBV comparable; no interferon-free trials in HIV/HCV	No dose adjustment for mild hepatic impairment; no data or dose in moderate or severe hepatic impairment	No dose adjustment for mild, moderate or severe renal impairment; no data in severe renal impairment	High	Once daily dosing Used with PEG-IFN/RBV; or sofosbuvir with or without RBV, for 12 or 24 weeks Should not be given to patients who failed previous protease inhibitor therapy
Daclatasvir NS5A replication complex inhibitor	Pan-genotypic in vitro; studied in G1, G2, G3 and G4	SVR comparable	No dose adjustment for mild, moderate or severe hepatic impairment	No dose adjustment for mild, moderate or severe renal impairment	Moderate	Once daily dosing Used with PEG-IFN/RBV; or sofosbuvir with or without RBV, for 12 or 24 weeks (depending on genotype, cirrhosis) No in vivo data for G5 and G6
Ledipasvir/ sofosbuvir FDC: nucleotide polymerase inhibitor (NS5B) and NS5A inhibitor	G1, G3, G4 and G6	SVR comparable	No dose adjustment for mild, moderate or severe hepatic impairment	No dose adjustment for mild or moderate renal impairment; no data or dose for severe renal impairment	Moderate	Once daily dosing Duration 8, 12 or 24 weeks depending on viral load, treatment experience, cirrhosis RBV required in G3 (limited data); under study in G2; no in vivo data for G5; limited in vivo data for G6

Table 4 *continued*

DAA/regimen Pharmacological class	Genotype(s)	Data in HIV/HCV	Hepatic impairment	Renal impairment	Propensity for DDIs	Dosing, duration, combination
Ombitasvir/paritaprevir/ritonavir and dasabuvir FDC: NS5A inhibitor, ritonavir-boosted HCV protease inhibitor, non-nucleoside polymerase inhibitor	G1 and G4 only	SVR comparable	Not recommended for Child-Pugh B; contraindicated in Child-Pugh C	No dose adjustment for mild, moderate or severe renal impairment	High	Once or twice daily dosing Used with or without RBV for 12 weeks (24 weeks in patients with G1a and cirrhosis, and previous null response). RBV not required for HCV G1b infection, thus complex subtyping required

[a] Source: adapted from reference *182*.

Abbreviations: DAA: direct-acting antiviral; DDI: drug–drug interactions; FDC: fixed-dose combination; G: genotype; NS3:non-structural protein 3; NS5A: non-structural protein 5A; NS5B: non-structural protein 5B: PEG-IFN/RBV: peginterferon and ribavirin; RBV: ribavirin; SVR: sustained virological response.

Data from a large cohort of patients with HCV (more than 120 000) from the US Veterans Administration showed that only 24% of patients received treatment following HCV diagnosis and that only 16% of treated patients achieved an undetectable viral load (HCV RNA) after treatment (*185*). The observed low percentage of patients receiving treatment would suggest that up until now, most patients were "either healthy or too sick for hepatitis C treatment" (*186*). A 2013 study evaluating treatment uptake in 16 countries reported that, in nine of the countries, less than 1.5% of the HCV-infected population received treatment and that the treatment rate exceeded 5% only in France. The authors concluded that the current rates of treatment and efficacy are inadequate to address the burden of disease associated with HCV (*187*).

HCV is classified into 6 genotypes (and subtypes) with distinct geographical distribution. In general, genotype 1 is the most common, accounting for approximately 46% of infections, and genotype 3 has a global prevalence of approximately 30%. Due to variable genotype-dependent treatment responses, current regimens require HCV genotype testing. Identification of host single nucleotide polymorphism of the interleukin 28B (IL28B) gene on chromosome 19, which varies markedly by ethnic group, may be useful in predicting response to HCV therapy (*188*). Assessment of HCV viral load (i.e. HCV RNA) is required both before and after HCV treatment. These tests are frequently unavailable in resource-poor countries.

The standard antiviral treatment regimen for all HCV genotypes was based for many years on pegylated interferon (PEG-IFN) injections and oral ribavirin (RBV) (*189*). PEG-IFN/RBV treatment was limited by partial response, with achievement of a sustained virological response (SVR, defined as undetectable serum HCV RNA by a clinical polymerase chain reaction assay at 12–24 weeks following the end of treatment) in less than 50% of patients (*182*). Treatment regimens with PEG-IFN/RBV were complex and resource-intensive and were accompanied by significant adverse events; the suboptimal treatment responses resulted in large numbers of patients ultimately progressing to cirrhosis. In contrast, patients who achieve an SVR experience a reduction in liver inflammation and in the rate of progression of liver fibrosis. Several long-term observational studies have shown that achievement of an SVR has been associated with fibrosis regression and reduced risk of hepatocellular carcinoma. Reductions in all-cause mortality have also been observed (*189*, *190*), highlighting the benefits of treating patients with advanced liver disease. However, PEG-IFN requires subcutaneous administration, must be used with caution in cirrhotic patients because of the risk of precipitating liver decompensation, and is not recommended in patients with decompensated cirrhosis as it can cause significant morbidity and mortality (*191*). Additionally, RBV requires twice-daily dosing, is associated with haemolytic anaemia and is highly teratogenic. Thus RBV-sparing regimens are also highly desirable.

The advent of effective, well-tolerated, IFN-free treatments means improved treatment options for patients with advanced liver disease. Patients with significant fibrosis should thus be prioritized for treatment. However, patients with chronic hepatitis C at an earlier stage can also benefit, with progression to late stage of disease being interrupted and the risk of other extrahepatic complications of infection reduced. Expanding anti-HCV treatment capacity to target patients at risk of infecting others is also beneficial from a public health perspective. Several new anti-HCV DAA regimens proposed for inclusion on the EML have been developed and registered in recent years. These new treatments have been shown to be more effective, better tolerated and safer than the older therapies (i.e. PEG-IFN/RBV in combination with first-generation protease inhibitors or DAAs such as boceprevir and telaprevir); several also exhibit broader genotypic activity than previous options. It is expected that inclusion of the proposed DAAs in the Model List will help facilitate the global scale-up of chronic hepatitis C treatment and focus the attention of all stakeholders on the need to increase the affordability of and access to DAAs.

In April 2014, WHO issued guidelines for treating hepatitis C (*183*), which will be updated on a regular basis as new drugs and new research findings become available. The 2014 guidelines strongly recommend sofosbuvir- and simeprevir-containing regimens.

The Expert Committee acknowledged that, based on multiple clinical studies, use of DAA-containing regimens results in much higher SVR rates assessed at 12 weeks post-treatment (i.e. SVR12) than IFN-based regimens. The new regimens generally have response rates in excess of 90% in both treatment-naive and previously treated patients and an improved adverse event profile; treatment duration is reduced and administration and monitoring are simplified.

Sofosbuvir

Sofosbuvir is a once-daily oral HCV-specific nucleotide analogue polymerase inhibitor. It is proposed for inclusion in the EML as a treatment for chronic hepatitis C in adult patients (≥ 18 years) as part of a combination regimen.

The data for HCV genotypes 1, 2, 3 and 4 are based primarily on five published phase III studies – NEUTRINO (*192*), FISSION (*192*), POSITRON (*193*), FUSION (*193*) and VALENCE (*194*) – in which 12 or 24 weeks' treatment with sofosbuvir plus ribavirin was found to be superior or non-inferior to either standard of care (a PEG-IFN/RBV-containing regimen) or historical controls, resulting in higher rates of sustained virological response. A sixth clinical trial – PHOTON-1 – supports the use of sofosbuvir + RBV in HCV patients co-infected with HIV (*195*). Only limited data are available for efficacy in persons infected with HCV genotypes 5 or 6. Sofosbuvir is currently considered the backbone of many first-line regimens, since it has a wide genotype spectrum, can be used in cirrhosis, and has low propensity for drug–drug interactions (DDIs).

Sofosbuvir + simeprevir

Sofosbuvir in combination with simeprevir was studied in one phase IIb study (COSMOS) in which patients were randomized to simeprevir and sofosbuvir with or without ribavirin (*196*). Two cohorts of patients infected with HCV genotype 1 were treated for either 12 or 24 weeks, stratified in two subgroups (prior IFN null responders with absent-to-moderate fibrosis; and treatment-naive patients and prior IFN null responders with advanced fibrosis or compensated cirrhosis). Overall the results from the COSMOS study show that a dual regimen of sofosbuvir + simeprevir results in high SVR12 rates in patients infected with HCV G1 and the addition of RBV to this regimen did not improve SVR rates.

Safety

Sofosbuvir-based IFN-free treatment regimens have been associated with low rates of treatment discontinuation due to adverse events. In a study comparing simeprevir + sofosbuvir with sofosbuvir + PEG-IFN/RBV in treatment-naive and treatment-experienced patients with compensated cirrhosis, 31 patients were randomly assigned to the IFN-based regimens. Four of those 31 patients dropped out, refusing to take IFN, and three were forced to discontinue treatment because of serious adverse events (*197*). Overall, the IFN-based regimen was less safe and effective than the simeprevir + sofosbuvir combination therapy (75% versus 93% SVR).

Sofosbuvir + RBV treatments were discontinued in 1–2% of treated patients, as compared with discontinuation in 11% of patients receiving PEG-IFN/RBV. In the FISSION and POSITRON trials, analysis of the impact of HCV treatment on health-related quality of life showed that sofosbuvir + RBV was better than PEG-IFN/RBV (and similar to placebo). Improved health-related quality of life was also associated with the SVR achieved with sofosbuvir + RBV therapy (*198*).

Daclatasvir

Daclatasvir is an oral nonstructural protein 5A (NS5A) inhibitor that is licensed for treatment of HCV in combination with other HCV medicines. Daclatasvir has demonstrated potent pan-genotypic activity (genotypes 1–6) in vitro studies (*199*) and has been clinically evaluated in genotypes 1-4. A favourable efficacy profile has been apparent in a number of different combinations, importantly in several IFN-free regimens.

Efficacy

Genotype 1

Several phase IIa studies have evaluated daclatasvir with either another oral DAA, asunaprevir (a nonstructural protein 3 protease inhibitor), PEG-IFN/

RBV, or both asunaprevir and PEG-IFN/RBV. The all-oral daclatasvir + asunaprevir combination achieved cure in a minority (15%) of patients with genotype 1a infection (*200*), but had greater efficacy in genotype 1b infection. It was therefore decided that the daclatasvir + asunaprevir combination would be tested only in patients with genotype 1b infection. In the daclatasvir + asunaprevir + PEG-IFN/RBV subgroup, however, SVR was 90–100% (*200*). In the COMMAND-1 and COMMAND-2 trials, treatment of genotype 1 or 4 patients with daclatasvir and PEG-IFN/RBV resulted in variable SVR rates, depending on genotype, drug combination, drug dose and previous treatment response status. Overall, regimens including daclatasvir were associated with better outcomes (*201*, *202*). Several other studies have confirmed the efficacy of combination treatment with daclatasvir + asunaprevir in achieving SVR in previous PEG-IFN/RBV null or partial responders (*203–205*). The Expert Committee has noted that the manufacturer of asunaprevir (Bristol Myers Squibb) has chosen to discontinue further development of asunaprevir as a dual combination therapy with daclatasvir. However, an all-oral triple therapy regimen containing daclatasvir, asunaprevir and a non-nucleoside NS5B inhibitor (beclabuvir) is being studied (*206*).

Non-genotype 1

The SVR12 rate in patients with HCV genotype 2 or 3 infection treated with daclatasvir and PEG-IFN/RBV for 12 or 16 weeks ranged from 52% (placebo and PEG-IFN/RBV, genotype 3) to 88% (daclatasvir and PEG-IFN/RBV, genotype 2) (*207*). SVR24 was 83% in daclatasvir recipients with genotype 2 infection in the 12-week arms compared with 63% in the placebo group. In patients with genotype 3, 69% of daclatasvir recipients achieved SVR24 in the 12-week arms compared with 59% in the placebo group (*207*). When daclatasvir was used in combination with sofosbuvir in treatment-naive or treatment-experienced patients with HCV genotype 2 or 3 infection, cure rates were also very high (*208–210*).

In patients with genotype 4 infection, treatment with daclatasvir plus PEG-IFN/RBV resulted in SVR12 being achieved in 67–100% of patients, compared with 50% of patients treated with PEG-IFN/RBV alone (*201*). In the COMMAND-4 study, investigators compared daclatasvir + PEG-IFN/RBV with PEG-IFN/RBV plus placebo; SVR12 was achieved in 82% versus 43% of patients respectively, showing the superiority of the daclatasvir + PEG-IFN/RBV combination (*211*).

Daclatasvir in combination with other DAAs

Adding another oral DAA, beclabuvir (a non-nucleoside NS5B inhibitor), to daclatasvir and asunaprevir has also led to high SVR rates in patients infected with genotype 1 HCV (*212*, *213*). Studies of this combination considered

treatment-naive patients, null responders to PEG-IFN/RBV and cirrhotic patients; results were similar regardless of treatment duration (12 or 24 weeks), of whether patients were infected with HCV genotype 1a or 1b, and of host IL28B genotype.

The ALLY studies evaluated the all-oral DAA combination of daclatasvir + sofosbuvir in patients with cirrhosis or post-liver transplant (ALLY-1), with HIV co-infection (ALLY-2) or with genotype 3 infection (ALLY-3). ALLY-1's primary end-points showed that the combination achieved high cure rates, with 94% of post-transplant genotype 1 patients and 82% of genotype 1 patients with advanced cirrhosis achieving SVR12 (*214*). Similarly high SVR rates were noted in ALLY-2, which tested the same combination in patients with HIV and HCV co-infection (including HCV genotypes 1-6). Importantly, high HCV cure rates were achieved without the need to alter existing anti-HIV antiviral regimens (*215*). The ALLY-3 study reported an overall 96% SVR12 rate in treatment-nave and treatment-experienced patients with genotype 3 infection without cirrhosis (*209*).

Daclatasvir was evaluated in combination with sofosbuvir, with or without ribavirin, in patients with chronic HCV genotype 1, 2 or 3 in an open randomized study (AI444040) in 211 adults without cirrhosis (HCV genotype 1 patients were mostly treatment-nave with a minority resistant to prior first-generation protease inhibitor regimen, i.e. boceprevir and telaprevir) (*208*). SVR12 was achieved in 98% of patients with HCV genotype 1, 92% of those with genotype 2 and 89% of those with genotype 3. The combination was associated with high SVR rate among patients with characteristics that were previously associated with a poor response to treatment (i.e. HCV genotypes 1a and 3, specific IL28B genotype, and black race). The treatment response rates were similar among patients whose treatment did and did not contain ribavirin; however, ribavirin recipients had a greater reduction in haemoglobin level.

Safety

The most frequently reported adverse reactions of at least Grade 3 severity (frequency of 1% or greater) were neutropenia, anaemia and lymphopenia (*216*). From the 12-week results of the phase IIb COMMAND-2 study of daclatasvir + PEG-IFN/RBV, the rates of serious adverse events were 5.9% (12/203), 5.0% (10/199) and 17.6% (3/17), for the daclatasvir 20 mg, 60 mg and placebo groups, respectively (*202*). For the combination of daclatasvir + sofosbuvir, the most frequently reported adverse events were fatigue, headache and nausea. Low phosphorus and high glucose were the most common grade 3 or 4 laboratory abnormalities. Anaemia was an issue only in patients treated with RBV (*208*). In all-oral daclatasvir-containing regimens, adverse events were similar in patients with and without cirrhosis (*217*).

Simeprevir

Simeprevir is a DAA that selectively inhibits the HCV NS3/4A protease. It has activity against HCV genotypes 1, 2, 4, 5 and 6.

Efficacy

In the development of the 2014 WHO guidelines for the screening, care and treatment of persons with hepatitis C infection, data were considered from four RCTs comparing simeprevir + PEG-IFN/RBV with PEG-IFN/RBV in persons with chronic HCV infection (*218–221*). The combined SVR rate was 79.2% for patients treated with simeprevir + PEG-IFN/RBV and 45.6% for patients treated with PEG-IFN/RBV (*183*). The efficacy of simeprevir + PEG-IFN/RBV is greatest among treatment-naive patients and prior relapsers. Treatment-experienced patients who had prior partial or null response to interferon and ribavirin therapy and patients with cirrhosis tend to have lower SVR rates (*219–221*). For patients eligible for an IFN-free regimen, simeprevir in combination with sofosbuvir results in SVR rates of greater than 90%, including in prior null responders, as noted above (*196*). However, simeprevir therapy is limited in patients with HCV genotype 1a infection if they carry a specific HCV genome polymorphism (i.e. Q80K). The Q80K viral variant in patients with genotype 1a infection has been associated with decreased response rates to simeprevir + PEG-IFN/RBV. In the COSMOS trial, the SVR rates in patients with genotype 1a infection with a baseline Q80K mutation were 89% compared with 96% in the cohort with genotype 1b infection (*196*), a difference of some clinical relevance.

Safety

Simeprevir sometimes causes photosensitivity and is also associated with rash and dermatological reactions, which may reduce acceptability. Overall the rate of adverse events is low (*183*) and related mostly to the side-effects of concomitant IFN/RBV therapy.

Ledipasvir + sofosbuvir

Ledipasvir (90 mg) and sofosbuvir (400 mg) have been co-formulated as an oral once-daily fixed-dose combination indicated for the treatment of HCV genotype 1 infection in adults. The FDC is highly effective for both treatment-naive and experienced patients, even those with cirrhosis. The duration of therapy with ledipasvir + sofosbuvir is 12 weeks for treatment-naive and non-cirrhotic treatment-experienced patients and 24 weeks for cirrhotic treatment-experienced patients. Eight weeks of treatment may be sufficient in treatment-naive non-cirrhotic patients with a viral load less than 6 million IU/mL at baseline. In most patient populations, efficacy does not appear to be significantly improved

by the addition of RBV. However, in treatment-experienced cirrhotic patients with HCV genotype 1 infection who failed sequential treatment with PEG-IFN/RBV as well as PEG-IFN/RBV protease inhibitor-based therapy, the combination of sofosbuvir + ledipasvir + RBV for 12 weeks or sofosbuvir + ledipasvir for 24 weeks resulted in SVR12s of 96% and 97% respectively (*222*).

Efficacy

The efficacy of ledipasvir + sofosbuvir FDC was evaluated in several phase III studies in patients with HCV genotype 1 infection (*223–227*). The trials showed very high SVR rates at 12 weeks (> 90%) in both treatment-naive patients and treatment-experienced patients (*225*, *227*) SVR rates were also consistently high (> 90%) among different subgroups, including those that usually have been considered poor responders to interferon-based treatment (e.g. non-CC IL28B genotype, high viral load at baseline, black race, genotype 1a infection). A shorter duration of therapy also appears to be highly effective in patients without cirrhosis (*225*). Extension of the treatment to 24 weeks and addition of ribavirin did not substantially increase SVR (*223*, *225*, *228*), except in the subgroup of treatment-experienced cirrhotic patients who failed prior triple therapy with a protease inhibitor/PEG-IFN and RBV, as noted above (*222*).

Available data on the efficacy of ledipasvir + sofosbuvir FDC in patients with non-genotype 1 HCV are limited. The application stated that data (on file) from small patient populations in phase II trials suggest treatment is associated with high cure rates in patients with genotypes 3, 4 and 6 HCV infection.

HCV resistance monitoring showed that sofosbuvir has a high genetic barrier to resistance, and that efficacy of the FDC remained high despite the presence of specific baseline mutations (*223*, *225*, *227*).

Safety

A good safety and tolerability profile with a very low rate of discontinuations has been demonstrated for ledipasvir + sofosbuvir FDC. The most common adverse events were fatigue, headache and insomnia (*227*). Serious adverse events were reported by a minority (< 8%) of patients, and most adverse events were considered to be unrelated to treatment.

Ombitasvir + paritaprevir + ritonavir co-formulated tablet with or without dasabuvir

The FDC tablet of ombitasvir + paritaprevir + ritonavir (used as a pharmacological booster for paritaprevir) administered with dasabuvir, and with or without RBV, is indicated for use as a treatment for chronic HCV genotype 1 infection in adults, regardless of fibrosis stage or previous treatment history with PEG-IFN/RBV. However, it is not recommended in patients with moderate hepatic impairment

(Child-Pugh B) and is contraindicated in patients with severe hepatic impairment (Child-Pugh C). Additionally, in Europe a simplified regimen of the ombitasvir + paritaprevir + ritonavir FDC administered with ribavirin has been licensed for the treatment of chronic HCV genotype 4 infection in adult patients.

Efficacy

Phase III randomized clinical trials suggest that ombitasvir + paritaprevir + ritonavir with dasabuvir, with or without ribavirin, is a highly efficacious regimen for treatment of chronic HCV genotype 1 infection, regardless of treatment history or the presence of cirrhosis. SVR12 rates were always above 90% in treatment-naive genotype 1 patients without cirrhosis (*229*–*232*), and non-cirrhotic genotype 1 patients who had failed prior PEG-IFN/RBV therapy (*230*, *233*). The only exceptions were cirrhotic patients with genotype 1a infection: in the TURQUOISE-II study, 80% of patients had an SVR after 12 weeks (*234*). Thus treatment duration of 24 weeks is beneficial in cirrhotic patients with HCV genotype 1a infection.

For patients with HCV genotype 1a and HCV genotype 1b and cirrhosis, concurrent administration of ribavirin is recommended to maximize response rate. Given the consistently high SVR12 rates observed, baseline characteristics such as age, gender, race, and IL28B host genotype have no apparent effect on response rate.

While the complete regimen consisting of ombitasvir + paritaprevir + ritonavir FDC, plus dasabuvir, with or without ribavirin, is licensed only for the treatment of genotype 1 infection, the alternative drug regimen, consisting of ombitasvir + paritaprevir + ritanovir with or without ribavirin (i.e. without dasabuvir) has been investigated in non-cirrhotic patients with genotype 4 HCV. The dasabuvir-free regimen was again highly effective (*235*).

Only a limited number of patients with genotypes 2 and 3 HCV have been treated with ombitasvir + paritaprevir + ritonavir, and more data are needed to fully elucidate the clinical value of this regimen in combination with other DAAs for the treatment of patients with genotypes 2 and 3 infection.

Safety

Safety data from available clinical trials show an excellent tolerability profile. In total, more than 3000 genotype 1 patients and almost 200 non-genotype 1 patients from more than 25 countries have completed phase II or III clinical trial programmes to assess the efficacy and safety of ombitasvir + paritaprevir + ritonavir and dasabuvir. The regimen appears to be well tolerated in patients with HIV-1/HCV co-infection and those who have undergone liver transplantation, although drug–drug interactions are more common (*236*, *237*).

Expert Committee considerations

In general, the Expert Committee considered that DAAs (individually and used within the considered regimens) are effective and well tolerated. However, the Committee noted that there is as yet no substantial experience with the safety and effectiveness of these medicines in real-life, non-trial settings, particularly in patients living in low- and middle-income countries. In the USA, the "real-world" TARGET study showed overall approximately 10% lower rates of SVR compared with clinical trial data (*238*). In addition, several new hepatitis C drugs are in advanced clinical development or submitted for regulatory approval. Merck have developed a novel regimen consisting of grazoprevir (an NS3/4A protease inhibitor) and elbasvir (an NS5A inhibitor), which demonstrated high SVR12 rates in treatment-naive cirrhotic and non-cirrhotic patients with genotype 1, 4 or 6 infections. Virological failure was associated with baseline NS5A polymorphisms and emergent NS3- or NS5A-resistant associated variants (RAVs) or both (*239*).

The magnitude of the effect and the consistency of safety and efficacy data across various patient groups and genotypes highlight the importance of DAAs as key, essential medicines to treat HCV. With expanded use in populations that have been excluded from trials, new adverse events and drug–drug interactions may be expected to emerge and should be monitored. Moreover, as with HIV, the evolution and emergence of drug resistance (i.e. RAVs) should be monitored globally (*240*). Given the challenges of using existing diagnostic tests, highly effective, pan-genotypic treatment strategies that do not require these tests should become the focus of a global approach and a priority for independent research, with clinical trials comparing various DAA combinations. The Expert Committee also noted the need for robust clinical trials to assess the suitability of DAAs for use in paediatric patients and for determination of appropriate, therapeutic anti-HCV regimens in the paediatric population.

In the USA, the entry prices for sofosbuvir (used in combination with ribavirin) and ledipasvir/sofosbuvir were US$ 84 000 and US$ 94 500, respectively, for a 12-week course, and the launch price for a 12-week treatment course with co-formulated ombitasvir + paritaprevir + ritonavir with or without dasabuvir was US$ 83 300. The approximate price of generic ribavirin is US$ 700 for 12 weeks.

Although these prices are extremely high, substantial price reductions have been achieved through special agreements on tiered prices with the originator companies. For example, Egypt negotiated a 99% price reduction for sofosbuvir to US$ 900 for a 12-week course. Jurisdictions in some high-income countries have also negotiated significant discounts on listed prices with different manufacturers, and WHO is working to promote the rapid introduction of prequalified generic formulations as well as supporting countries/jurisdictions in negotiating lower drug prices.

Nevertheless, widespread access to interferon-free combinations is limited by high total costs in most healthcare systems. Evidence from two recent studies suggests that the manufacturing costs for a 12-week all-oral DAA regimen could be a fraction of current market prices (*7*, *241*). Specifically, the analyses suggest that 12-week regimens could cost as little as US$ 118 for the as-yet unapproved Merck DAA combination, US$ 149 for treatment with sofosbuvir plus ribavirin and US$ 193 for sofosbuvir + ledipasvir. This cost analysis has not been completed for the ombitasvir + paritaprevir + ritonavir and dasabuvir combination, but it is reasonable to suppose that similar manufacturing costs might result. The Expert Committee saw reason to believe that significant price reductions could be achieved.

In the application for sofosbuvir, the manufacturer (Gilead) states "three basic pricing bands have been set to serve as the starting point for negotiations with national governments. Countries are categorized within the bands according to gross national income per capita and hepatitis C prevalence. Final prices are determined on a country-by-country needs basis." Gilead issued voluntary licences to seven Indian generic companies to produce sofosbuvir and market it in 91 countries (excluding Brazil and China) (*10*). Less is known about the plans of other companies (notably AbbVie, Janssen and BMS) to ensure widespread access to their medicines in low- and middle-income countries (LMICs).

Affordability and opportunity cost in the context of a country's total health or pharmaceutical expenditure need to be considered before widespread access to treatment can become a reality: it is only with low prices that widespread access to HCV treatment in LMICs could become a realistic goal. Inclusion in EML should also provide the impetus for countries to use pricing policies known to be effective in reducing prices and promoting competition, through means such as voluntary or compulsory licences, procurement strategies (e.g. tendering, pooled procurement), and generic substitution (when quality-assured generic products are available).

Expert Committee recommendations

The Expert Committee recommended the inclusion of all of the requested direct-acting antivirals on the core list of the EML, under a new section (Medicines for the treatment of Hepatitis C) and subsections (pharmacological classes). The Committee intends to review these recommendations regularly in line with evolving WHO guidelines.

Currently available direct-acting all-oral antiviral regimens (with or without ribavirin) for treatment of chronic HCV infection show significantly improved SVR12 rates and reduced side-effect profiles compared with interferon-based regimens. However, optimal use of these medicines requires multidisciplinary, specialist medical care as well as diagnostic tests for HCV (i.e., genotyping and viral load measurement); these are currently expensive and have

limited availability in many countries, which may limit uptake and access, even where the drugs are affordable. Thus, the ideal scenario is a simple diagnostic assay to establish HCV infection (e.g. buccal swab), a highly effective, affordable and well-tolerated once daily pan-genotypic medication to be taken for a limited period (8–12 weeks or less) and a single blood test 12 weeks after therapy is completed to establish the clearance of chronic hepatitis C infection.

Noting and accepting the clinical benefit of the new DAAs, the Expert Committee recommended that an interferon-free DAA combination regimen should be the preferred option for treatment of hepatitis C, as it avoids the substantial toxicity associated with interferon use. However, DAA monotherapy should not be used because of its poor efficacy and the potential for development of resistance. The Committee recognized that interferon-containing regimens have a place in the treatment of some patients.

As the treatment regimens are still being developed and are changing rapidly, the Expert Committee recommended that the List present the products subdivided by pharmacological class, as for the presentation of anti-HIV medicines. The expectation is that, in the future, there will be options within classes so that a square box listing may be appropriate.

Inclusion on the EML of all DAAs proposed in the applications received aims at promoting competition among available alternatives and allowing for the selection of optimal combination treatment regimens, which may or may not be existing fixed-dose combinations. The Committee also recommended that WHO continue to work on existing approaches to managing prices and evaluate alternative strategies to improve affordability and access in order to reduce the global burden of chronic HCV infection.

Section 8: Antineoplastics and immunosuppressives

8.1: Immunosuppressive medicines

Azathioprine (new indication) – EML

An application was submitted by neurologists Dr Maria Donata Benedetti, Azienda Ospedaliera Universitaria Integrata, Verona; Dr Luca Massaces, Azienda Ospedaliero-Universitaria Careggi, Florence; and Dr Graziella Filippini Fondazione IRCCS Instituto Neurologico Carlo Besta, Milan, for the inclusion of azathioprine on the Model List for the treatment of multiple sclerosis. Azathioprine is already included for other indications: in Section 8.1, Immunosuppressive medicines (complementary list), and in Section 30.2, Disease-modifying agents used in rheumatoid disorders (DMARDs).

Expert reviews of the application were prepared by two members of the Expert Committee. No public comments were received in relation to this application.

Multiple sclerosis (MS) is one of the world's most common causes of non-traumatic neurological disability in young adults. Worldwide, prevalence estimates range from 2.1–2.2 per 100 000 in sub-Saharan Africa and east Asia to 108–140 per 100 000 in the highest risk areas (Europe and North America), with a north–south gradient; incidence is lower closer to the Equator and in men (*242*, *243*). Disease onset is typically between 20 and 40 years of age, with relapsing–remitting symptoms and signs involving different regions of the central nervous system. During the chronic course, over 30 years or more, a high proportion of affected individuals experience progressive disability; this has a huge impact on their quality of life and major implications for social costs (*242*).

The Expert Committee acknowledged that:

- The costs of multiple sclerosis therapies are continuously increasing as newer, patented, immunomodulating medicines are incorporated into clinical practice.
- Inequalities have been reported in the availability of and access to disease-modifying therapies in the world: government-funded disease-modifying therapies were available in 96% of high-income countries but in only 45% of lower-middle-income countries and in none of the countries of the low-income group (*242*).
- Affordability has been ranked by many countries, especially low- and lower-middle-income countries, as the most common reason why not all people with multiple sclerosis are receiving treatment (*242*).
- Patients with a definite diagnosis of multiple sclerosis might benefit from early disease-modifying therapy although the impact of such treatment on the progression of brain lesions is still unclear.

Trials of azathioprine in MS that were conducted in the 1980s and early 1990s (*244–247*) suffered from methodological limitations such as low power and lack of magnetic resonance imaging (MRI) evaluation. However, a more recent meta-analysis, including five parallel-group, randomized, placebo-controlled trials, found that, in 698 patients, azathioprine was associated with a relevant reduction in the number of patients with relapses and disability progression during the first three years of treatment (relative risk reduction approximately 20% for relapse and 42% for disability progression) (*248*). Since the advent of MRI, few studies have evaluated azathioprine efficacy in MS. In a small, open-label, before and after study of patients with short disease duration and at least three gadolinium-enhancing brain lesions at MRI, azathioprine up to 3 mg/kg daily reduced new gadolinium-enhancing brain lesions and was well tolerated (*249*). The relative efficacy of interferon beta (IFN) products and azathioprine was compared in two small randomized trials (*250*, *251*). In the first, a single-blind trial, the mean number of relapses was lower in the azathioprine than in the IFN arm, and more patients in the azathioprine arm remained relapse-free (76.6% versus 57.4%) (*250*). The second, an independent, multicentre, non-inferiority trial found that azathioprine was at least as effective as IFNs for relapse rate and new lesions (*251*). A recent network meta-analysis on immunomodulators and immunosuppressants for MS showed that azathioprine was apparently effective in reducing clinical relapses at 36 months and is likely to reduce disability to a relevant extent (*252*).

Azathioprine is well tolerated and is associated with limited toxicity. In the meta-analysis by Casetta et al (*248*), gastrointestinal disturbances, bone marrow suppression and hepatic toxicity were greater in the azathioprine group than in the placebo group. However, these adverse events were anticipated and were managed with monitoring and dosage adjustment. Withdrawals due to adverse effects, mainly gastrointestinal intolerance (5%), were few and occurred mostly during the first year of azathioprine treatment. In view of the potential risk of cancer, due to the inhibitory effect on the immune system, there are concerns about the safety profile of azathioprine. However, conflicting conclusions on cancer risk – including results from sources other than clinical trials – have been reported; an overview of the data shows long-term risks, if any, to be related to treatment duration in excess of ten years (cumulative doses above 600 g) (*248*). Azathioprine is not recommended in pregnancy.

According to the International Drug Price Indicator Guide 2013, the median price of azathioprine was US$ 0.1671/tab-cap (lowest price US$ 0.1233/tab-cap (South Africa); highest price US$ 0.2300/tab-cap (Namibia)) (*253*). The cost of treating a person with MS using azathioprine is around US$ 16 per month; by comparison, the cost of treatment using IFNs is around US$ 1000 per month.

The Expert Committee noted that use of azathioprine for treatment of MS is off-label in many countries. In the USA, azathioprine is currently approved

by the Food and Drug Administration (FDA) for use in kidney transplantation from human donors, and for rheumatoid arthritis. The drug has been used in some patients with MS, usually if they have problems with standard FDA-approved medications or if they are unable to tolerate injection. Azathioprine is still widely used in Europe for patients with relapsing–remitting MS who do not respond to IFNs, and in countries where market availability of IFNs is limited.

The Expert Committee acknowledged the significant public health burden of multiple sclerosis and noted the availability of a number of new immunomodulating medicines for this condition. The Committee therefore recommended that a comprehensive review be undertaken of all medicines used for the management of relapsing–remitting and other forms of multiple sclerosis for consideration at its next meeting. This recommendation was supported by the WHO Department of Mental Health and Substance Abuse. The Expert Committee did not recommend extending the availability of azathioprine on the EML to include use in the treatment of multiple sclerosis at this time.

8.2: Cytotoxic and adjuvant medicines & 8.3 Hormones and antihormones

Comprehensive review of cancer medicines

At the 2013 meeting of the Expert Committee, during discussion of the addition of imatinib and trastuzumab to Section 8.2 of the Model List, the Expert Committee acknowledged the growing global public health importance of cancer. The Committee recognized the need for countries to consider the addition to national EMLs of highly effective but high-cost medicines for cancer treatment in the context not only of evidence-based treatment regimens but also of ensuring comprehensive systems and interventions for cancer care. The Committee requested a review of the section on cytotoxic medicines, using a process in which the most treatable tumours, and the medicines required to treat them, are systematically identified within the context of a stepwise development of cancer care systems in overall health system development (*11*).

In response to the request of the 2013 Expert Committee, a collaborative review process involving WHO, the Union for International Cancer Control (UICC), the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) was undertaken; 29 indication-based applications for inclusion on the EML and EMLc of medicines for treatment of specific cancers (23 adult and 6 paediatric) were prepared and considered by the 2015 Expert Committee. The review of cancer medicines followed a tumour-based approach, identifying specific cancers with high incidence whose treatment produces a clinically relevant survival benefit and cancers (irrespective of incidence) for which the goal of systemic treatment is cure or long term-remission. Cancers for which systemic treatment achieved only palliation of symptoms without significant survival benefit were not included.

A Working Group of cancer experts was convened by the EML Secretariat in November 2014 to develop and review the applications before their submission for Expert Committee consideration in December 2014. The Working Group agreed on the following guiding principles:

- Consideration must be given to the magnitude of clinical benefit associated with treatment (although no specific fixed threshold was defined).
- Any observed clinical benefit must be patient-relevant and/or of public health relevance.
- Medicines proposed for inclusion must be supported by substantial clinical evidence of comparative efficacy and safety, with due attention given to the overall quality of evidence.
- Consideration must be given to a range of feasibility issues associated with treatment, including diagnostic, testing and monitoring requirements, care requirements, management of adverse events and cost considerations.

The 29 applications before the Expert Committee proposed that a total of 22 new cancer medicines be added to the Model Lists, including some new (patented), expensive medicines that have been found to produce relevant clinical benefit, supported by high-quality evidence.

Each application was reviewed by two members of the Expert Committee. Comments in support of the applications were received from the Young Professionals Chronic Disease Network.

A summary of the medicines recommended by indication is presented in Table 5.

Table 5
Summary of medicines recommended by cancer type

Indication	Medicines		
Acute lymphoblastic leukaemia (EML and EMLc)	Asparaginase Cyclophosphamide Cytarabine Daunorubicin Doxorubicin	Etoposide Mercaptopurine Methotrexate Tioguanine Vincristine	Dexamethasone Hydrocortisone Methylprednisolone Prednisolone
Acute myelogenous leukaemia (EML)	Cytarabine Daunorubicin		

Table 5 *continued*

Indication	Medicines		
Acute promyelocytic leukaemia) (EML)	All-*trans* retinoic acid Cytarabine	Daunorubicin Mercaptopurine	Methotrexate
Burkitt lymphoma (EML and EMLc)	Calcium folinate Cyclophosphamide Cytarabine	Doxorubicin Etoposide Vincristine	Prednisolone
Chronic lymphocytic leukaemia (EML)	Bendamustine Chlorambucil Cyclophosphamide	Cyclophosphamide Fludarabine	Rituximab Prednisolone
Chronic myeloid leukaemia (EML)	Hydroxycarbamide Imatinib		
Diffuse large B-cell lymphoma (EML)	Cyclophosphamide Doxorubicin	Rituximab Vincristine	Prednisolone
Head and neck cancer (EML)	Cisplatin		
Early-stage breast cancer (EML)	Carboplatin Cyclophosphamide Docetaxel Doxorubicin	Fluorouracil Methotrexate Paclitaxel Trastuzumab	Anastrozole Leuprorelin Tamoxifen
Early-stage cervical cancer (EML)	Cisplatin		
Early-stage colon cancer (EML)	Calcium folinate Capecitabine	Fluorouracil Oxaliplatin	
Early-stage rectal cancer (EML)	Calcium folinate Capecitabine	Fluorouracil	
Epithelial ovarian cancer (EML)	Carboplatin Gemcitabine	Paclitaxel	

Table 5 *continued*

Indication	Medicines		
Ewing sarcoma (EML and EMLc)	Cyclophosphamide Doxorubicin	Etoposide Ifosfamide	Mesna Vincristine
Follicular lymphoma (EML)	Bendamustine Cyclophosphamide	Doxorubicin Rituximab	Vincristine Prednisolone
Gastrointestinal stromal tumour (EML)	Imatinib		
Gestational trophoblastic neoplasia (EML)	Calcium folinate Cyclophosphamide	Dactinomycin Etoposide	Methotrexate Vincristine
Hodgkin lymphoma – adults* and paediatric (EML and EMLc)	Bleomycin* Cyclophosphamide Dacarbazine*	Doxorubicin* Etoposide Vinblastine*	Vincristine Prednisolone
Kaposi sarcoma (EML)	Bleomycin Doxorubicin	Paclitaxel Vinblastine	Vincristine
Metastatic breast cancer (EML)	Capecitabine Cyclophosphamide Docetaxel	Doxorubicin Paclitaxel Trastuzumab	Vinorelbine Anastrozole Tamoxifen
Metastatic colorectal cancer (EML)	Calcium folinate Capecitabine	Fluorouracil Irinotecan	Oxaliplatin
Metastatic prostate cancer (EML)	Docetaxel Bicalutamide	Leuprorelin	
Nasopharyngeal cancer (EML)	Carboplatin Cisplatin	Fluorouracil Paclitaxel	
Non-small cell lung cancer (EML)	Carboplatin Cisplatin	Etoposide Gemcitabine	Paclitaxel Vinorelbine
Osteosarcoma (EML and EMLc)	Calcium folinate Carboplatin Cisplatin	Doxorubicin Ifosfamide	Mesna Methotrexate

Table 5 *continued*

Indication	Medicines		
Ovarian germ cell tumours (EML and EMLc)	Bleomycin Cisplatin Etoposide	Ifosfamide Mesna	Paclitaxel Vinblastine
Retinoblastoma (EML and EMLc)	Carboplatin Etoposide	Vincristine	
Rhabdomyosarcoma (EML and EMLc)	Cyclophosphamide Dactinomycin	Ifosfamide Mesna	Vincristine
Testicular germ cell tumours (EML and EMLc)	Bleomycin Cisplatin	Etoposide Ifosfamide	Mesna Vinblastine
Wilms tumour (EML and EMLc)	Dactinomycin Doxorubicin	Vincristine	

Acute myelogenous leukaemia (AML) including Acute promyelocytic leukaemia (APML) – EML

The application sought endorsement of cytarabine and daunorubicin, already listed on the Model List, for the treatment of acute myelogenous leukaemia (AML) and acute promyelocytic leukaemia (APML) as induction and consolidation therapy. The application also sought the addition of all-*trans* retinoic acid (ATRA) and arsenic trioxide to the Model List as induction therapy for APML, and the endorsement of 6-mercaptopurine and methotrexate, already listed on the Model List, for maintenance therapy of APML.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

AML is a heterogeneous haematological malignancy involving the clonal expansion of myeloid blasts in the bone marrow and peripheral blood with possible spread to liver and spleen. An estimated 18 860 people were diagnosed in USA in 2014, 10 460 of whom will die from their disease. The median age at diagnosis is 66 years; 54% of patients are aged over 65 years and 33% over 75 years (*254*). Among patients diagnosed at a later age, the diagnosis is often associated with underlying myelodysplastic syndromes (MDS), sometimes linked to cancer chemotherapy and radiotherapy exposure.

Public health relevance

GLOBOCAN estimates the worldwide total leukaemia incidence for 2012 to be 351 965, with an age-standardized rate (ASR) of 4.7 per 100 000 per year, a 5-year prevalence of 1.5% and a male:female ratio of approximately 1:4 (*255*). In countries with a medium level value on the Human Development Index (HDI),[2] the 2012 ASR was 3.8 per 100 000 per year; in countries with a low level value on the HDI it was 2.5 per 100 000 per year. Mortality was 265 461 worldwide, with an ASR of 3.4 per 100 000 per year. The ASR was higher (3.2 per 100 000) in countries with "medium human development" than in countries of "low human development" (2.4 per 100 000). Unfortunately, the International Agency for Research on Cancer (IARC) does not sub-classify leukaemias into acute and chronic, and myeloid or lymphoid, in its GLOBOCAN analysis.

Classification

Currently, AML is classified as follows, using the WHO classification of 2008 (*256*), which replaces the French–American–British (FAB) classification and an earlier (2001) WHO classification:

[2] See: http://hdr.undp.org/en/content/human-development-index-hdi.

Acute myeloid leukaemia with recurrent genetic abnormalities
- AML with t(8;21)(q22;q22); RUNX1-RUNX1T1
- AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
- APL with t(15;17)(q22;q12); PML-RARA
- AML with t(9;11)(p22;q23); MLLT3-MLL
- AML with t(6;9)(p23;q34); DEK-NUP214
- AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1
- AML (megakaryoblastic) with t(1;22)(p13;q13); RBM15-MKL1
- Provisional entity: AML with mutated NPM1
- Provisional entity: AML with mutated CEBPA

Acute myeloid leukaemia with myelodysplasia-related changes

Therapy-related myeloid neoplasms

Acute myeloid leukaemia, not otherwise specified
- AML with minimal differentiation
- AML without maturation
- AML with maturation
- Acute myelomonocytic leukaemia
- Acute monoblastic/monocytic leukaemia
- Acute erythroid leukaemia
  - Pure erythroid leukaemia
  - Erythroleukaemia, erythroid/myeloid
- Acute megakaryoblastic leukaemia
- Acute basophilic leukaemia
- Acute panmyelosis with myelofibrosis

Myeloid sarcoma

Myeloid proliferations related to Down syndrome
- Transient abnormal myelopoiesis
- Myeloid leukaemia associated with Down syndrome

Blastic plasmacytoid dendritic cell neoplasm

Prognostic factors for AML

Cytogenetic and genetic factors: chromosome and gene abnormalities

Favourable prognostic abnormalities:

- t(8;21) (AML M2)
- inversion of chromosome 16 or t(16;16) (AMML M4 eos)
- t(15;17) (APML M3).

Intermediate prognostic abnormalities:

- normal karyotype.

Unfavourable prognostic abnormalities:

- deletion/loss of chromosome 5 or 7 – may be secondary to alkylating agent chemotherapy
- translocation or inversion of chromosome 3
- t(6;9)
- t(9:22) – transformed CML or de novo AML or ALL
- chromosome 11q23 abnormalities – secondary to topoisomerase inhibitor chemotherapy
- monosomal karyotype involving a monosomy (loss of an entire chromosome) plus additional structural aberrations or more than a single monosomy
- complex karyotype often involving ≥ 3 chromosomal abnormalities (no specific AML type).

Note: In patients with normal karyotype the following have prognostic implications:

- Mutation in the *FLT3* gene results in a poorer outcome. One in three patients have an internal tandem duplication (ITD) mutation in the *FLT3* gene which results in a poorer outcome, especially when both alleles are involved (resulting in a high *FLT3*-ITD/normal *FLT3* ratio).
- Patients with mutations in the *NPM1* gene (and no other abnormalities) have a better prognosis, as do patients with mutations in both alleles of the *CEBPα* gene (so called biallelic gene mutations).

Based on cytogenetics and the novel molecular parameters, updated prognostic risk group stratification for AML has been described. The European LeukemiaNet standardized reporting for correlation of cytogenetic and molecular genetic data in AML with clinical data is shown in Table 6 (*257*).

Table 6
European LeukemiaNet standardized reporting for correlation of cytogenetic and molecular genetic data in AML with clinical data

Genetic group	Subsets
Favourable	t(8;21)(q22;q22); RUNX1-RUNX1T1
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
	Mutated NPM1 without *FLT3*-ITD (normal karyotype)
	Mutated CEBPA (normal karyotype)

Table 6 *continued*

Genetic group	Subsets
Intermediate-I	Mutated NPM1 and *FLT3*-ITD (normal karyotype)
	Wild-type NPM1 and *FLT3*-ITD (normal karyotype)
	Wild-type NPM1 without *FLT3*-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); MLLT3-MLL
	Cytogenetic abnormalities not classified as favourable or adverse
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1
	t(6;9)(p23;q34); DEK-NUP214
	t(v;11)(v;q23); MLL rearranged
	−5 or del(5q); −7; abnl(17p); complex karyotype[a]

[a] Defined as three or more chromosome abnormalities in the absence of one of the WHO-designated recurring translocations or inversions, that is, t(15;17), t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23), t(6;9), inv(3) or t(3;3).

Clinical markers of prognosis

Age:

- Older patients (over 60 years) do not fare as well as younger patients: they are more likely to have unfavourable chromosome abnormalities as well as comorbid medical conditions that can make it more difficult to use intense chemotherapy regimens. Older patients also suffer more from AML secondary to previous myelodysplastic syndrome, which confers a worse prognosis.

White blood cell count:

- A high white blood cell count (>100 000) at the time of diagnosis is linked to a worse outlook.

Prior blood disorders or cancers:

- Preceding haematological disorders (e.g. polycythaemia vera or marrow failure syndromes (Fanconi, congenital neutropenia and others) and myelodysplastic syndromes are linked to a poor outcome of AML.

Treatment-related AML:

- AML after previous chemotherapy or radiotherapy for another cancer or other disease (e.g. autoimmune disease) is linked to a worse outcome.

Requirements for diagnosis, treatment and monitoring

Diagnostics

Definitive diagnosis of AML requires laboratory access:

Peripheral blood:

- A phlebotomist (nurse, physician or laboratory technician) is required to draw peripheral blood and make smears from a patient presenting with one or more of anaemia, abnormal bleeding and infection.
- A trained laboratory technician with access to a haematology counter is required to establish the initial diagnosis by demonstrating a low/normal/high white blood cell count with a low platelet count and anaemia.
- A trained haematologist is required to confirm the diagnosis by identifying "blast cells" in peripheral blood smears and to plan a bone marrow aspiration and biopsy.

Bone marrow aspiration and biopsy:

- Bone marrow aspirates are part of the routine evaluation of AML. Whenever there is a "dry tap" or absence of material in the aspirate, a bone marrow biopsy will also be required. Otherwise a biopsy is not required for standard evaluation and care. Smears (touch preps) of the biopsy should also be evaluated.
- This requires disposable or reusable biopsy needles and a doctor trained to perform bone marrow aspiration and biopsy.
- Laboratory facilities to stain the bone marrow samples and a trained haematopathologist are needed for morphological evaluation of the marrow specimens, both at diagnosis and on follow-up.

Flow cytometry:

- A flow cytometry laboratory is needed to help sub-classify the AML and evaluate for prognostic factors.

Cytogenetic and molecular diagnostics:

- Conventional cytogenetics is required to demonstrate translocations, deletions, additions, monosomies and trisomies.
- Fluorescence in situ hybridization may substitute only for specific cytogenetic abnormalities for which probes are available but it does not provide a complete karyotype. It is more sensitive than conventional cytogenetics testing and is employed when certain aberrations are suspected.

- Real-time polymerase chain reaction is the most sensitive assay for demonstrating translocations or certain molecular aberrations such as *FLT-3*, *NPM1* and *CEBPα*.
- DNA sequencing is needed to demonstrate certain subtle mutations.

Monitoring

Definitive diagnostic tests:

- Complete blood count (CBC), clotting parameters (international normalized ratio, partial thromboplastin time), liver and kidney function tests, uric acid, bone marrow aspirate.
- In certain cases, cytogenetics and sequencing may also be necessary.

Supportive testing:

- Microbiology and biochemistry laboratory testing as well as radiology, including plain X-rays (chest) and computerized tomography scanning (brain, chest, abdomen/pelvis).

Follow-up testing:

- CBC and clotting parameters (daily), renal and liver functions (2–7 times weekly), microbiology (as needed), radiology (as needed), bone marrow aspiration and biopsy (after every remission-induction cycle and consolidation and thereafter every 6 months and when indicated because of suspected or possible relapse), cytogenetic/molecular testing as needed.

Administration and care of patients

Patients should be treated in reverse barrier nursing isolation facilities, with adequate trained medical, nursing and pharmacy support. Central venous access and infusion pumps are needed for administration of chemotherapy. Intensive care facilities are needed to provide support in case of septic shock, as well as safe blood products, antibiotics and blood pressure support.

Supportive care

Blood products:

- Red blood cells, preferably filtered to remove contaminating white blood cells from the red cell concentrate or irradiated.
- Platelets: pheresis (preferred) and pooled.
- Fresh-frozen plasma – especially in APML.

Note: Blood product access may be limited by high incidence of HIV, HBV and HCV in certain countries.

Antibiotics:

Note: This section is included to acknowledge that patients undergoing treatment for AML are at high risk for many infections, caused by a variety of organisms, some of which may be resistant to multiple antibiotics. The availability of a wide spectrum of antibiotics can improve outcome for these patients. The following are some examples of infectious etiologies for these patients and the antibiotics that can be used to treat them; some of the antibiotics are not currently on the EML.

- Gram-negative bacilli, e.g. *Klebsiella*, *Pseudomonas*:
  Sensitive: piperacillin/tazobactam; cefipime; ceftazidime; ertapenem
  Extended-spectrum beta-lactamases: meropenem; imipenem
  Carbapenem-resistant Enterobacteriaceae: colimycin; tigecycline
- Gram-positive cocci, e.g. *Staphylococcus*, *Streptococcus*
  Sensitive: amoxicillin/clavulinate; cloxacillin
  Methicillin-resistant Staphylococcus aureus: vancomycin; linezolid
- Fungi, e.g. *Candida*, *Aspergillus*
  Candida: amphotericin B; fluconazole
  Aspergillus: amphotericin B; voriconazole.

Haematopoietic growth factors:

- Granulocyte colony-stimulating factor – absolute need only in case of planned stem cell transplantation for stem cell mobilization and collection – not to be used during the treatment outlined below.

Overview of regimens

Standard regimens for AML (excluding APML)

- **Induction therapy (< 60 years and fit patients > 60 years): 7+3 cytarabine and daunorubicin (1–2 cycles)**
  - cytarabine 100 mg/m² per day continuous IV infusion x 7 days
  - daunorubicin 60–90 mg/m² per day IV x 3 days
- **Consolidation therapy: HiDAC (2–4 cycles)**
  - cytarabine 2–3 g/m² IV over 2–3 hours twice daily on days 1, 3 and 5 (patients <60 years)
  - cytarabine 500 mg/m² IV over 1 hour twice daily on days 1–6 (patients >60 years)

Notes:

1. In patients > 65 years, daunorubicin dose may be reduced to 45 mg/m².
2. In very frail patients consider low-dose cytarabine, 5-azacitidine or hydroxyurea cytoreduction and best supportive care only.
3. Allogeneic stem cell transplantation consolidation is not included because of limited availability and the fact that, where it is available, resources are likely to be greater and necessary medicines and supportive care available.
4. Corticosteroid eye drops are essential with HiDAC.

Standard regimen for APML

- **Induction therapy**
  - ATRA 45 mg/m² per day orally in divided doses until remission
  - daunorubicin 60–90 mg/m² IV on days 1–3
  - cytarabine 100–200 mg/m² IV on days 1–7
- **Consolidation therapy**

  Option 1
  - arsenic trioxide 0.15 mg/kg per day IV x 5 days for 5 weeks
  - ATRA 45 mg/m² per day orally x 7 days
  - daunorubicin 50 mg/m² IV x 3 days

  Repeated for 2 cycles.

  Option 2
  - daunorubicin 60 mg/m² IV on days 1–3
  - cytarabine 100–200 mg/m² IV on days 1–7

  for 1 cycle followed by:
  - cytarabine[3] 2 g/m² IV every 12 hours x 5 days
  - daunorubicin 45 mg/m² IV on days 1–3
- **Maintenance therapy**
  - TRA 45 mg/m² orally x 15 days every 3 months
  - 6-mercaptopurine 100 mg/m² per day orally
  - methotrexate 10 mg/m² orally weekly

  All x 2 years.

[3] Cytarabine dose = 1.5 g/m² for patients > 60 years old.

Review of benefits and harms

Overview

Induction combination chemotherapy for AML with cytarabine and an anthracycline has been the standard of care since the late 1970s. Gale et al. showed an 82% complete remission rate in 68 patients receiving high-dose induction chemotherapy with cytarabine, daunorubicin and 6-tioguanine; median duration of remission was 13 months and median survival 21 months (*258*). Rowe et al. found no benefit with induction idarubicin or mitoxantrone versus daunorubicin in older AML patients, suggesting that daunorubicin remains the standard induction anthracycline (*259*). However, subsequent meta-analyses that included this and other randomized controlled trials showed a slight advantage of idarubicin over daunorubicin or other anthracyclines, when used with cytosine arabinoside as induction chemotherapy for newly diagnosed AML, particularly in younger patients (*260*, *261*). The number of trials was limited, however, with some heterogeneity of effects between trials, and the differences between idarubicin and daunorubicin were not large; careful interpretation of the results is thus necessary.

Because the high complete remission rate was not translated into long-term survival, most subsequent studies have concentrated on consolidation therapy. Mayer et al. treated 1088 adult AML patients with induction cytarabine plus daunorubicin and then randomized the 693 patients in complete remission to different doses of cytarabine (*262*). All patients received four cycles of maintenance cytarabine plus daunorubicin thereafter. At 52 months, the probability of remaining disease-free was higher in the group treated with higher doses (3 g/m² over 3 hours twice daily on days 1, 3 and 5 (HiDAC)). In patients under 60 years of age, the 4-year disease-free survival rate was 24% for the 100 mg/m² group compared with 29% and 44% for the 400 mg/m² and HiDAC groups respectively. Notably, less than 30% of elderly patients were able to complete four cycles of maintenance therapy because of toxicity. Bloomfield et al. analysed a subgroup of patients of the same study (*263*). They showed that 5-year complete remission rate for patients receiving HiDAC was 78% for those with favourable karyotype compared with 40% for those with normal karyotype; in patients receiving 400 mg/m², 5-year complete remission rate was 57% for those with favourable karyotype compared with 37% for those with normal karyotype. The 5-year complete remission rate for patients with other abnormalities was less than 21%, regardless of therapy given.

In a study by Appelbaum et al., 111 patients with newly diagnosed acute non-lymphoblastic leukaemia were treated with induction chemotherapy. In the 90 patients who achieved complete remission, the outcome of marrow transplantation was compared with that of continued chemotherapy: 33 of 44 patients who had available donors received transplants, while 46 patients without

histocompatible donors received continued chemotherapy (*264*). Estimates of 5-year disease-free survival were higher for the transplant group than for the chemotherapy group. A recent Cochrane systematic review included results from 14 trials and 3157 patients (*265*). The meta-analysis for overall survival showed the superiority of the donor versus no donor group with a hazard ratio (HR) of 0.86 (95% CI: 0.77–0.97; $P = 0.01$), and no significant heterogeneity between trials.

Cassileth et al. compared HiDAC with autologous and allogeneic stem cell transplantation for adults with AML in first remission who did not have a histocompatible sibling donor (*266*). They found no significant difference in disease-free survival and a marginal benefit for HiDAC versus autotransplantation and allotransplantation. This result was confirmed in a meta-analysis that compared the efficacy of consolidation therapy with autologous bone marrow transplantation versus non-myeloablative chemotherapy alone or no further treatment following induction therapy (*267*). The ratio of overall survival probabilities was 1.01 (95% CI: 0.89–1.15; $P = 0.86$). However, autologous bone marrow transplantation was associated with a statistically significant greater risk of death during first remission (odds ratio from 6 studies 2.63; 95% CI: 1.6–4.32; $P < 0.001$).

In a three-year American inter-group study involving 346 patients with previously untreated APML, three courses of chemotherapy were compared with ATRA treatment followed by two courses of chemotherapy (*268*). The incidence of relapse was significantly reduced in patients who received ATRA (33% versus 68% at 3 years, $P < 0.01$); overall survival was also better in the ATRA group (50% versus 67% at 3 years, $P < 0.003$). In a systematic review exploring efficacy and safety of maintenance therapy in APML patients, maintenance with ATRA alone improved disease-free survival compared with observation (HR 0.47; 95% CI: 0.33–0.66); ATRA-containing regimens (ATRA alone or ATRA combined with chemotherapy) compared with observation achieved a significantly better disease free-survival (HR 0.48; 95% CI: 0.35–0.66); and in maintenance treatment, ATRA-based regimens were also associated with improved disease-free survival compared with non-ATRA-based regimens (HR 0.72; 95% CI: 0.51–1.01) (*269*). Results for overall survival were less straightforward.

In 2010, Powell et al. showed that the addition of arsenic trioxide (As_2O_3) consolidation to induction with ATRA plus chemotherapy in APML improved 3-year event-free survival from 63% to 80% ($P < 0.0001$) and 3-year overall survival from 81% to 86% ($P = 0.059$) when compared with two courses of consolidation therapy with ATRA plus daunorubicin (*270*). Other randomized controlled trials explored the efficacy and safety of As_2O_3 consolidation compared with different controls (*271*), but data on comparison with the current standard treatment regimen (ATRA plus chemotherapy) are lacking.

Overall benefits of AML therapy

With remission induction chemotherapy:

- Up to 80% complete remission (CR) rate, especially < 60 years.

HiDAC consolidation:

- Good risk karyotype: 60–80% 5-year CR rate.
- Intermediate risk karyotype: ~40% 5-year CR rate.
- Poor risk karyotype: 10–20% 5-year CR rate (not recommended).

Harms and toxicity considerations

Common

Patients treated with the regimens described above will typically experience severe pancytopenia, often requiring blood and platelet transfusions. Pancytopenia is also associated with a high risk of infection; precautions should be taken to reduce exposure to pathogens and prophylaxis should be considered. The chemotherapy combination commonly causes gastrointestinal damage, resulting in mucositis and/or diarrhoea in 10–25% of patients (*272*). Other common chemotherapy-specific risks include fever or influenza-like syndrome with cytarabine and alopecia associated with anthracyclines.

Approximately 26% of patients treated with ATRA, especially those with high baseline white blood cell count, experience a retinoic acid syndrome characterized by respiratory distress, fever, interstitial pulmonary infiltrates and pleural or pericardial effusions, which can be life-threatening. In most cases, however, the syndrome is reversible with a short course of dexamethasone (*268*). Increased rates of grade 3/4 adverse events have been reported for any maintenance treatment compared with observation, as well as for maintenance combining ATRA and chemotherapy compared with ATRA alone, which may limit patient adherence to treatment (*269*).

Serious

Potentially serious cardiotoxicity leading to congestive heart failure can be seen with anthracyclines, including daunorubicin and idarubicin. Although transient changes in the electrocardiogram may be observed, the risk of congestive heart failure is minimal, particularly in the dose regimens described above (*273*).

High-dose cytarabine (≥ 3 g/m² every 12 hours) can cause central nervous system toxicity, including acute cerebellar syndrome in >10% of patients. Severe haemorrhagic conjunctivitis is also a complication of high-dose cytarabine but can be prevented by corticosteroid eyedrops. Caution should be exercised, particularly when there is underlying abnormal renal or hepatic function (*274*).

Recommendations

The Expert Committee agreed that, although drugs needed for induction and consolidation chemotherapy for AML and APML can be accessed in both low- and middle-income countries, these conditions cannot be treated in a vacuum. Unless safe blood products, isolation facilities, and intensive care support, as well as haematology and molecular laboratory and radiology support, are available, appropriate definitive treatment is not feasible and consideration may need to be given to referring patients to centres (or even countries) that have these resources.

Where these critical resources are available, the Committee agreed that induction treatment for AML with cytarabine plus daunorubicin (or idarubicin), followed by high-dose cytarabine consolidation therapy, demonstrates relevant clinical benefit in patients with favourable and intermediate-risk karyotype (5-year CR rate of 60–80% and approximately 40%, respectively). The Committee also agreed that salvage chemotherapy should be recommended only in settings where there are allogeneic stem cell transplant facilities.

For patients with APML, the Committee agreed that induction treatment with ATRA plus daunorubicin (or idarubicin), followed by consolidation cycles with anthracyclines and ATRA, is associated with a relevant clinical benefit (17% increase in 3-year survival). In the maintenance setting, ATRA – with or without 6-mercaptopurine and methotrexate – is also associated with benefit.

The Committee noted that addition of arsenic trioxide as consolidation therapy for APML does not produce a clinically relevant increase in overall survival in naïve patients. The Committee also noted the extremely high price and low availability of arsenic trioxide, and considered that this would be unaffordable in many low- and middle-income countries.

On the basis of the available evidence, the Expert Committee made the following overall recommendations:

- cytarabine and daunorubicin, currently on the complementary list, should be specifically endorsed for the treatment of AML;
- cytarabine, daunorubicin, mercaptopurine and methotrexate, currently on the complementary list, should be specifically endorsed for the treatment of APML;
- all-trans retinoic acid (ATRA) should be added to the complementary list for the treatment of APML;
- arsenic trioxide should not be added to the EML for treatment of APML.

Chronic lymphocytic leukaemia (CLL) – EML

The application sought endorsement of cyclophosphamide, vincristine and prednisone, already listed on the Model List of Essential Medicines, for the treatment of chronic lymphocytic leukaemia (CLL). The application also sought the addition of fludarabine, rituximab and bendamustine to the core list for this indication.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Chronic lymphocytic leukaemia is the most common form of leukaemia in the developed world, but is significantly less frequent in Asia. The median age of diagnosis in Australia, Europe and USA is approximately 70 years, with about 25% of patients aged under 65 years and approximately 6% under 50 years (*275*, *276*). Male patients predominate and are more likely than females to have disease progression and require therapy. The disease is highly heterogeneous: patients with indolent disease may never require therapy while others can progress rapidly and require therapy shortly after presentation. The most common presentation in developed countries is an asymptomatic lymphocytosis, detected by incidental blood tests. Patients with progressive disease have a rising lymphocytosis, adenopathy, hepatosplenomegaly and bone marrow infiltration resulting in bone marrow failure with anaemia and thrombocytopenia (*277*). These clinical findings are the basis for the two principal staging systems (*277*, *278*).

Only patients with progressive disease require therapy. The proportion of patients who require therapy varies from approximately 50% with a community referral base to the absolute majority in tertiary referral institutions. Common complications of CLL are hypogammaglobulinaemia and infection (*279*), autoimmune haemolysis and thrombocytopenia (*280*), and progression to high-grade lymphoma ("Richter transformation") (*281*, *282*).

CLL therapy has undergone momentous changes over the past few decades. The first major change was the evolution from single alkylator-based therapy to immunochemotherapy; the second – now in progress – is the introduction of small molecular inhibitors of B-cell receptor (BCR) signalling and other key biological survival and apoptotic pathways. Previously, the oral alkylator chlorambucil (Cbl) was the basis of therapy. The use of fludarabine was pioneered during the 1990s and 2000s, initially as a single agent, then in combination with cyclophosphamide (FC) and finally with the addition of rituximab (FCR) (*283–286*).

Other chemotherapy regimens have also been successfully combined with rituximab for treatment of untreated or relapsed patients with CLL:

bendamustine in association with rituximab has been shown to be effective and well tolerated in a phase II trial in high risk patients (*287*), and this regimen has been evaluated in a randomized controlled trial: the interim analysis shows that FCR might be associated with longer progression-free survival (PFS), but with a significantly higher rate of severe adverse events (*288*).

There has been substantial progress in documenting the genetic basis for the heterogeneity of CLL, particularly with lesions in the *TP53* and *ATM* genes on chromosomes 17 and 11, respectively, which predict poorer survival (*289*). The mutational status of the immunoglobulin heavy chain variable gene (*IGHV*) is another factor, as are mutations in *Notch1*, *SF3B1* and others. Recently, inhibitors of the BCR signal pathway (ibrutinib and idelalisib) and of bcl-2 (Abt-199) have shown promising results in patients with *TP53* defects and those with relapsed and refractory disease, leading to the recent approval of these two BCR inhibitors by the U.S. Food and Drug Administration. Ibrutinib and idelalisib are recommended for use in treatment of adult patients with CLL who have received at least one prior treatment, as well as for first-line treatment of patients with a specific genetic mutation that makes them unsuitable for chemoimmunotherapy. Trials of these medicines as first-line therapy are now underway; however, because they are not currently widely available and their use has been confined to trials, these agents are not proposed for addition to the EML at this time.

Public health relevance

GLOBOCAN estimates the worldwide total leukaemia incidence in 2012 to be 351 965 cases, with an age-standardized rate (ASR) of 4.7 per 100 000. The incidence of leukaemia in more-developed regions in 2012 was estimated as 141 274 (ASR of 7.2 per 100 000) compared with 210 691 (ASR of 3.8 per 100 000) in less-developed regions (*255*). GLOBOCAN does not provide specific information about CLL.

A USA study published in 2004 estimated the worldwide incidence of CLL to be between < 1 and 5.5 per 100 000 people (*290*); the highest incidence rates that year were found to be in Australia, Ireland, Italy and USA. The study suggested that CLL is more common in adult males than in females and in Caucasians than in people of black race. The median age of diagnosis is between 64 and 70 years. In the USA in 2004, five-year survival rate was 83% for those under 65 years of age and 68% for those aged 65 years and above. In Germany about 3000 men and 2000 women are newly diagnosed with CLL each year, with the median age at diagnosis being between 70 and 75 years (*291*). Family history of CLL is a noted risk factor for development of the disease (*292*).

Requirements for diagnosis, treatment, and monitoring

Diagnostics

A full blood count with morphological examination of the peripheral blood film is essential. An immunophenotype of CD20, CD19 and CD5 positivity (usually also with CD23 positivity), to document the characteristic CLL phenotype by flow cytometry, is also required to differentiate CLL from other lymphoproliferative disorders. A bone marrow assessment is performed only to assess marrow reserves and for genetic analysis before treatment and to assess response after completion of treatment. After initial therapy, minimal residual disease – detectable by flow cytometry in marrow or blood – in patients in remission predicts earlier relapse and shorter progression-free and overall survival. Flow cytometry requires a significant skill set and training.

Testing

Regular full blood counts are essential during the course of therapy to monitor response and evaluate potential treatment-related adverse effects such as anaemia, neutropenia and thrombocytopenia. Autoimmune haemolytic anaemia occurs in approximately 15% of patients with CLL; the direct antiglobulin test, together with biochemical analysis for bilirubin and lactate dehydrogenase, is important to diagnose and monitor this complication. A bone marrow examination is important for evaluation before treatment and for assessing response (*293*). Flow cytometric evaluation is also important for monitoring response.

Where available, fluorescence in-situ hybridization or karyotypic analysis is essential to detect the common adverse genetic abnormalities (11q- and 17p-), but adds significant cost. Testing for IGHV mutational status and molecular mutations is not currently routine practice in most clinical environments. Criteria for assessment of response have been published in the International Workshop of CLL (*293*).

Administration and care of patients

Administration requires intravenous infusion capacity for rituximab and regular patient access to clinical care. Fludarabine and cyclophosphamide may be given intravenously or orally. In developed countries, rituximab administration is usually performed in outpatient facilities; in other settings, however, patients may be treated in inpatient facilities. Rituximab can cause severe allergic reactions and must be given slowly, with premedication including steroids and antihistamines; close monitoring is essential and additional supportive medicines must be readily available.

Monitoring requires that clinicians have access to laboratory facilities, as well as the ability to recognize and address potential adverse events caused by the

treatment itself, including bone marrow suppression, infection, allergic reactions to rituximab, and gastrointestinal toxicity. Social and financial well-being can be impacted by treatment side-effects and should also be monitored and addressed.

Patients with CLL should be followed indefinitely in view of the risk of disease relapse and further progression, and the potential need for further therapy. A proportion of patients with mutated IGHV genes have been followed for up to 10 years with no recurrence. By contrast, the long-term outlook for patients who progress within 2–3 years after front-line FCR was grave until recently when B-cell receptor pathway inhibitors became available.

Age, fitness and overall medical and performance status are critical components of the evaluation of the patient with CLL. For younger, fit patients, FCR provides markedly superior outcomes and progression-free survival, permitting a normal quality of life for a substantial period of time. This permits patients to continue to work and remain productive while their families reach maturity, resulting in a major social and psychological benefit for patients, their families and society. By contrast, elderly or infirm patients may have different treatment goals and the shorter period and less complete degree of disease control achieved with chlorambucil may be appropriate. Chlorambucil is already included in the List of Essential Medicines, and the application recommends it remain on the list for palliative care in CLL patients.

Overview of regimens

The regimens below include basic information on administration and dosing for treatment of CLL. The FCR regimen may be administered intravenously or orally, but it is important to note that the dose and duration of the FC component are different in the intravenous and oral regimens. The protocols exclude ancillary medications for the management of side-effects (e.g. prophylactic growth factor support to minimize neutropenia, and prophylactic antibiotics and antivirals to minimize infection risk).

Standard regimens

- **FCR regimen (planned 6 cycles)**

Note difference in doses and duration with IV vs. oral regimen. These IV and oral regimens are considered approximately dose-equivalent.

Using intravenous FC over 3 days

- fludarabine 25 mg/m² IV on days 1–3
- cyclophosphamide 250 mg/m² IV on days 1–3
- rituximab 375 mg/m² IV on day 1 of cycle 1, then 500 mg/m² on day 1 of cycles 2–6

Using oral FC over 5 days

- fludarabine 24 mg/m² orally on days 1–5
- cyclophosphamide 150 mg/m² orally on days 1–5
- rituximab 375 mg/m² IV on day of cycle 1 then 500 mg/m² on day 1 of cycles 2–6

- **Standard bendamustine–rituximab regimen (every 4 weeks; 4 cycles)**
  - bendamustine 90 mg/m² IV on days 1 and 2
  - rituximab 375 mg/m² IV on day 1

Note: It is recommended that rituximab be used as outlined above but, if it is unavailable or unaffordable, it can be omitted from these regimens. The results are inferior to rituximab-containing regimens, but benefit is still substantial.

The FCR regimen universally causes neutropenia. This in turn is commonly treated with growth factor support (granulocyte-colony stimulating factor, G-CSF), which may significantly increase therapy-related costs. The addition of G-CSF to the EML was considered in a separate application.

- **Alternative regimen for advanced symptomatic disease: R-CVP (every 3 weeks; 6 cycles)**
  - rituximab 375 mg/m² IV on day 1
  - cyclophosphamide 750 mg/m² IV on day 1
  - vincristine 1.4 mg/m² IV (cap dose at 2 mg) on day 1
  - prednisone 100 mg orally on days 1–5

Note: It is recommended that rituximab be used as outlined above, but if it is unavailable or unaffordable, this regimen can be used without rituximab. The results are inferior to rituximab-containing regimens, but benefit is still substantial.

Assessment of CLL response to therapy requires a bone marrow biopsy and imaging to document response as detailed in the International Workshop on CLL guidelines (*293*). Clearance of CLL cells from the peripheral blood is not an adequate therapy end-point and does not represent complete response.

Supportive care

Hypogammaglobulinaemia is a common complication of CLL. For patients with reduced IgG, CLL and recurrent episodes of bacterial infection, regular

immunoglobulin replacement therapy reduces infection rates and may improve quality of life (*294*).

Review of benefits and harms

Benefits

A large randomized controlled trial in the United Kingdom, the LRF CLL4 trial, documented the superiority of fludarabine plus cyclophosphamide (FC) to either fludarabine or chlorambucil alone in terms of median PFS – 43 months (95% CI: 35–51), 23 months (95% CI: 18–27) and 20 months (95% CI: 18–22), respectively (*295*). However, there were no significant differences in survival between treatment groups: at 5 years, survival was 59% (95% CI: 53–66) with chlorambucil, 52% (95% CI: 42–61) with fludarabine, and 54% (95% CI: 44–64) with FC. Subsequently, the large randomized CLL8 trial showed that the addition of rituximab to FC (FCR chemoimmunotherapy) produced superior results: PFS was longer in the chemoimmunotherapy group than in the chemotherapy group (median 51.8 months (95% CI: 46.2–57.6) versus 32.8 months (95% CI: 29.6–36.0)) (*296*). The CLL8 study planned six cycles of FCR therapy; most patients tolerated this treatment. The CLL8 study also documented that twice as many patients achieved a complete response (CR), and minimal residual disease (MRD) negativity, with six cycles than with three cycles of treatment (*297*). Generally, therefore, six cycles of therapy are recommended. However, for patients with recurrent and persistent cytopenia, or other persistent grade 3 or 4 toxicity, early cessation may be important. It is important to note that clearance of CLL cells from the peripheral blood is not evidence of complete remission. The documentation of CR requires a bone marrow biopsy and imaging as outlined in the International Workshop on CLL guidelines (*293*).

A subsequent Cochrane systematic review cumulated results from three randomized controlled trials ($n = 1421$) assessing the efficacy of monoclonal anti-CD20 antibodies (i.e. rituximab) plus chemotherapy compared with chemotherapy alone (*298*). The meta-analyses showed a statistically significant advantage for patients receiving rituximab in terms of overall survival (hazard ratio (HR) 0.78; 95% CI: 0.62–0.98) and progression-free survival (HR 0.64; 95% CI: 0.55–0.74). The number needed to treat for an additional beneficial effect was 12. Hence combination immunochemotherapy with FCR is now the standard of care for younger, fit patients; the time to second therapy with FCR is reaching 5–7 years compared with approximately 2 years with chlorambucil, and better quality of life reflects the much longer period of excellent disease control with FCR.

The LRF CLL4 trial began by using the FC combination intravenously over three days. During the course of the trial, an orally administered schedule was introduced, which administered the same drugs over five days rather than

three (*295*). An Australian study that focused on fit patients aged 65 years and over also adopted this five-day oral regimen as the method of administration (*299*), while the CLL-8 trial used the three-day intravenous schedule.

In a multicentre phase II trial by the German Chronic Lymphocytic Leukemia Study Group, safety and efficacy of bendamustine and rituximab were investigated in previously untreated patients with CLL. It was demonstrated that 90.5% of patients were alive at 27 months, and the median event-free survival was 33.9 months (*287*). These findings led to testing the non-inferiority in terms of efficacy and tolerability of BR compared to FCR as first-line therapy in physically fit patients with advanced CLL without del(17p) in a randomized controlled trial: the CLL10 trial (*288*). Results of a planned interim analysis showed FCR to be associated with a better complete response rate (CRR), PFS and event-free survival (EFS) than BR. CRR for FCR was 47.4% compared to 38.1% for BR ($P = 0.031$). Overall survival rates were the same in each treatment arm, however the duration of follow-up was too short to exclude potentially relevant differences between arms. With regard to adverse events, myelosuppression was more frequent in the FCR arm compared to the BR arm, with higher rates of severe haematotoxicity (90.0% vs 66.9% $P < 0.001$), severe neutropenia (81.7% vs 56.8%; $P < 0.001$), and severe infections (39.0% vs 25.4%; $P = 0.001$), especially in the elderly.

For patients who have comorbidities or are unable to tolerate one of the regimens outlined above, Cbl with the novel CD20 antibody obinutuzumab has been documented as superior to Cbl with rituximab which was in turn superior to Cbl alone in the large CLL11 study (*300*).

Harms and toxicity considerations

Common

Rituximab can cause allergic reactions and must be given slowly, with premedication including steroids and antihistamines; close monitoring is essential and supportive medicines must be readily available. Reactions are commonly mild following premedication (*285*).

Serious

The principal toxicity related to the FCR regimen is myelosuppression and infection, with high rates of severe neutropenia in up to 34–58% of patients and associated infection in 10–25% (*285*, *286*, *296*). Myelosuppression with this regimen may persist for more than 3 months and commonly requires growth factor support to shorten the duration of neutropenia and reduce the risk of infections (*296*, *301*). Thrombocytopenia and anaemia also occur, and blood transfusion support is frequently required.

Data regarding grade 3–4 adverse events are heterogeneous across trials. Reported grade 3 or 4 infection-related adverse events may be higher in patients treated with bendamustine compared with fludarabine (*298*); other grade 3 and grade 4 adverse events with bendamustine and fludarabine may be similar. The effect of bendamustine on quality of life is similar to that of chlorambucil.

Recommendations

On the basis of the evidence presented, the Expert Committee made the following recommendations in relation to treatments for chronic lymphocytic leukaemia:

- addition of fludarabine (oral and IV formulations) and rituximab to the complementary list of the EML;
- addition of bendamustine to the complementary list of the EML;
- endorsement of cyclophosphamide, vincristine and prednisone, already included on the complementary list, specifically for the treatment of CLL;
- endorsement of chlorambucil for use in palliative chemotherapy for CLL.

The Committee recommended that, in settings where rituximab is not available or affordable, the treatment regimens detailed in the application should be used without rituximab. The clinical benefits associated with their use, while not as great as when combined with rituximab, are nonetheless substantial and clinically relevant.

The Expert Committee acknowledged that the FCR regimen has been shown to be superior to FC for all clinical outcomes, including overall survival, in young and fit patients, and is the standard first-line treatment regimen for CLL. However, the Committee also noted that this disease occurs at a median age over 70 years, and comorbidities in this patient population may make FCR tolerability a major issue for a proportion of elderly patients. Based on its efficacy and safety profile the Committee considered that first-line treatment with bendamustine, either alone or in combination with rituximab, is a reasonable alternative to FCR in patients for whom FCR is not appropriate or not tolerated (e.g. older patients), or in patients wishing to improve quality of life or decrease toxicity.

Chronic myelogenous leukaemia (CML) – EML

The application sought the addition of imatinib, nilotinib and dasatinib to the core list of the Essential Medicines List for the treatment of chronic myelogenous leukaemia in adult and paediatric patients.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Chronic myelogenous leukaemia (CML) is a myeloproliferative disorder affecting the haematopoietic stem cell compartment. It can occur in all age groups but is predominantly a disease of adults, accounting for 20% of adult leukaemias. The incidence rate in the United States is roughly 1.7 per 100 000. There appears to be no association with race or ethnicity (*302*). While there are few reliable data from resource-poor countries, extrapolation from existing data would suggest that CML will affect more than 100 000 patients worldwide every year and represent a significant global health burden. Because treatment with imatinib results in prolonged remissions in the majority of patients, the prevalence of CML is much higher and it may account for up to 15% of all leukaemias in the developed world (*303*), although global prevalence is not known.

CML arises from a translocation between the BCR gene on chromosome 22 and the *ABL* gene on chromosome 9. This reciprocal translocation creates the Philadelphia chromosome t(9;22) and the consequent formation of a unique *BCR-ABL* protein product. This protein has constitutive kinase activity that drives uncontrolled proliferation of haematopoietic stem cells. The natural history of CML is characterized by progression through three phases – chronic phase, accelerated phase and blast crisis (*304*). Patients presenting in the chronic phase can be relatively asymptomatic or have fatigue, early satiety or complications of hyperviscosity such as visual disturbances or priapism. The chronic phase is characterized by a proliferation of white blood cells, and sometimes platelets, and splenomegaly. Symptoms can be controlled by agents such as hydroxyurea or interferon. However, neither can prevent progression to accelerated phase, where a progressive loss of white cell differentiation with an accumulation of blasts occurs, or to eventual blast crisis, characterized by a disease indistinguishable from acute myelogenous leukaemia or acute lymphoblastic leukaemia. This blast phase is refractory to treatment and results in imminent death. The median survival for patients is 3–5 months (*305*) and conventional therapies such as hydroxyurea and interferon do not alter the course of disease. However, the applicant proposed that hydroxyurea (hydroxycarbamide) remain in the List of Essential Medicines as a part of CML patient care. While CML is less common in the paediatric population there is no evidence that there are significant biological differences based on age (*306*, *307*).

Before the advent of imatinib the only therapy that could offer long-term survival was allogeneic bone marrow transplantation (BMT), a modality not available in most of the world. Even in developed countries BMT is costly and associated with a significant treatment-related mortality. While BMT can lead to long-term disease survival in 50–70% of patients, toxicity markedly increases with age and even in younger patients major obstacles exist. Another obstacle is that for up to 60% of patients no appropriate donor can be identified (*308*); this number is even larger in patients of African or Hispanic descent because of underrepresentation in international registries. Transplant has associated morbidities (infertility, graft-versus-host disease) and mortality (20–50% at one year depending on patient and donor characteristics). Most critically, allogeneic BMT requires a sophisticated and expensive infrastructure and complicated extended follow-up care. It is thus offered only in tertiary-care hospitals. There are limited facilities able to perform BMT in the WHO Eastern Mediterranean Region and currently none in sub-Saharan Africa (*309*).

Public health relevance

According to GLOBOCAN, worldwide total leukaemia incidence for 2012 is estimated at 351 965, with an age-standardized rate (ASR) of 4.7 per 100 000 per year, a 5-year prevalence of 1.5% and a male:female ratio of approximately 1:4. Leukaemia incidence in more developed regions in 2012 was estimated at 141 274 (ASR of 7.2 per 100 000) compared with 210 691 (3.8 per 100 000) in less developed regions (*255*). GLOBOCAN provides no specific information about CML.

Information on CML incidence and prevalence is scarce, as CML is a rare disease. A European study published in 2007 estimated annual incidence to be 1 or 2 cases per 100 000 people (*310*). The same study stated that CML is most common in older populations, with a median age at diagnosis of around 65 years, and is more common in men (although women tend to have a higher survival rate than men). Disease incidence appears to be consistent across geography and ethnicity, although it is noted that survival rates in some countries are likely to be impacted by the availability of drugs and diagnostic technologies. In the United States, for instance, rates for new CML cases have been stable over the past 20 years, but death rates have dropped significantly, with 5-year relative survival rising from about 30% to 63% (*302*).

Requirements for diagnosis, treatment, and monitoring

Diagnostics

Imatinib is a selective inhibitor of the *BCR-ABL* tyrosine kinase. Imatinib is effective only in patients whose leukaemia cells carry the t(9;22) chromosomal translocation, and identification of the translocation is therefore critical before

a decision is made to use imatinib therapy. Although more than 90% of CML cases do indeed demonstrate this translocation, CML can be confused with other myeloproliferative diseases that do not.

Testing can be performed by a variety of molecular techniques; it is routinely available in most cancer centres in the developed world but often unavailable in laboratories in developing countries. Where testing is unavailable, it is possible for centres to partner with referral laboratories to have testing performed. Newer technology is rapidly making tests more generally available in developing countries.

Administration and care of patients

Until haematological remission (i.e. normalization of blood counts) has been achieved, weekly or two-weekly testing is needed to ensure that neutropenia or thrombocytopenia does not develop. Once haematological remission has been demonstrated by a normal complete blood count (CBC), further CBCs and physical examinations may be warranted every 3–6 months to assess continuing response, as well as patient education about reporting possible adverse events.

Overview of regimens

The following are the basic details of administration and dosing for treatment of CML.

- **Standard regimen**
  - imatinib 400 mg orally daily (adults)
  - imatinib 260–340 mg/m² per day (children) (*307*).

Approximately one fifth of patients are intolerant of imatinib and will discontinue therapy. The Unmet Needs in CML (UNIC study), a cross-sectional study with retrospective chart review of patients currently treated for CML across eight European countries, estimated the proportion of imatinib-treated patients who experienced imatinib resistance and/or intolerance (*311*, *312*). A total of 20–23% of patients stopped – and did not restart – imatinib during the study period.

The most common toxicities that lead to drug discontinuation include nausea, vomiting, diarrhoea and muscle cramps. Other less common reasons for discontinuing imatinib include oedema, heart failure, rash and arthralgias as well as severe myelosuppression and hepatic toxicity.

In addition, five years of more after achievement of complete cytogenetic remission, therapeutic effects of imatinib will be unsatisfactory in about one third of patients; recurrent disease will then develop (*313*, *314*). Second-generation tyrosine kinase inhibitors – nilotinib and dasatinib – have therefore been developed.

- **Alternative regimens for patients who are intolerant of, or whose disease develops resistance to imatinib**
  - nilotinib 300 mg orally every 12 hours for newly diagnosed patients (chronic phase)
  - nilotinib 400 mg orally every 12 hours for patients resistant to or intolerant of imatinib (chronic or accelerated phase)

  or

  - dasatinib 100 mg orally daily for newly diagnosed patients (chronic phase)
  - dasatinib 140 mg orally daily for patients resistant to or intolerant or imatinib (accelerated or blast phase)

Review of benefits and harms

Benefits

Imatinib

In the seminal study of its use, imatinib was shown to produce major cytogenetic responses in almost two thirds of patients with interferon-refractory CML (*315*). This was followed by an international randomized trial (IRIS) involving more than 1000 patients in 16 countries. Imatinib, 400 mg orally per day, was compared with interferon/low-dose cytarabine as first-line therapy for patients with chronic-phase CML (*316*). Haematological and cytogenetic responses were achieved in significantly more patients in the imatinib arm. Imatinib was more effective (96% vs 80% freedom from disease progression at one year) and better tolerated. Together, these studies supported the use of imatinib as the standard of care for patients with newly diagnosed chronic-phase CML.

Six-year follow-up of patients in the IRIS trial found no reports of disease progression to accelerated phase or blast crisis in patients who had been newly diagnosed with chronic-phase CML and randomized to receive imatinib as first-line therapy (*313*). The estimated event-free and overall survival at six years were 83% and 88%, respectively; overall survival was 95% when only CML-related deaths were taken into account. The toxicity profile remained unchanged after six years.

The toxicity profile for imatinib is substantially better than that of interferon/low-dose cytarabine, resulting in greatly improved quality of life for patients. Indeed, relevant data – including a large recently published study – suggest that the quality of life for patients on imatinib for a median of five years was comparable to that of population norms (*317*).

Cost–effectiveness of imatinib has been estimated at US$ 43 000 per quality-adjusted life-year (QALY) (*318*). This estimate is likely to become much

more favourable as the cost of imatinib falls with expiry of patents and survival of patients treated with imatinib improves with better management.

There is a small body of published literature on imatinib use in developing countries (*319–321*). Response rates similar to those in developed countries were reported among 275 patients in Pakistan, with a major cytogenetic response in almost two thirds of patients after a median follow-up of 18 months. Patients demonstrated good compliance and there was limited toxicity. The concordance between the timing and degree of response suggests that the biology of CML may be similar throughout the world.

Results of imatinib trials in adult patient populations have been extrapolated to children, and imatinib is being used increasingly for treatment of CML in children (*322*).

Dasatinib/nilotinib

Both dasatinib and nilotinib were developed for use in patients with CML who are intolerant of imatinib or have imatinib-resistant disease. The most common reason for development of resistant disease is the occurrence of mutations within the binding region. Approximately 50% of patients who are resistant to imatinib will achieve a complete cytogenetic remission when treated with either nilotinib or dasatinib (*323*, *324*); responses are durable in about 80% of patients. The application stressed the importance of having alternative treatments for patients with CML who are intolerant of or develop resistance to imatinib-based therapy.

A phase II open-label study investigated the effectiveness of nilotinib, 400 mg twice daily, in 321 patients with chronic-phase CML who had failed or were intolerant of imatinib (*324*). All patients were followed for more than 24 months. The rate of major cytogenetic response was 59%. Forty-four percent of the patients who achieved a major cytogenetic response attained a complete response. Estimated survival at 12 months was 87%. Adverse events were reported to be mild to moderate, with grades 3–4 neutropenia and thrombocytopenia occurring in 30% of patients.

Dasatinib, 70 mg twice daily, has been investigated in imatinib-resistant or -intolerant patients with CML in the myeloid or lymphoid blast phase in phase II trials (*323*, *325*). In the study by Cortes et al., after at least 12 months' follow-up, major cytogenetic responses were achieved in 33% and 52% of patients respectively. Twenty-six percent of myeloid blast-phase patients and 46% of lymphoid blast-phase patients achieved a complete cytogenetic response. Median progression-free survival was 6.7 months and 3.0 months in myeloid blast-phase and lymphoid blast-phase patients, respectively; median overall survival was 11.8 months and 5.3 months. Dasatinib was associated with acceptable tolerability.

A systematic review and network meta-analysis assessed the efficacy of imatinib, dasatinib and nilotinib in newly diagnosed CML (*326*). Eight

randomized controlled trials (RCTs) (3520 participants) were included. At 18 months, compared with imatinib 400 mg, the probability of a complete cytogenetic response was greater, and statistically significant, for dasatinib 100 mg (79.1%; 95% credibility interval (CrI): 72.0–85.1%), nilotinib 600 mg (83.1%; 95% CrI: 76.7–88.4%), and nilotinib 800 mg (80.0%; 95% CrI: 73.0–85.5%). In indirect comparisons with each other, dasatinib and nilotinib showed similar efficacy. However, evidence is weak and limited as findings are based on comparisons of only one or two RCTs, with high uncertainty. Other clinically relevant outcomes, such as survival, were not explored.

A second systematic review, with economic analyses, showed both dasatinib and nilotinib to be associated with a statistically significant advantage compared with imatinib in terms of complete cytogenetic and major molecular response (*327*). However, in the first-line treatment setting and assuming cost–effectiveness based on a willingness-to-pay decision threshold of £20 000 – £30 000 per QALY, nilotinib was found to be cost–effective compared with imatinib, while dasatinib was not. Again, data were based on immature surrogate outcomes, assumptions of life expectancy, and extreme uncertainty. More and longer-term data are needed for assessing the predictive usefulness of surrogate outcomes within the CML population, especially for dasatinib and nilotinib.

Harm considerations

Common

Tyrosine kinase inhibitors (TKIs) are well tolerated by the vast majority of patients. The most common non-haematological adverse reactions are oedema, muscle cramps and gastrointestinal symptoms including nausea, vomiting, diarrhoea and abdominal pain; most adverse effects are mild, however (*319*, *328*). In the initial patient cohort, at 6 years of follow-up, only 5% of patients discontinued imatinib because of side-effects or adverse events (*313*).

Specifically, dasatinib is associated with gastrointestinal bleeding in up to 25% of patients; however, the bleeding is typically mild to moderate and resolves given a drug holiday. Patients treated with dasatinib may also experience pulmonary complications including pleural effusions which can be grade 3–4 in up to 10% of patients (*329*).

Serious

Oedema can occasionally be severe and may result in cardiac complications in patients treated with imatinib who have underlying cardiac disease and/or heart failure (*328*). Additionally, nilotinib and dasatinib are associated with QT prolongation (*328*). Nilotinib is also associated with peripheral vascular disease and atherosclerosis-related events; however, the incidence of this adverse effect is low (< 5%).

Recommendations

On the basis of the evidence presented, the Expert Committee recommended the addition of imatinib to the complementary list of the Model List of Essential Medicines for the treatment of CML. The Committee noted the extreme rarity of the disease in children and considered that specific listing of imatinib on the EMLc for paediatric patients with CML was not warranted. The Committee considered that inclusion of imatinib on the EML would allow for its use in children.

The Committee did not recommend addition of nilotinib and dasatinib to the EML for this indication. The Committee accepted that a clinical need may exist for effective treatment of patients with CML who have failed or are intolerant of first-line imatinib, but considered the evidence presented on the use of dasatinib or nilotinib in the second-line setting was insufficient to warrant a recommendation for the addition of these medicines to the EML.

Diffuse large B-cell lymphoma – EML

The application sought the endorsement of medicines already included on the complementary list of the EML (cyclophosphamide, vincristine, doxorubicin and prednisone) for use in the "CHOP" regimen for diffuse large B-cell lymphoma. The application also sought the addition of rituximab to the core list of the EML, for use in combination with CHOP in the "R-CHOP" regimen. In settings where rituximab is not available or feasible, the application proposed that CHOP be the recommended fundamental regimen for this disease.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL), constituting about 30% of all cases of NHL globally (*330*). This subtype of cancer is heterogeneous and aggressive, yet scientific advances in the past quarter of a century have rendered it curable with chemotherapy or with combined chemotherapy and immunotherapy. Until 1998, the standard regimen for treatment of DLBCL included cyclophosphamide, vincristine, doxorubicin and prednisone (the CHOP regimen). The standard of care in Europe, the United States and other high-income settings now includes a combination of these four chemotherapy medicines plus immunotherapy with rituximab – the humanized monoclonal antibody directed at the CD20 antigen (the R-CHOP regimen). Research demonstrates 55.8% survival at 6 years among patients receiving CHOP only and 74.3% among patients receiving R-CHOP (*331*). The chance of survival without chemotherapy is 0%. Thus, with the addition of CHOP alone, gains in survival go from 0% to 56%. Drugs comprising CHOP are all old, off-patent drugs, while rituximab remains on-patent, more costly and technically more difficult to administer. Adding rituximab to CHOP results in an average additional increase in long-term survival of about 20%. Since many patients are young this results in many life-years gained.

Public health relevance

Non-Hodgkin lymphoma is the most common type of lymphoma and DLBCL is the most common type of NHL. DLBCL is a fast-growing, aggressive form of NHL. It is fatal if left untreated but, with timely and appropriate treatment, approximately 70% of all patients can be cured. The incidence of DLBCL in the United States is approximately 7 cases per 100 000 population per year. The disease affects adults over 60 years of age to a greater extent, but it occurs in patients of all ages, including children (*330*). Although global epidemiological

data on DLBCL burden are limited, the combined information generated by discrete studies and international estimates of the overall burden of NHL (e.g. GLOBOCAN 2012 (*255*)) warrants urgent action to expand access to chemotherapy and, where possible, immunotherapy.

The International Agency for Research on Cancer estimates the age-standardized incidence rate of NHL among both sexes worldwide to be 5.0 per 100 000 people. Data from GLOBOCAN 2012 show the age-standardized rate in more developed regions to be more than double that in less developed regions (8.6 and 3.6, respectively). However, it is plausible that this difference reflects differences in detection and diagnostic capacity. A similar scenario was observed in USA in the late 20th century: improvements in detection methods in the 1980s are considered to be one of the reasons for the significant increases in incidence during this period, which have since been followed by a plateau. A growing epidemic of human immunodeficiency virus (HIV) infection in USA at that time is also understood to have contributed to the increased incidence (*332*). The difference in mortality rates between more and less developed regions of the world (2.7 and 2.3 per 100 000 respectively) is less pronounced than the difference in incidence (*255*).

Research on DLBCL offers further insight into the impact of this disease in under-resourced parts of the world. A recent study reported on the burden of NHL subtypes in central and South America, analysing 1028 consecutive cases drawn from four academic medical centres and one private laboratory (*333*). This research showed that DLBCL constituted 40% of all forms of NHL – a slightly higher proportion than that recorded in Europe and USA. A retrospective adult cohort analysis in Mashhad, Islamic Republic of Iran, analysed data on 391 patients and also showed DLBCL to be the most common subtype of NHL (*334*). These studies, coupled with epidemiological data from GLOBOCAN, support the conclusions that the burden of DLBCL is not confined to high-income settings and that treatment options must be made available internationally.

Requirements for diagnosis, treatment, and monitoring

Diagnostics

Pathological analysis of surgically excised lymph node or extranodal tissue is required for diagnosis. If treatment with R-CHOP is possible, basic immunohistochemistry is required to detect the presence of the antigen CD20, located on the surface of the malignant B-lymphocytes, which is targeted by rituximab. A minimum diagnostic panel (where possible) should also include serum lactate dehydrogenase (LDH) (for International Prognostic Index (IPI) determination). When available, an enhanced diagnostic panel might include

CD10, BCL6, MUM-1 to distinguish germinal centre and ABC subtypes of DLBCL.

Testing

It has been recommended that pretreatment tests include staging, using contrast-enhanced computerized tomography (CT), and blood counts and chemistries to assess critical organ function, including renal and hepatic function. The role of pretreatment cardiac assessment with echocardiography is uncertain: it is possible that it does not modify the treatment strategy or predict toxicities (*335*). Hepatitis B and C status should be assessed and monitored closely if positive.

Administration and care of patients

Administration requires intravenous infusion capacity and regular patient access to clinical care. In developed countries, administration is usually performed in outpatient facilities; in other settings, patients may be treated in inpatient facilities. Intravenous hydration and antiemetics should accompany administration of both CHOP and R-CHOP. Doxorubicin and vincristine require care to prevent soft tissue extravasation, which can cause severe local reactions and necrosis. Rituximab can cause severe allergic reactions and must be given slowly, with close monitoring, and supportive medicines must be readily available, including adrenaline, steroids and antihistamines. Premedication with paracetamol 650 mg orally, hydrocortisone 100 mg IV, and diphenhydramine 25–50 mg IV 30–60 minutes before rituximab (at least before the first rituximab dose) is recommended and can be scaled back if there is no reaction to the first dose. If the patient has evidence of hepatitis B or C infection, this should be monitored since administration of rituximab can reactivate either of these infections. Given the severe consequences associated with reactivated infection, screening and prophylaxis against hepatitis B is recommended.

Monitoring requires that clinicians have access to laboratory facilities, as well as the ability to recognize and address potential adverse events caused by the treatment itself, including bone marrow suppression, infection, allergic reactions to rituximab and gastrointestinal toxicity. Social and financial well-being can be impacted by the side-effects of treatment and should also be monitored and addressed.

Overview of regimens

The following provides basic information on administration and dosing for CHOP and R-CHOP; no details are given of ancillary medications pertaining to the management of adverse events. For both CHOP and R-CHOP, six cycles of therapy are recommended.

Standard regimen

- **R-CHOP: chemotherapy plus monoclonal antibody (6 cycles)**
  - rituximab 375 mg/m² IV infusion
  - cyclophosphamide 750 mg/m² IV infusion
  - doxorubicin 50 mg/m² IV injection
  - vincristine 1.4 mg/m² IV infusion (cap dose at 2 mg)
  - prednisone 100 mg orally (liquid or tablet)

Alternative regimen

- **CHOP: chemotherapy (6 cycles)**
  - cyclophosphamide 750 mg/m² IV infusion
  - doxorubicin 50 mg/m² IV injection
  - vincristine 1.4 mg/m² IV infusion (cap dose at 2 mg)
  - prednisone 100 mg orally (liquid or tablet)

CHOP or R-CHOP can be given every 21 days without haematopoietic growth factor support. Both regimens can also be given every 14 days with growth factor (G-CSF) support, but the benefit of this shorter regimen is unclear and the additional cost of G-CSF support is substantial.

Review of benefits and harms

Benefits

Given that patients with DLBCL cannot survive without treatment, the benefits of the R-CHOP and CHOP regimens are highly significant. In the GELA LNH-98.5 study, previously untreated patients (60–80 years of age) had improved progression-free survival (PFS) and overall survival (OS) on both chemotherapy and chemotherapy plus rituximab. Addition of rituximab to the regimen significantly improved outcomes: OS at 2 years was 70% for R-CHOP compared with 57% for CHOP (*336*). A similar study among younger adult patients (18–60 years) produced similar results: event-free survival at 3 years was 59% among patients on CHOP-like chemotherapy and 79% among those on CHOP-like chemotherapy plus rituximab (*337*). A systematic review by Cheung and colleagues compiled these and other studies to compare outcomes among patients on chemotherapy with those in patients on chemotherapy plus rituximab (R-CHOP) for the treatment of lymphoma (*338*). As a subset of the larger review, 11 randomized controlled trials (RCTs) concerned with the treatment of DLBCL were analysed. This review is consistent with several other reviews and meta-analyses that have demonstrated the clinically important benefits in terms of PFS

and OS among patients on chemotherapy alone or chemotherapy with rituximab (*339–341*). The difference in OS associated with rituximab shown in the RCT by Coiffier et al., in which two-year survival was recorded in 70% (95% CI: 63–77%) of those receiving R-CHOP and 57% (95% CI: 50–64%) of those receiving CHOP alone (*336*), has not been replicated in under-privileged settings. In a Mexican retrospective cohort study of patients with DLBCL, OS was 87% at 80 months for those treated with R-CHOP and 84% at 145 months for those treated with CHOP (*342*). However, the Committee noted the observational nature of the study, the high attrition and the likelihood that those patients who remained in remission at 5 years were cured of their disease and had a high probability of leading normal lives.

Harms and toxicity considerations

Common

The Committee noted that treatment with CHOP and R-CHOP is associated with alopecia and with blood count suppression, particularly neutropenia, which increases the risk of infection. The incidence of grade 3 or 4 infection in patients treated with these regimens is 7–20% (*336*, *337*, *343*, *344*). Neuropathy from vincristine is rare and usually mild and reversible.

Rituximab can cause significant systemic allergic reactions, neutropenia and, infrequently, viral infection or reactivation of latent viral infection, including viral hepatitis.

Serious

Doxorubicin is associated with a risk of congestive heart failure. This risk is dose-dependent; at the doses delivered in six cycles of CHOP or R-CHOP (300 mg/m^2), the risk is small and was considered by the Committee to be outweighed by the potential benefits of treatment. The risk of long-term bone marrow damage, including secondary malignancies such as myelodysplastic syndrome or acute myeloid leukaemia, is very small (less than 1%). The risk of other secondary malignancies with CHOP and R-CHOP is also small (*337*).

Recommendations

On the basis of the evidence presented in the application, the Expert Committee recommended that cyclophosphamide, vincristine, doxorubicin and prednisone be specifically endorsed on the Model List for treatment of diffuse large B-cell lymphoma. The Committee also recommended that rituximab be added to the complementary list of the Model List of Essential Medicines for the treatment of DLBCL. In terms of overall survival, the Committee considered that the magnitude of clinical benefit demonstrated by CHOP over no treatment, and by

R-CHOP over CHOP (when available and/or affordable), was well established and supported this recommendation. Rituximab should be administered using the standard regimen of every 3 weeks.

The Committee considered that R-CHOP should be the preferred treatment option where possible; where rituximab is unavailable or not affordable, CHOP should be used, since many patients will benefit from this alternative regimen.

The Committee noted that an alternative regimen of R-ACVBP (rituximab, cyclophosphamide, doxorubicin, vindesine, bleomycin and prednisolone) showed overall survival advantage over R-CHOP in a prospective randomized study (*345*). However, the Committee considered that R-CHOP and CHOP remained the standard of care since this trial might have been flawed, R-ACVBP is not widely accepted, and vindesine is often unavailable.

Early-stage breast cancer – EML

The application sought the inclusion of treatment options for early-stage breast cancer on the core list of the EML and proposed that trastuzumab and anastrozole (representing the therapeutic class of aromatase inhibitors) be added to the Model List. Medicines proposed for the treatment of early-stage breast cancer already included on the Model List include doxorubicin, cyclophosphamide, paclitaxel, docetaxel, methotrexate, 5-fluorouracil, carboplatin and tamoxifen.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Early-stage breast cancer is defined as disease confined to the breast, with or without regional lymph node involvement, in the absence of distant metastatic disease. This is based on the fact that early-stage breast cancer is potentially curable, while distant metastatic disease is not. In developed countries, more than 80% of patients with early-stage breast cancer have long-term survival after surgery, and in some cases with systemic therapy such as chemotherapy, hormone therapy, targeted therapy, and local radiation (*346*). By contrast, breast cancer patients with distant metastases are rarely long-term survivors.

Treatment of early-stage breast cancer always includes surgical removal of the breast tumour and of some axillary lymph nodes. Surgery alone will result in long-term survival for some patients. Systemic therapy and local radiation can significantly improve the chances for long-term survival, depending on the stage of disease and the molecular subtype of breast cancer. Systemic therapy should therefore be viewed as providing incremental benefit beyond surgery alone (*347–350*). Systemic therapy includes hormone therapy (tamoxifen and aromatase inhibitors), chemotherapy, and targeted therapy such as trastuzumab.

Breast cancer can be viewed as four subtypes, as follows:

1. Hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative
2. HR-positive/HER2-positive
3. HR-negative/HER2-positive
4. HR-negative/HER2-negative.

These molecular subtypes determine which therapies are likely to be efficacious. Hormone therapy is beneficial only for patients with HR-positive tumours, and trastuzumab and similar HER2-targeted therapies are helpful only in women with HER2-positive cancers.

For many patients, surgical removal of the primary breast tumour and axillary node sampling is the first procedure, followed by systemic therapy and

radiation if indicated. In these circumstances, patients can be treated either with modified radical mastectomy or lumpectomy. In patients who undergo lumpectomy, it is critical for the cancer to be completely removed, with negative margins on pathological assessment, and these patients should always receive whole-breast radiation. Patients treated with mastectomy will benefit from post-mastectomy radiation if they have extensive breast tumours or involved axillary lymph nodes (*351*, *352*).

Locally advanced disease refers to a cancer that is still confined to the breast and regional lymph nodes but is sufficiently extensive to preclude initial surgical resection. Large tumours, tumours that are attached to skin or underlying chest wall structures, and those with extensive axillary involvement often qualify as denoting locally advanced disease. Patients with locally advanced disease are often treated with systemic therapy before surgery and, if response to therapy is adequate, can then undergo surgical resection of the cancer. Locally advanced disease is seen more commonly in the developing world than in developed countries (*353*).

Public health relevance

Breast cancer comprises one quarter of all new cancer cases in women and men worldwide, with an estimated 1.67 million cases in 2012 alone, according to GLOBOCAN 2012, the database of the International Agency for Research on Cancer. Although highly treatable with systemic therapy, surgery and radiation therapy, breast cancer was the cause of death of approximately half a million women worldwide in 2012 (*255*). In sub-Saharan Africa alone, it is believed that nearly 50 000 women died from the disease during that one year. The ratio of incidence to mortality in high-, middle- and low-income countries varies dramatically, reflecting disparities in access to resources, clinical knowledge and medicines (as is the case for all cancers). According to one study in 2010, the 5-year survival rate for breast cancer ranged from 12% in Gambia, an extremely poor country, to 79% in the Republic of Korea, a high-income country (*354*). It has been noted that women suffering from breast cancer in the developing world are more likely to present to health facilities at later stages because of structural barriers to care, absence of treatment options, or inadequate information being disseminated to the public (*355*). Women who receive treatment for early-stage breast cancer (localized disease) have a significantly higher chance of survival than those treated for metastatic disease. Even in less developed regions of the world, such as Costa Rica, India, Philippines, Saudi Arabia, and Thailand, overall survival at 5 years for women treated for localized disease was 73.6% on average, compared with 47.4% for women with regional disease (*354*).

Requirements for diagnosis, treatment, and monitoring

Diagnostics

The treatment of breast cancer should always be determined by pathological evaluation of the primary cancer. Biopsy is often performed by ultrasound-guided core needle technique, although incisional biopsy is useful to distinguish between in-situ and invasive cancer. Fine-needle aspiration can play a role but does not allow a distinction between in-situ and invasive cancer and often does not give adequate material for immunohistochemistry. Evaluation of the biopsy by an experienced pathologist will yield the molecular subtype and grade of the cancer. Immunohistochemistry (IHC) analysis for estrogen receptors, and in some cases progesterone receptors, is critical since this will determine whether the cancer is potentially sensitive to hormone therapy. HER2 can be assessed either by IHC, or by fluorescence in situ hybridization (FISH) if IHC is equivocal, and is critical to determine whether the cancer might be sensitive to HER2-targeted therapy with agents such as trastuzumab.

Evaluation of surgical specimens, either lumpectomy or mastectomy, should include pathological confirmation of the histology as well as assessment of surgical margins. Evaluation of axillary lymph nodes should record the total number of nodes resected and the number of nodes involved with cancer.

Testing

It is important to determine whether the primary breast tumour is resectable or not. Generally, involvement of the skin and/or chest wall structures indicates that resection is unlikely to be successful. Breast ultrasound can help to determine this, although physical examination is very helpful. Metastatic disease should be ruled out, preferably with computerized tomography scans and a bone scan. When these are not available, chest X-ray and liver ultrasound can give important information. Complete blood count (CBC), liver function tests, electrolytes and renal function testing are all essential to determine a patient's fitness to undergo both surgery and systemic therapies.

Administration and care of patients

Hormone therapies (tamoxifen and aromatase inhibitors) are largely administered orally. No special testing or administrative resources are necessary for the use of these drugs, although a reliable supply is important.

Cytotoxic chemotherapy requires the ability to administer intravenous chemotherapy, with particular consideration of avoidance of extravasation with doxorubicin and of allergic reactions with taxanes. Chemotherapy can be administered in an outpatient infusion setting or an inpatient setting, although this is not required. Intravenous fluids and antiemetics are required

and hypersensitivity medicationsmust be available. Monitoring of CBC, renal function, electrolytes and liver functions tests are required.

Trastuzumab and similar anti-HER2 targeted therapies are generally administered intravenously. Administration is relatively straightforward and is usually done in outpatient infusion facilities.

Cardiac monitoring is recommended for patients receiving trastuzumab or an anthracycline, although the incidence of serious cardiac toxicity is low – and in most cases reversible – and the potential benefit in disease control is substantially increased with use of these agents in patients with HER2-positive disease (*356*, *357*).

As with all cancer treatment, social support, clean water and adequate nutrition are essential.

Overview of regimens

The following provides basic information on administration and dosing for the four molecular subtypes of breast cancer, followed by specific regimens.

HR-positive/HER2-negative tumours

Tamoxifen has been shown to reduce systemic recurrence rates by 50% (*347*). For decades, five years of therapy was considered standard, although recent studies have shown a small additional benefit for 10 years of hormonal therapy (*358–360*). Absolute mortality reduction of about 2% has been shown for women with HR+ breast cancer who continue on tamoxifen for 10 years compared with those who stop after five years (*358*). The recommendations in the American Society of Clinical Oncology clinical practice guideline on adjuvant endocrine therapy were updated on the basis of emerging data on the longer optimal duration of treatment, particularly adjuvant tamoxifen (*347*). Aromatase inhibitors are not recommended for premenopausal women. For postmenopausal patients, use of aromatase inhibitors in place of tamoxifen, or after a course of tamoxifen, had a small incremental benefit for reducing distant recurrences, though only a marginal benefit for overall survival (*361*): aromatase inhibitors produced a 3.1% absolute decrease in recurrence compared with tamoxifen (5.0% versus 8.1%), and an absolute decrease in breast cancer mortality of 0.7% (1.7% versus 2.4%). Aromatase inhibitors should be advised only in patients at high risk of disease progression. When chemotherapy is administered, hormone therapy should always be initiated after the completion of chemotherapy.

Chemotherapy will add to benefit, particularly for women with large cancers and involved axillary lymph nodes (*348*).

For patients with locally advanced cancer requiring preoperative (neoadjuvant) therapy, chemotherapy is usually the treatment of choice,

although hormone therapy can sometimes be used in place of chemotherapy (in postmenopausal women).

Tamoxifen or an aromatase inhibitor plus ovarian suppression with a luteinizing hormone–releasing hormone (LHRH) agonist or oophorectomy can be considered for premenopausal patients at high risk of recurrence. The TEXT (Tamoxifen and Exemestane Trial) and SOFT (Suppression of Ovarian Function Trial) trials compared the effect on disease-free survival of the aromatase inhibitor exemestane and of tamoxifen in premenopausal women also treated with ovarian suppression, and assessed the value of ovarian suppression in women receiving adjuvant tamoxifen. Primary analysis of these two phase III trials included data from 4690 patients. Disease-free survival for exemestane plus ovarian suppression and for tamoxifen plus ovarian suppression was 91.1% and 87.3%, respectively, after a median follow-up of 68 months (*362*). The SOFT trial included 1084 women who remained premenopausal after completion of chemotherapy and were deemed to be at higher risk of recurrence. In this cohort, tamoxifen plus ovarian suppression compared with tamoxifen alone was associated with a 25% reduction in the relative risk of recurrence (*363*).

HR-positive/HER2-positive tumours

As above, hormone therapy should be a component of the therapy for these patients. Chemotherapy plus trastuzumab should be administered to all patients except those with very small (< 0.5 cm), node-negative tumours (*349*). Combined hazard ratios (HR) for both overall survival and disease-free survival significantly support addition of trastuzumab (0.66 and 0.60, respectively). The risk of congestive heart failure and left ventricular ejection fraction decline was significantly increased by addition of trastuzumab (risk ratio 5.11 and 1.83 respectively), but the benefit far outweighed the risk for patients with high risk of recurrence and healthy heart (*364*). The study with the longest follow-up concluded that, at 10 years, overall survival rate increased from 75.2% to 84.0% with the addition of trastuzumab to chemotherapy (HR 0.63) (*365*). Trastuzumab should be administered for one year; typically, it is given concurrently with a taxane but not concurrently with an anthracycline. HER2-directed agents and hormone therapy can be given concurrently.

For patients receiving preoperative therapy, the combination of a taxane, trastuzumab and pertuzumab has been shown to be more effective than a taxane and trastuzumab alone (*366*). However, the Expert Committee noted that further efficacy and safety data from clinical trials other than a single sponsor-driven trial are needed. The addition of pertuzumab as part of postoperative adjuvant therapy has not been shown to be beneficial. The role of trastuzumab–emtansine

(T-DM1) as adjuvant therapy remains undefined; its effectiveness has been explored only in metastatic disease.

Neither pertuzumab nor trastuzumab–emtansine was proposed or recommended for inclusion in the EML at this time.

HR-negative/HER2-positive tumours

Hormone therapy is not indicated. Trastuzumab chemotherapy combinations are indicated.

HR-negative/HER2-negative tumours

Hormone therapies and trastuzumab-containing regimens are not indicated for these patients.

Standard chemotherapy regimens (non-trastuzumab regimens)

- **AC – doxorubicin and cyclophosphamide (every 3 weeks x 4 cycles), for subtypes 1 and 4 (and 2 and 3 if trastuzumab is unavailable)**
  - doxorubicin 60 mg/m² IV
  - cyclophosphamide 600 mg/m² IV
- **AC-T – doxorubicin/cyclophosphamide followed by paclitaxel or docetaxel for subtypes 1 and 4 (and 2 and 3 if trastuzumab is unavailable)**
  - doxorubicin 60 mg/m² IV every 3 weeks x 4 cycles
  - cyclophosphamide 600 mg/m² IV every 3 weeks x 4 cycles

  followed by
  - paclitaxel 175 mg/m² IV every 3 weeks x 4 cycles

  or
  - paclitaxel 80 mg/m² IV every 1 week x 12 weeks

  or
  - docetaxel 100 mg/m² IV every 3 weeks x 4 cycles

  Note: For paclitaxel the weekly schedule is superior to the 3-weekly schedule and should be used unless the patient is unable to come for weekly treatment.
- **TC – docetaxel/cyclophosphamide (every 3 weeks x 4 cycles) for subtypes 1 and 4 (and 2 and 3 if trastuzumab is unavailable)**
  - cyclophosphamide 600 mg/m² IV
  - docetaxel 75 mg/m² IV

- **Oral CMF (every 28 days for 6 cycles)**
  - cyclophosphamide 100 mg/m² orally, daily on days 1–14
  - methotrexate 40 mg/m² IV on days 1 and 8
  - 5-FU 600 mg/m² IV on days 1 and 8

Alternative regimen (if other regimens above are unavailable)

- **FAC (every 3 weeks x 6 cycles)**
  - 5-FU 500 mg/m² IV
  - doxorubicin 50 mg/m² IV
  - cyclophosphamide 500 mg/m² IV

Standard regimens including trastuzumab, for HER2-positive disease

- **AC-TH – doxorubicin/cyclophosphamide followed by paclitaxel/ trastuzumab for subtypes 2 and 3**
  - doxorubicin 60 mg/m² IV every 3 weeks x 4 cycles
  - cyclophosphamide 600 mg/m² IV every 3 weeks x 4 cycles

  followed by
  - paclitaxel 80 mg/m² IV every 1 week x 12 weeks
  - trastuzumab[4] 2 mg/kg IV every 1 week x 12 weeks

  or
  - docetaxel 100 mg/m² IV every 3 weeks x 4 cycles
  - trastuzumab 2 mg/kg IV every 1 week x 12 weeks

  followed by
  - trastuzumab 6 mg/kg IV every 3 weeks to finish 1 year of therapy
- **TCH – docetaxel/carboplatin/trastuzumab for subtypes 2 and 3**
  - docetaxel 75 mg/m² IV every 3 weeks x 6 cycles
  - carboplatin AUC 6 IV every 3 weeks x 6 cycles
  - trastuzumab[5] 6 mg/kg IV every 3 weeks x 6 cycles

[4] Trastuzumab 4 mg/kg loading dose first week of therapy. (Alternatively, trastuzumab can be used with an 8-mg/kg bolus and maintenance of 6mg/kg every 3 weeks.)

[5] First dose of trastuzumab: loading dose 8 mg/kg.

followed by

– trastuzumab 6 mg/kg IV every 3 weeks to complete 1 year of therapy

The application stated that epirubicin can be substituted for doxorubicin at an equipotent dose, and proposed that it be included in the EML as a class agent with doxorubicin for treatment of breast cancer. The Expert Committee considered that there was insufficient evidence to support the inclusion of epirubicin along with doxorubicin in the EML and did not recommend the inclusion of epirubicin as a within-class alternative to doxorubicin.

Standard hormone regimens (pre- and postmenopausal women)

tamoxifen 20 mg/day orally x 5 years

LHRH agonist (goserelin) 3.6 mg/28 days SCI x 2–5 years[6]

Standard regimen for postmenopausal women who have contraindications to or are intolerant of tamoxifen

anastrozole 1 mg/day orally x 5 years

The application proposed that anastrozole be added to the EML with a square box symbol as the pharmacological representative of the class of aromatase inhibitors and that this class should include letrozole and exemestane. The Expert Committee considered that this was reasonable.

With regard to hormone regimens, **premenopausal women** should receive tamoxifen for at least five years. Treatment for 10 years offers a small benefit compared with treatment for five years. For premenopausal women who have an absolute contraindication to, or are intolerant of, tamoxifen, ovarian suppression by surgery, radiation or medication in combination with an aromatase inhibitor is an acceptable alternative. Ovarian suppression plus tamoxifen or exemestane has been associated with improved disease-free survival and breast cancer-free survival in women at higher risk of recurrence.

Postmenopausal women can be treated with five years of an aromatase inhibitor, or two to three years of tamoxifen followed by an aromatase inhibitor to complete five years. Alternatively, five years' treatment with tamoxifen can be followed by five years of an aromatase inhibitor. Treatment for 10 years offers a small benefit compared with treatment for five years. If aromatase inhibitors are

[6] Premenopausal patients at high risk of recurrence.

unavailable or if the patient is intolerant of an aromatase inhibitor, treatment with tamoxifen for the entire course is acceptable. Use of an aromatase inhibitor in the treatment course offers a small benefit for disease-free survival and marginal benefit for overall survival.

For postmenopausal women, five years of treatment with tamoxifen, followed by five years of treatment with an aromatase inhibitor, should be considered only in high-risk patients (e.g. node-positive).

Review of benefits and harms

Benefits

Hormone therapy reduces the risk of systemic recurrence by 50%, although the absolute benefit relates to the overall risk of relapse, which relates in turn to tumour size and grade and axillary nodal involvement. The improvement in relapse-free survival with chemotherapy varies by molecular subtype as well as overall risk of relapse, again based on tumour size and grade and axillary nodal status. For patients with HER2-positive disease, the addition of trastuzumab to chemotherapy further reduces the risk of relapse significantly compared with chemotherapy alone. Moreover, the addition of trastuzumab to chemotherapy as preoperative therapy for locally advanced disease dramatically increases the response rate.

Harms and toxicity considerations

Common

Risks of treatment include common short-term toxicities such as alopecia, neutropenia, fever and infection, and neuropathy from taxanes. Paclitaxel and trastuzumab are associated with infusion reactions in up to 30–40% of patients; most reactions are mild and easily managed (*367*, *368*).

Tamoxifen can cause hot flushes, mood changes and, rarely, thromboembolic disease and endometrial cancer. Tamoxifen generally has a positive effect on bone density. Aromatase inhibitors can cause hot flushes, mood changes, musculoskeletal complaints and bone loss.

Serious

Cardiac muscle suppression or damage can occur after therapy with anthracyclines and trastuzumab, and administration of both agents together increases the risk. For the regimens described above, the risk of congestive heart failure is small and reversible upon discontinuation in most cases (*273*, *356*, *369*).

Bone marrow damage, myelodysplastic syndrome and acute leukaemia can occur after therapy with cyclophosphamide and doxorubicin but are rare.

Recommendations

On the basis of the evidence presented in the application, the Expert Committee recommended that the medicines in the following chemotherapy regimens, currently included on the complementary list of the EML, be specifically endorsed for the treatment of early-stage breast cancer. These regimens are suitable for use in HER2-positive and -negative disease, and in HR-positive and -negative disease.

Regimen	Medicines
AC	doxorubicin and cyclophosphamide
AC-T	doxorubicin and cyclophosphamide followed by paclitaxel
CMF	cyclophosphamide, methotrexate and 5-fluorouracil

The Committee also recommended that trastuzumab be added to the complementary list for treatment of HER2-positive early-stage breast cancer for use in AC-TH (doxorubicin and cyclophosphamide followed by trastuzumab and paclitaxel) and TC-H (docetaxel, carboplatin and trastuzumab) regimens. Where trastuzumab is unavailable, the chemotherapy regimens listed above should be used (with or without hormone therapy as appropriate).

The Committee recommended that tamoxifen (already listed) be specifically endorsed for treatment of HR-positive early-stage breast cancer. In addition, the Committee recommended addition of anastrozole to the complementary list, with a square box symbol as the representative of the pharmacological class of aromatase inhibitors.

The Committee also considered that goserelin should be included on the complementary list for early-stage breast cancer. However, having earlier in the meeting recommended the listing of leuprorelin with a square box symbol as representative of the pharmacological class of LHRH agonists for treatment of metastatic prostate cancer, the Committee considered that a separate listing for goserelin was unnecessary as its availability would be captured by the square box listing for leuprorelin.

Early-stage cervical cancer – EML

The application sought the addition of cisplatin to the core list of the Model List of Essential Medicines for the treatment of early stage cervical cancer.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Cervical cancer has significant impact in developing countries because of limited economic resources, screening opportunities, health services access, medical treatments and monitoring difficulties. Globally, the incidence of cervical cancer is 14 per 100 000 inhabitants and the mortality rate is 6.8 per 100 000 inhabitants; 87% of deaths occur in developing countries and incidence is highest in Africa (*255*).

The available evidence shows that virtually all cases of invasive cervical cancer arise from persistent infection by high-risk serotypes of human papilloma virus (HPV). WHO recognizes three categories of invasive cervical carcinoma: squamous, adenocarcinoma and other epithelial tumours. Squamous is the most common histological type, accounting for 70–80% of cases, followed by adenocarcinoma (10–15%) (*370*).

The staging of invasive cervical cancer is clinical, partly because of the high prevalence of cervical cancer in resource-limited settings, where highly technical imaging studies and other assays may not be readily available. The International Federation of Gynecology and Obstetrics (FIGO) staging is as follows:

- Stage I tumours are confined to the cervix.
- Stage II tumours extend beyond the cervix without involving the pelvic walls.
- Stage III denotes extension to the pelvic walls, which may cause hydronephrosis, or invasion of the lower third of the vagina.
- Stage IV denotes cancer that is distantly metastatic or invades the bladder or rectal mucosa.

Some authorities recommend surgical staging of cervical cancer through regional lymphadenectomy; however, this intervention has not been shown to improve survival and is generally not recommended outside the setting of clinical trials.

The stage-specific five-year survival rates reported by the Cancer Joint American Committee for 2000–2002 are 60–93% for early stages of disease (FIGO stages IA, IB1 and IIA1), 16–58 % for locally advanced stages (FIGO stages IB2, IIA2, IIB, IIIA, IIIB and IVA) and 15% for advanced stages (FIGO stage IVB) (*371*).

Survival in early-stage cervical cancer appears comparable for patients treated either with surgery or with radiotherapy. Most patients with smaller tumours are treated with primary surgery. Acceptable treatment options for early stage cervical cancer include the following:

Stage IA1

- Cervical conization.
- Total hysterectomy.
- Cervical brachytherapy if there is a high surgical risk.

Stage IA2

- Total hysterectomy plus pelvic lymphadenectomy.
- Teletherapy plus brachytherapy if there is a high surgical risk.
- Teletherapy plus brachytherapy (70–80 Gy to point A), if there is a high surgical risk.

Stages IB1–IIA1

- Radical hysterectomy plus pelvic lymphadenectomy.
- External radiation therapy plus brachytherapy (80–85 Gy to point A) plus concurrent chemotherapy with cisplatin.

Surgical management

Patients with stage IA1 or IA2 cervical cancer who have lymphatic or vascular space invasion (LVSI) are treated with radical surgery and lymphadenectomy. Further, in patients undergoing surgery for early-stage cervical cancer, ovaries that appear normal can potentially be preserved. Where it is available, fertility-sparing surgery appears to be a safe and reasonable option for selected patients with early-stage cervical cancer. Total and radical hysterectomy and lymphadenectomy can be performed using laparoscopic methods.

Patients who undergo surgery for early-stage cervical cancer are designated low, intermediate or high risk for recurrence according to pathological criteria:

- Low risk (risk of recurrence and death limited and usually below 10%):
  - tumour occupying less than half of the cervical volume
  - tumour < 2 cm
  - no LVSI

- Intermediate risk (risk of recurrence and death up to 30% after surgery alone):
  - presence of LVSI plus deep one third stromal invasion and tumour of any size
  - presence of LVSI plus middle one third stromal invasion and tumour size ≥ 2 cm
  - presence of LVSI plus inner one third stromal invasion and tumour size ≥ 5 cm
  - no LVSI but deep or middle one third stromal invasion and tumour size ≥ 4 cm
- High risk (risk of recurrence and death of up to 50% after surgery alone):
  - positive surgical margins
  - pathologically confirmed involvement of the pelvic lymph nodes
  - microscopic involvement of the parametrium

Post-surgical chemoradiation with cisplatin is used for women with early-stage cervical cancer determined to be at high risk for recurrence after surgery.

Public health relevance

GLOBOCAN indicates that global cervical cancer prevalence in 2012 was 1 547 000, making this the fourth most common cancer in women (*372*). There were an estimated 528 000 new incidences in 2012; about 85% (444 300) of those cases occurred in less developed regions and 15% (83 000) in more developed regions. Highest-risk regions include eastern and central Africa.

Cervical cancer is highly preventable and – if detected in its early stages – treatable. GLOBOCAN estimated that in 2012 there were 266 000 deaths from cervical cancer, 87% of which occurred in less developed regions. While GLOBOCAN does not provide specifics about early-stage cervical cancer, the data do suggest that overall cervical cancer disproportionately impacts less developed regions.

Requirements for diagnosis, treatment and monitoring

Diagnostics

The diagnosis of cervical cancer is based on direct tissue biopsy. This can usually be done by vaginal examination without anaesthesia in an outpatient setting.

Histology

The diagnosis of invasive cervical cancer can be made by a pathologist on the basis of haematoxylin and eosin stains.

Imaging

Invasive cervical cancer is a clinically staged disease. Evaluation of the bladder and rectum by cystoscopy and proctoscopy is advised when available. Intravenous pyelogram (IVP) is recommended for patients at risk for ureteral obstruction; at many centres, however, computerized tomography (CT) or magnetic resonance (MR) is now substituted for this evaluation. CT can be useful to evaluate tumour size, correlation with anatomical structures, metastases and nodal involvement. Nuclear MR gives high resolution of soft tissues, particularly for the cervix, parametrial invasion, bladder or rectal invasion, ureteral obstruction, and lymph node enlargement. Positron emission tomography–computerized tomography (PET-CT) in particular allows for increased sensitivity in assessing lymphatic invasion. Though not part of the clinical staging, evaluation for regional or distant metastases using CT, MR or PET-CT may help guide treatment planning. Routine imaging is not recommended for patients who have completed primary therapy.

Administration and care of patients

The administration of chemotherapy with a platinum base requires that the patient have regular access to clinical care and that there is adequate venous access. In developed countries, administration is usually done in outpatient centres; in other settings, patients can be treated in inpatient facilities. Patients should be encouraged to increase fluid intake from the day before treatment. A minimum of 500 mL of normal saline should be administered intravenously 1 hour before cisplatin. Cisplatin doses of 40 mg/m² should be diluted in normal saline and infused at a rate of 1 mg/min. Because of the risk of dehydration and renal toxicity, intravenous hydration both before and after chemotherapy is highly recommended. Many physicians administer 500–1000 mL or more normal saline intravenously as post-chemotherapy hydration. Cisplatin is administered on the first day of external radiotherapy, preferably 4 hours before the radiotherapy, and repeated weekly for four to six cycles of treatment.

Overview of regimens

Standard regimen

Cisplatin 40 mg/m² (maximum dose 70 mg) administered at 1 mg/min, weekly for six cycles, on days 1, 8, 15, 22, 29 and 36.

Prescription

Cisplatin, available in vial of dry powder of 10 mg and 50 mg.

Adverse effects

Leukopenia, thrombocytopenia, anaemia, nausea, vomiting, nephrotoxicity, ototoxicity, peripheral neuropathy, electrolyte imbalance, hypocalcaemia, hypomagnesaemia, ocular toxicity and allergic reactions.

Postoperative radiotherapy

Prognostic factors representing high risk for relapsing:

- pelvic lymph nodes involved
- microscopic tumour involvement of the section lines
- microscopic tumour involvement, less than 3 mm to the section line
- deep stromal invasion, more than 50%
- lymphatic invasion
- vascular invasion
- cervical cancer treated non-surgically
- parametrial commitment.

Radiotherapy

Radiotherapy planning involves simulation or evaluation of tumour burden using the radiotherapy treatment unit or X-ray equipment. Four-field radiotherapy is used.

Anterior and posterior areas:

- Upper limit: the gap between L4 and L5. In patients with hysterectomy and lymphadenectomy without nodal involvement, the limit may be reduced to L5–S1.
- Lower limit: the lower edge of the obturator foramina.
- Lateral limits: 2 cm outside the bone pelvic wall, according to the parametrial involvement.

Lateral fields:

- Anterior limit: middle portion of the pubic symphysis.
- Posterior limit: S2–S3 (rectal half).
- Upper and lower limits: the same limits are preserved as for anteroposterior fields.

Pelvic area with central protection:

For overprint from 450–504 Gy, protecting the medium line with a rectangular lead of 4 x 10 cm.

Teletherapy

Megavoltage energy is used (cobalt or accelerator).
White volume: the tumour volume is included along with pelvic nodal disease. Two to four fields are used (anteroposterior and/or laterals). Therapy involves 18–20 Gy fractionation five times a week to complete a cumulative dose of 440–504 Gy.

Brachytherapy

Brachytherapy can be administered by intrauterine catheter or by ovoid or intravaginal cylinder and a low or high dose rate can be used. Isotopes used include radium-226, caesium-137 and iridium-192.

Review of benefits and harms

Benefits

Cisplatin has been shown in cell lines to be synergistic with radiotherapy (*373*). High-risk patients – with parametrial involvement, positive pelvic nodes or positive surgical margins – who undergo radical hysterectomy and pelvic lymphadenectomy for carcinoma of the cervix, benefit from a postoperative combination of cisplatin-containing chemotherapy and pelvic irradiation. The addition of concurrent cisplatin-based chemotherapy to pelvic radiotherapy significantly improves progression-free and overall survival in early-stage cervical cancer (*374*). At 4 years, patients treated with radiotherapy alone were found to have a lower rate of progression-free survival (63% versus 80%) and a lower overall survival rate (71% versus 81%) than patients treated with radiotherapy and chemotherapy. The average length of follow-up was 42 months. Grades 3 and 4 haematological and gastrointestinal toxicity were increased with combined chemoradiation therapy, but high-risk patients remain strong candidates for this approach.

These results were confirmed in a large Cochrane systematic review, including 24 trials comparing concomitant chemotherapy and radiation therapy with radiotherapy for locally advanced cervical cancer (*375*). The review strongly suggests that chemoradiation improves overall survival and progression-free survival with absolute benefits of 10% and 13% respectively. Fifteen trials used concomitant cisplatin-based chemoradiation. Chemoradiation also showed significant benefit for local recurrence and a suggestion of a benefit for distant recurrence. There was limited evidence that the effect was greater in trials

including a high proportion of stage I and II patients. Application to the developing world requires the regimen to be cheap and simple to administer, and the Cochrane review suggests that weekly cisplatin may fit these criteria.

Another Cochrane review of early-stage cervical cancer investigated whether chemotherapy with cisplatin given after surgery, after radiotherapy, or both, offered additional benefits or risks to women with risk factors for recurrence (*376*). Although more limited, the evidence again suggested that the addition of cisplatin chemotherapy to radiotherapy prolongs survival and delays progression of the cancer when given after surgery to women with cervical cancer stage IA2–IIA with risk factors for recurrence.

The role of chemotherapy for patients with persistent, recurrent or metastatic cervical cancer, in which surgery is not an option or is a palliative option only, was investigated in a further Cochrane review (*377*). The most commonly used dose was cisplatin 50 mg/m² on the first day of each 21-day cycle, and median overall survival was 8 months. Cisplatin-based chemotherapy combinations appeared to have the highest response rates although median overall survival remained poor at 9–12 months, with progression-free survival of 4–5 months, but with the cost of increased side-effects. Nearly all patients in these studies were relatively fit and well before starting treatment, despite their cancer; results might be different in patients who are not fit and well.

Studies of chemoradiotherapy in patients at moderate risk for recurrence, such as GOG 263 (ClinicalTrials.gov Identifier: NCT01101451), are ongoing. Outside the setting of a clinical trial, most such women are treated with radiotherapy alone.

Harms and toxicity considerations

General

Because of the increased toxicity of chemotherapy and a lack of proven benefit, women at intermediate risk for recurrence are treated with radiotherapy alone. Compared with radiotherapy alone, chemoradiation is associated with statistically significant increases in acute haematological and gastrointestinal toxicities (*375*) In addition, based on trials involving women treated primarily with radiotherapy and chemotherapy for advanced-stage disease, treatment with cisplatin alone can be used to reduce the toxicity seen with the addition of 5-fluorouracil (*374*, *378*).

Common

Cisplatin is highly emetogenic. Prophylactic antiemetics are necessary to reduce nausea and vomiting in all patients (*379*). Mild peripheral neuropathy is common. Patients should be followed carefully and dose reduction or discontinuation of treatment may be required for moderate or severe symptoms. Ototoxicity

is also observed and is more common with increasing dose and number of cycles. Audiometry should be considered for monitoring patients with toxicity; vestibular defects are less common.

Serious

Renal toxicity caused by cisplatin can be significant and may result in electrolyte abnormalities. Patients should be monitored for hypomagnesaemia, hypocalcaemia and hypokalaemia and deficits should be corrected. Intravenous hydration both before and after administration of cisplatin is recommended to reduce the incidence of renal toxicity (*380*).

Recommendations

On the basis of the evidence presented in the application, the Expert Committee recommended the addition of single-agent cisplatin to the complementary list of the EML for the treatment of early-stage cervical cancer for use concurrently with radiotherapy in women at high risk of recurrence following surgery. The Committee acknowledged that this treatment produced clinically meaningful improvements in progression-free survival and overall survival at four years.

The Committee also noted that chemoradiation with cisplatin and radiotherapy as appropriate treatment in patients for whom surgery is not considered to be curative is also associated with clinically meaningful benefits compared with radiotherapy alone. In this group of patients the addition of cisplatin to radiotherapy results in a 10% gain in absolute survival and a 40% relative reduction in risk of death.

Early-stage colon cancer – EML

The application sought endorsement of calcium folinate and fluorouracil (5-FU), already listed on the Model List of Essential Medicines, for the treatment of early-stage colon cancer. The application also sought the addition of oxaliplatin and capecitabine to the core list of the Model List for the same indication.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Surgical resection, the cornerstone of treatment in early disease, is potentially curative as a single-modality therapy in stage I, II and III colorectal cancer. Multiple clinical trials have demonstrated that 5-FU-based adjuvant chemotherapy can increase the cure rate of stage III colon cancer, and this is an option in countries with sufficient resources to administer chemotherapy and monitor its side-effects. In wealthy countries, the standard of care is the FOLFOX regimen (5-FU, calcium folinate, and oxaliplatin) or the CapeOx (XELOX) scheme (capecitabine and oxaliplatin), or single-agent capecitabine. In countries that cannot afford oxaliplatin, 5-FU/calcium folinate chemotherapy, administered as a weekly bolus, is still an effective regimen.

Public health relevance

Colorectal cancer is one of the most common, and deadly, malignancies; it has been estimated that there are 1.2 million new cases a year worldwide. Globally, colorectal cancer is the fourth most common cause of cancer-related deaths in men and the third in women, killing an estimated 320 600 men and 288 100 women annually (*381*).

In the developed world, the death rate from colorectal cancer has been falling, largely as a result of colonoscopy screening, which allows both the removal of precancerous polyps and the detection of early-stage, curable disease. Because 90% of colon cancers occur in patients who are at least 50 years old, the recommendation in countries that are able to afford colonoscopy is for screening of the general population to begin at age 50 (*382*).

Because of the expense of colonoscopy, population-based screening programmes are not usually feasible in many parts of the world. Added to poor access to health care, this means that patients in low- and middle-income countries often present with more advanced stages of colorectal cancer.

In the United States, 40% of colorectal cancer patients have localized disease (stage I and II), 36% are regionally advanced (stage III) and 20% have metastases at presentation (*383*).

Requirements for diagnosis, testing, and administration

Harms and toxicity considerations

Localized colorectal cancer often presents with one of the following symptoms: change in bowel habits, blood in the stools, abdominal discomfort and weight loss. The symptoms of metastatic colorectal cancer depend on the site of metastasis (liver: right upper quadrant abdominal pain, jaundice; lungs: chest pain, shortness of breath).

The primary mass in colorectal cancer can be diagnosed by rectal examination, sigmoidoscopy or colonoscopy. A biopsy can be performed during endoscopy so that the diagnosis of cancer may be confirmed pathologically.

A critical aspect of the evaluation of a colorectal cancer patient is establishing whether metastatic disease is present. In high-resource health systems, computerized tomography scan of the chest, abdomen and pelvis is performed routinely. In resource-constrained settings, systemic evaluation with the less costly abdominal and pelvic ultrasound is commonly employed. Preoperative cancer staging, which evaluates the T and N stage of the tumour, is also important in establishing the degree of loco-regional invasiveness of the tumour. Where available, it is performed by either magnetic resonance imaging or endoscopic ultrasound, complex and highly specialized methods with limited availability in resource-constrained settings.

Administration and care of patients

Administration requires intravenous infusion capacity and regular patient access to clinical care. Treatment can be carried out in outpatient facilities; in settings where ambulatory infusion of 5-FU is not feasible it is common for patients to be treated in inpatient facilities. Antiemetics need to be available. Monitoring requires that clinicians have access to laboratory facilities, as well as the ability to recognize and address potential adverse events caused by the treatment itself. Importantly, inpatient facilities capable of supporting patients with severe infections and dehydration need to be readily available. Social and financial well-being can be impacted by the side-effects of treatment and should also be monitored and addressed.

There are several regimens of 5-FU/calcium folinate with equal efficacy. The modified de Gramont regimen is typically used because of its safety profile, but it requires continuous intravenous infusion of 5-FU over 46 hours and hence is more complex to administer. The Roswell Park regimen and single-agent oral capecitabine are alternatives that do not require infusional 5-FU. The corresponding oxaliplatin-containing regimes are FOLFOX, FLOX and CapeOx.

Management of chemotherapy side-effects

When chemotherapy is employed, laboratory evaluations play an important role in monitoring patient safety. A complete blood count with differential

assesses whether patients are myelosuppressed and neutropenic. A comprehensive metabolic panel monitors renal and hepatic function as well as electrolyte imbalances.

Overview of regimens

Surgery for stage I and II colon cancer

For stage I and II disease, surgery alone is potentially curative and postoperative chemotherapy does not improve outcome. While there is considerable controversy, 5-FU-based chemotherapy may be beneficial in a highly selected patient population with stage II colon cancer (i.e. T4 tumours; poorly differentiated histology; lymphovascular or perineural invasion; perforated or obstructed lesion; fewer than 12 lymph nodes in the surgical specimen).

Surgery and adjuvant chemotherapy for stage III colon cancer

Surgery alone is potentially curative for stage III disease and should be used even in the absence of postoperative chemotherapy. The addition of postoperative chemotherapy to surgery increases the likelihood of a patient remaining disease-free and of improving overall survival.

Standard regimens for stage III colon cancer

- **Modified FOLFOX6 regimen (2-week cycle; 12 cycles)**
  - calcium folinate 400 mg/m² IV on day 1 of each 14-day cycle
  - 5-FU 400 mg/m² IV bolus on day 1 of each 14-day cycle
  - 5-FU 1200 mg/m² daily as continuous infusion over 46 hours (days 1 and 2 of each 14-day cycle)
  - oxaliplatin 85 mg/m² IV on day 1 of each 14-day cycle.
- **CapeOx (3-week cycle; 8 cycles)**
  - capecitabine 1000 mg/m² orally twice daily on days 1–14 of each 21-day cycle
  - oxaliplatin 130 mg/m² IV over 2 hours on day 1 of each 21-day cycle.
- **FLOX (8-week cycle; 3 cycles)**
  - 5-FU 500 mg/m² IV bolus weekly for 8-week cycle
  - calcium folinate 500 mg/m² IV weekly for 6 weeks of each 8-week cycle
  - oxaliplatin 85 mg/m² IV on day 1 of weeks 1, 3 and 5 of each 8-week cycle.

Note: It is acceptable to use low-dose calcium folinate, i.e. 20 mg/m² instead of higher doses (*384*). Fixed-dose 50 mg calcium folinate is also an option.

Acceptable regimens where oxaliplatin is unavailable or contraindicated

- **Roswell Park regimen of adjuvant chemotherapy with 6 cycles of 5-FU and calcium folinate (6 months)**
  - calcium folinate 500 mg/m² IV bolus on days 1, 8, and 15 of each 28-day cycle (i.e. weeks 1, 2 and 3 of each 4-week cycle)
  - 5-FU 500 mg/m² IV bolus on days 1, 8 and 15 of each 28-day cycle (i.e. weeks 1, 2 and 3 of each 4-week cycle).
- **Modified de Gramont regimen of adjuvant chemotherapy with 12 cycles of 5-FU and calcium folinate (6 months)**
  - calcium folinate 400 mg/m² IV on day 1 of each 14-day cycle
  - 5-FU 400 mg/m² IV bolus on day 1 of each 14-day cycle
  - 5-FU 1200 mg/m² daily as continuous infusion over 46 hours (days 1 and 2 of each 14-day cycle).
- **Capecitabine as a single agent**
  - capecitabine 1000 – 1250 mg/m² twice daily for 14 days of each 21-day cycle for 8 cycles.

Note: It is acceptable to use low-dose calcium folinate, i.e. 20 mg/m², instead of higher doses (*384*). Fixed-dose 50 mg calcium folinate is also an option.

The Committee did not support use of the Mayo clinic regimen of bolus 5-FU, given that it is associated with greater toxicity than infusional 5-FU regimens: grade 3 or 4 neutropenia occurs more frequently (7.3% Mayo regimen versus 1.9% infusional regimen). Non-haematological toxicities such as diarrhoea (7.3% versus 1.9%) and mucositis (12.7% versus 1.9%) also occur more frequently (*385*).

Overview of regimens

Benefits

Early-stage colon cancer is a potentially curable illness. The most critical treatment for patients with early-stage colon cancer is surgery: patients with stage I, II and III colon cancer can be cured with surgery alone. The survival rates for stage I and stage II are so high (the cancer-specific 5-year survival for

stage I is greater than 95% and for stage II is 71–87%) that, even in developed countries, the vast majority of these patients are treated with surgery alone. The benefits – and therefore administration – of adjuvant chemotherapy in patients with stage II colon cancer remain unclear, although there is a subset of patients with high-risk clinicopathological features for whom adjuvant chemotherapy is, at a minimum, discussed.

Colon cancers that spread to regional lymph nodes, i.e. stage III cancers, have a higher risk of recurrence. Many clinical trials have demonstrated that adjuvant chemotherapy lowers the risk of recurrence. Initial adjuvant therapy trials showed that adjuvant 5-FU, combined with either levisamole (an agent no longer used) or calcium folinate, reduced the risk of recurrence by 40% and the risk of death by 35% when compared with no adjuvant treatment (*386*, *387*). In one seminal inter-group trial, Moertel et al. demonstrated that for colorectal cancer patients with Dukes class C cancer (i.e. node-positive stage III disease) survival at 3.5 years was 55% for the observation arm and 71% for the 5 FU/levisamole arm (*387*). In the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-03 study, an increase in both 3-year disease-free survival (73%; 95% CI: 69–77%, compared with 64%; 95% CI: 60–68%) and overall survival (84% vs 77%; $P = 0.007$) was recorded with bolus 5-FU and calcium folinate compared with lomustine, vincristine and 5-FU (*388*). Similar benefit was noted in a study by the North Central Cancer Treatment Group, in which patients were randomly allocated to either bolus 5-FU and calcium folinate or observation, and in the International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) study, in which data were pooled from three separate trials undertaken in Canada, France and Italy. In the three IMPACT trials, patients received treatment based on one of two regimens: Roswell Park (RPMI), consisting of 500 mg/m² 5-FU and 500 mg/m² calcium folinate a week for 6 of 8 weeks; or Mayo, comprising 370–425 mg/m² 5-FU and 20 or 200 mg/m² calcium folinate daily for 5 days every 28 days. In subsequent trials, comparable clinical benefit has been noted between RPMI and Mayo bolus 5-FU regimens and between high-dose and low-dose calcium folinate. However, toxic effects differ between the RPMI and Mayo regimens: Mayo is associated with increased neutropenia and stomatitis, whereas RPMI leads to more cases of diarrhoea. Based on these differences, the RPMI regimen is generally preferred. One additional advantage of the RPMI regimen is that subsequent weekly doses can be delayed in the event of dose-limiting toxicity.

In addition to bolus regimens, those that include 5-FU infusions and oral capecitabine have been assessed. Several randomized studies show that, while infusional 5-FU regimens are not superior to the Mayo 5-FU and calcium folinate regimen, they are less toxic. In a phase III trial, capecitabine was non-inferior to the Mayo regimen in terms of disease-free survival and had fewer toxic effects. Three-year disease-free survival (64% vs 61%; $P = 0.05$) and overall survival (81% vs 78%; $P = 0.07$) were increased with capecitabine, although the difference was

not statistically significantly. These results have been corroborated by a recent meta-analysis, which confirmed the non-inferiority of capecitabine (*389*). In general, bolus and infusional 5-FU and oral capecitabine are acceptable options, and choice depends on local practices and economic considerations (*390*).

The standard of care for adjuvant treatment of stage III colon cancer is now a combination of oxaliplatin and a fluoropyrimidine, such as FOLFOX and FLOX, which contain 5-FU, calcium folinate and oxaliplatin, or CapeOx, in which capecitabine, an oral drug, substitutes for 5-FU. The MOSAIC trial compared adjuvant FOLFOX4 with adjuvant 5-FU/calcium folinate. It demonstrated that FOLFOX4 improved survival in stage III colon cancer by 20% compared with 5-FU/calcium folinate (*391*). The 6-year survival rate for stage III colon cancer patients treated with FOLFOX was 72.9% compared with 68.7% in patients treated with 5-FU/calcium folinate (*391*). The rate of grade 3 and 4 neutropenia was higher in the FOLFOX4 arm than in the 5-FU/calcium folinate arm (41.1% vs 4.7%) (*392*). The rate of febrile neutropenia was also higher in the FOLFOX4 arm (1.8% vs 0.2%). Grade 3 neuropathy occurred in 12.4% of the patients treated with FOLFOX4 (*392*). For ease of administration, most institutions use the modified FOLFOX6 regimen, in which the bolus of 5-FU on the second day of chemotherapy is eliminated.

The FLOX regimen was compared with 5-FU alone in the NSABP C-07 trial. For the intent-to-treat analysis, with both stage II and III patients included, the hazard ratio (HR) favouring FLOX was 0.82 and disease-free survival estimates at 5 years were 64.2% for 5-FU/calcium folinate and 69.4% for FLOX. For stage III patients, HR for disease-free survival was 0.78. Improvements in overall survival with FLOX compared with 5-FU/calcium folinate bordered on significance for stage III patients (HR 0.85; 95% CI: 0.72–1.00; P = 0.052). For stage III patients, the 5-year overall survival estimates were 73.8% for 5-FU/calcium folinate and 76.5% for FLOX (*393*).

Similar results were obtained with the CapeOx (capecitabine and oxaliplatin) regimen, which improved progression-free survival compared with 5-FU/calcium folinate (*394*). The 3-year disease-free survival rate was 70.9% with CapeOx and 66.5% with 5-FU/calcium folinate. Overall survival at 5 years was 77.6% with CapeOx and 74.2% with 5-FU, but the difference was not statistically significant ($P = 0.15$).

Toxicities associated with capecitabine also vary with ethnicity and geographical location; the drug is generally well-tolerated by Asians, and western Europeans have better tolerance than North American patients in terms of reduced incidence of hand–foot syndrome, mucositis and diarrhoea (*394*). One advantage of the capecitabine-containing regimen is that it obviates the need for long-term intravenous catheter access and the 46-hour infusion associated with the FOLFOX regimen and its variants.

Despite caveats associated with comparisons across phase III trials, the bolus 5-FU and calcium folinate backbone in the NSABP C-07 seems to be the most toxic. Grade 3–4 diarrhoea was noted in 37% of patients receiving 5-FU and oxaliplatin (FLOX) versus 32% of those who received bolus 5-FU and calcium folinate alone (*393*). By comparison, grade 3–4 diarrhoea was reported in only 11% of individuals who received FOLFOX (*392*) and 19% of those who received CapeOx (*395*). Overall, the FOLFOX and CapeOx regimens seem to have slightly different but comparable toxic effect profiles, as has been noted in the metastatic setting.

FOLFOX or CapeOx is preferred to FLOX because of the poorer toxicity profile seen with FLOX. Patients with resected stage III colon cancer should receive a fluoropyrimidine alone only if they are not candidates for oxaliplatin (for either medical or financial reasons). Either an infusional 5-FU regimen or an oral fluoropyrimidine, such as capecitabine, for 6 months is preferred to bolus 5-FU and calcium folinate because of lesser toxic effects and, possibly, superior efficacy (for capecitabine).

If a bolus 5-FU and calcium folinate regimen must be chosen for financial or logistic reasons, the RPMI regimen is preferred to the Mayo regimen because of its better haematological toxicity profile.

The health-care systems in some countries may not be able to afford the costs associated with chemotherapy administration and toxicity monitoring and management. For these countries, it should be emphasized that surgical resection alone is potentially curative for stage I, II and III colon cancer. Since patients with early-stage colon cancer are potentially cured with surgery alone, adjuvant chemotherapy should not be administered unless it can be done safely.

Finally, several studies have demonstrated equivalence between low-dose (20 mg/m²) and high-dose (500 mg/m²) calcium folinate when administered with 5-FU (*384*); the Committee considered that low-dose calcium folinate should be the default recommendation.

Harms and toxicity considerations

Common

Frequent adverse effects of 5-FU/calcium folinate combination therapy include diarrhoea and associated dehydration, neutropenia (uncommonly leading to infection in < 2% of patients), anaemia and mucositis (*392*, *396*). Palmar–plantar erythrodysaesthesia (hand–foot) syndrome is associated with 5-FU and capecitabine, with an increased incidence of up to 60% in patients treated with capecitabine; typically, it resolves following interruption of treatment (*397*).

Oxaliplatin-containing regimens can lead to sensory neuropathy (24–92% of patients), which is often acute and reversible but may be persistent at high cumulative doses (*391*, *392*, *394*). Peripheral neuropathy of greater than grade 2 severity should be managed with dose reduction or delay.

Serious

Diarrhoea occurs in up to 50% of patients treated with 5-FU or capecitabine. It can be severe, may require hospital admission for intravenous fluid replacement, and is often dose-limiting (*392*, *396*).

Recommendations

Based on the evidence presented in the application, the Expert Committee recommended the addition of capecitabine and oxaliplatin to the complementary list of the Model List of Essential Medicines for the treatment of early-stage (stage III) colon cancer. In addition, the Committee endorsed the use of already-listed calcium folinate and fluorouracil for this indication. The Committee was satisfied that the proposed treatment regimens for stage III colon cancer involving these medicines produce clinically relevant improvements in overall survival. However, the Committee did not support use of the Mayo clinic regimen of bolus fluorouracil, given that it is associated with greater toxicity than infusional fluorouracil regimens.

Early-stage rectal cancer – EML

The application sought endorsement of calcium folinate and fluorouracil (5-FU), already listed on the Model List of Essential Medicines, for the treatment of early-stage rectal cancer. In addition, the application sought the addition of oxaliplatin and capecitabine to the core list of the Model List for the same indication.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Early-stage rectal cancer is a potentially curable illness. Surgery is the most critical component of the treatment for this malignancy. Over the past few decades, improvements in surgical technique, specifically the development of the total mesorectal excision (TME), have had a major impact on patient survival. Stage I rectal cancers are curable with surgery alone. The treatment of stages II and III rectal cancer is more complex and should involve a multidisciplinary approach: neoadjuvant chemoradiation with intravenous 5-FU or oral capecitabine is the standard of care for patients with T4 and clinically node-positive disease, and for some patients with T3 disease with low rectal tumours.

Public health relevance

Colorectal cancer is one of the most common, and deadly, malignancies; it has been estimated that there are 1.2 million new cases a year worldwide. Globally, colorectal cancer is the fourth most common cause of cancer-related deaths in men and the third most common in women, killing an estimated 320 600 men and 288 100 women annually (*381*).

In the developed world, the death rate from colorectal cancer has been falling, largely as a result of colonoscopy screening, which allows both the removal of precancerous polyps and the detection of early-stage, curable disease. Because 90% of colon cancers occur in patients who are at least 50 years old, the recommendation in countries that are able to afford colonoscopy is for screening of the general population to begin at age 50 (*382*).

Because of the expense of colonoscopy, population-based screening programmes are not usually feasible in many parts of the world. Added to poor access to health care, this means that patients in low- and middle-income countries often present with more advanced stages of colorectal cancer.

In the United States, 40% of colorectal cancer patients have localized disease (stage I and II), 36% are regionally advanced (stage III) and 20% have metastases at presentation (*383*).

Requirements for diagnosis, treatment, and monitoring

Diagnostics

Localized colorectal cancer often presents with one of the following symptoms: change in bowel habits, blood in the stools, abdominal discomfort, and weight loss. The symptoms of metastatic colorectal cancer depend on the site of metastasis (liver: right upper quadrant abdominal pain, jaundice; lungs: chest pain, shortness of breath).

The primary mass in colorectal cancer can be diagnosed by rectal examination, sigmoidoscopy or colonoscopy. A biopsy can be performed during endoscopy so that the diagnosis of cancer may be confirmed pathologically.

A critical aspect of the evaluation of a colorectal cancer patient is establishing whether metastatic disease is present. In high-resource health systems, computerized tomography scan of the chest, abdomen and pelvis is performed routinely. In resource-constrained settings, systemic evaluation with the less costly abdominal and pelvic ultrasound is commonly employed. Preoperative rectal cancer staging, which evaluates the T stage (the extent of spread through the layers that form the wall of the rectum) and N stage (the extent of lymph node involvement) of the tumour, is also important in establishing the degree of loco-regional invasiveness of the tumour. Where available, it is performed by either rectal magnetic resonance imaging or endoscopic ultrasound, complex and highly specialized methods with limited availability in resource-constrained settings.

Administration and care of patients

Administration requires intravenous infusion capacity and regular patient access to clinical care. In developed countries administration is usually performed in outpatient facilities; in other settings, patients may be treated in inpatient facilities. Antiemetics need to be available. Monitoring requires that clinicians have access to laboratory facilities, as well as the ability to recognize and address potential adverse events caused by the treatment itself. Importantly, inpatient facilities capable of supporting patients with severe infections and dehydration need to be readily available. Social and financial well-being can be impacted by the side-effects of treatment and should also be monitored and addressed.

There are several regimens of 5-FU/calcium folinate with equal efficacy. The modified de Gramont regimen is typically used because of its safety profile, but it requires continuous IV infusion of 5-FU over 46 hours and hence is more complex to administer. The Roswell Park regimen and single-agent oral capecitabine are alternatives that do not require infusional 5-FU.

Management of chemotherapy side-effects

When chemotherapy is employed, laboratory evaluations play an important role in monitoring patient safety. A complete blood count with differential assesses whether patients are myelosuppressed and neutropenic. A comprehensive metabolic panel monitors renal and hepatic function as well as electrolyte imbalances.

Overview of regimens

Standard neoadjuvant regimens

- **Chemoradiation with 5-FU**
  - continuous infusion 5-FU (225 mg/m² per 24 hours) Monday to Friday throughout the course of radiation; or
  - bolus regimen: 5-FU 400 mg/m² bolus IV + calcium folinate 20 mg/m² IV for four days during weeks 1 and 5 of radiation.
- **Chemoradiation with capecitabine**
  - capecitabine 825 mg/m² twice daily Monday to Friday throughout the course of radiation.

Chemoradiation regimens with continuous infusional 5-FU or capecitabine are considered optimal, but bolus 5-FU is a reasonable alternative where the ability to safely deliver infusional 5-FU or capecitabine is not available. No clinical trials have shown superiority of these two options over a bolus regimen but expert opinion and clinical trials data suggest lower toxicity.

The Expert Committee noted that oxaliplatin is not used as part of neoadjuvant chemoradiation for resectable primary rectal cancer.

Standard adjuvant regimens (after neoadjuvant treatment)

- **FOLFOX-6 regimen for 8 cycles (4 months)**
  - calcium folinate 400 mg/m² IV on day 1 of each 14-day cycle
  - 5-FU 400 mg/m² IV bolus on day 1 of each 14-day cycle
  - 5-FU 1200 mg/m² daily as continuous infusion over 46 hours (days 1 and 2 of each 14-day cycle)
  - oxaliplatin 85 mg/m² IV on day 1 of each 14-day cycle.
- **CapeOx (3-week cycle; 6 cycles)**
  - capecitabine 1000 mg/m² orally twice daily on days 1–14 of each 21-day cycle

  - oxaliplatin 130 mg/m² IV over 2 hours on day 1 of each 21-day cycle.

- **FLOX (8-week cycle; 4 months)**
  - 5-FU 500 mg/m² IV bolus weekly for 8-week cycle
  - calcium folinate 500 mg/m² IV weekly for 6 weeks of each 8-week cycle
  - oxaliplatin 85 mg/m² IV on day 1 of weeks 1, 3 and 5 of each 8-week cycle.

Acceptable regimens where oxaliplatin is unavailable or contraindicated

- **Roswell Park regimen of adjuvant chemotherapy with 4 cycles of 5-FU and calcium folinate (4 months)**
  - calcium folinate 500 mg/m² IV bolus on days 1, 8 and 15 of each 28-day cycle (i.e. weeks 1, 2 and 3 of each 4-week cycle)
  - 5-FU 500 mg/m² IV bolus on days 1, 8 and 15 of each 28-day cycle (i.e. weeks 1, 2 and 3 of each 4-week cycle).

- **Modified de Gramont regimen of adjuvant chemotherapy with 8 cycles of 5-FU and calcium folinate (4 months)**
  - calcium folinate 400 mg/m² IV on day 1 of each 14-day cycle
  - 5-FU 400 mg/m² IV bolus on day 1 of each 14-day cycle
  - 5-FU 1200 mg/m2 daily as continuous infusion over 46 hours (days 1 and 2 of each 14-day cycle).

- **Capecitabine as a single agent (3-week cycle; 6 cycles–4 months)**
  - capecitabine 1000 – 1250 mg/m² twice daily for 14 days of each 21 day-cycle.

Note: it is acceptable to use low-dose calcium folinate, i.e. 20 mg/m² instead of higher doses (*384*). Fixed-dose 50 mg calcium folinate is also an option. If radiation therapy is not available, adjuvant chemotherapy for 6 months is likely to lead to benefits beyond surveillance alone.

The Committee did not support use of the Mayo clinic regimen of bolus 5-FU, given that it is associated with greater toxicity than infusional 5-FU regimens: grade 3 or 4 neutropenia occurs more frequently (7.3% Mayo regimen versus 1.9% infusional regimen). Non-haematological toxicities such as diarrhoea (7.3% versus 1.9%) and mucositis (12.7% versus 1.9%) also occur more frequently (*385*).

Review of benefits and harms

Benefits

Early-stage rectal cancer is a potentially curable illness. Compared with early-stage colon cancer, however, early-stage rectal cancers have a higher risk of local recurrence, and the treatment paradigm has evolved to address this higher risk. Patients with locally advanced rectal cancers receive multidisciplinary care involving surgery, radiation and chemotherapy. In low-income countries, treatment of rectal cancer can be very challenging because of the complexity and the cost of radiation, chemotherapy, imaging and supportive services.

As in colon cancer, surgery is the cornerstone of treatment for early-stage rectal cancer. Locally advanced tumours are removed by either a sphincter-saving low anterior resection or abdominoperineal resection. One of the biggest advances in the treatment of locally advanced rectal cancer was the development of the total mesorectal excision (TME), which involves a sharp dissection and complete removal of the mesorectum. The TME surgical approach reduces local recurrence rates from 12–25% to 5–6% (*398–400*). In advanced health-care systems, TME is the standard of care and, given the significant improvement in outcomes, strenuous efforts to adapt this surgical procedure should be made worldwide.

Neoadjuvant chemoradiation was developed to address the high risk of recurrence associated with the disease and, where resources allow, it is the standard of care for patients with stage II or III rectal cancer with T4 and clinically node-positive disease, and for some patients with T3 disease with low rectal tumours. Patients with preoperatively staged tumours that are T1–2/N0 can be treated with surgery alone. Following surgery, if the pathology shows a higher stage, these patients are candidates for postoperative chemoradiation and adjuvant chemotherapy.

The evidence for chemoradiation being effective in the treatment of locally advanced rectal cancer initially came from the GITSG protocol GI-7175 (*401*). This protocol randomized 227 patients into four groups: surgery alone, postoperative radiation, postoperative chemotherapy, and postoperative chemoradiation. The chemoradiation group had superior overall survival compared with the other groups, and this established chemoradiation as the standard of care (*402*).

The question of whether chemoradiation should be given before or after surgery was addressed by the German Rectal Cancer Study (*403*), which found that neoadjuvant chemoradiation improved local control compared with postoperative chemoradiation. There was no survival difference between the two arms. Notably, neoadjuvant chemoradiation increased the number of sphincter-sparing surgeries and had less toxicity than postoperative chemoradiation.

The overall five-year survival rates were 76% and 74% respectively ($P = 0.80$). The five-year cumulative incidence of local relapse was 6% for patients assigned to preoperative chemoradiotherapy and 13% in the postoperative-treatment group ($P = 0.006$) (*403*).

The NSABP trial R-04 demonstrated that chemoradiation with capecitabine is equivalent to chemoradiation with 5-FU (*404*). A German trial corroborated these findings and suggested that capecitabine may be a little more effective than 5-FU (*405*). Five-year overall survival in the capecitabine group was non-inferior to that in the 5-FU group (76% (95% CI: 67–82) vs 67% (95% CI: 58–74); $P = 0.0004$; post hoc test for superiority $P = 0.05$). Three-year disease-free survival was 75% (95% CI: 68–81) in the capecitabine group and 67% (95% CI: 59–73) in the 5-FU group ($P = 0.7$). Similar numbers of patients had local recurrences in each group (12 (6%) in the capecitabine group vs 14 (7%) in the 5-FU group; $P = 0{\cdot}67$), but fewer patients in the capecitabine group developed distant metastases (37 (19%) vs 54 (28%); $P = 0.04$).

Adjuvant 5-FU based chemotherapy is the standard of care in the developed world for patients who have undergone neoadjuvant chemoradiation. This recommendation is largely based on the successful use of adjuvant chemotherapy in colon cancer (*386*, *387*, *392*). In addition, a recent trial demonstrated that rectal cancer patients treated with eight cycles of adjuvant FOLFOX had improved disease-free survival compared with patients treated with eight cycles of adjuvant 5-FU/calcium folinate (*406*).

As regards use of oxaliplatin as part of FOLFOX or CapeOx regimens in the adjuvant treatment setting, however, the Expert Committee noted that the PETACC-6 study did not show a statistically significant difference in disease-free survival between CapeOx and single-agent capecitabine (*389*). Results from the German CAO/ARO/AIO-04 trial, which compared bolus 5-FU with FOLFOX, showed a difference in disease-free survival at 3 years of 75.9% versus 71.2% (hazard ratio (HR) 0.79; 95% CI: 0.64–0.98) favouring FOLFOX (*407*); however, no difference in overall survival was observed between the two groups. In the Phase II ADORE trial, 3-year disease-free survival was 71.6% in the FOLFOX group and 62.9% in the 5-FU + leucovorin group (HR 0.657; 95% CI: 0.434–0.994; $P = 0.047$) (*406*). Given the variability in the results of these trials regarding the benefit of oxaliplatin-containing treatment regimens, the Committee considered that the evidence was not sufficiently strong to support adjuvant treatment regimens containing oxaliplatin as the standard of care: it is possible that they deliver no additional benefit over 5-FU-based regimens or single-agent capecitabine.

The choice of fluoropyrimidine IV bolus or infusion 5-FU, or oral capecitabine depends upon local experience and the availability of resources. In

general, the toxicity of infusion and oral regimens is lower than that of bolus regimens. Several studies have demonstrated equivalence between low-dose (20 mg/m²) and high-dose (500 mg/m²) calcium folinate when administered with 5-FU (*384*); the Committee considered that low-dose calcium folinate should be the default recommendation.

Harms and toxicity considerations

Common

Frequent adverse effects of 5-FU/calcium folinate combination therapy are diarrhoea and associated dehydration, neutropenia (uncommonly leading to infection in < 2% of patients), anaemia, and mucositis (*392*, *396*, *406*). Palmar–plantar erythrodysaesthesia (hand–foot) syndrome is associated with 5-FU and capecitabine, with an increased incidence of up to 60% in patients treated with capecitabine; typically, it resolves following interruption of treatment (*397*).

Oxaliplatin-containing regimens such as FOLFOX can lead to sensory neuropathy (24–92% of patients), which is often acute and reversible but may be persistent at high cumulative doses (*392*). In one study, the FOLFOX regimen caused significant grade 3 neuropathy in 18% of patients (*408*).

Patients treated with chemoradiation may also experience rectal discomfort and skin breakdown, and female patients are at risk of vaginal stenosis and infertility (*396*, *403*, *409*).

Serious

Diarrhoea occurs in up to 50% of patients treated with 5-FU or capecitabine. It can be severe, may require hospital admission for IV fluid replacement, and is often dose-limiting (*392*, *396*).

Recommendations

Based on the available evidence, the Expert Committee recommended the addition of capecitabine to, and endorsed the use of already-listed fluorouracil and calcium folinate on, the complementary list of the Model List of Essential Medicines as neoadjuvant and adjuvant treatment of early-stage rectal cancer.

The Committee did not recommend addition of oxaliplatin to the Model List for this indication. The Committee noted that oxaliplatin is not used as part of neoadjuvant chemoradiation for resectable primary rectal cancer. Additionally, the Committee considered that current evidence was not sufficiently strong to support adjuvant treatment regimens containing oxaliplatin as the standard of care: it is possible that they deliver no additional benefit over fluorouracil-based regimens or single-agent capecitabine.

Early- and advanced-stage head and neck cancers – EML

The application sought the addition of cisplatin to the core list of the EML for the postoperative treatment, in combination with radiotherapy, of locally advanced head and neck squamous cell carcinoma (HNSCC). The application notes that, for this indication, carboplatin is not an acceptable alternative to cisplatin.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

About 90% of all head and neck cancers are squamous cell carcinomas, and HNSCC is the sixth leading cancer by incidence worldwide. Most HNSCCs arise in the epithelial lining of the oral cavity, oropharynx, larynx and hypopharynx (*410*, *411*). Approximately one third of patients present with early stage-disease (T1–2, N0, using the TNM staging system of the American Joint Committee on Cancer (AJCC)), and the 5-year overall survival rate of HNSCC patients is about 40–50%. Treatment for early HNSCC usually involves single-modality therapy – either surgery or radiation; survival is comparable for the two approaches. Early-stage cancers have a very favourable prognosis: cure rates are high with surgery or radiation alone and chemotherapy or concurrent chemotherapy/radiation is not indicated.

In pathologically staged III–IVa/b head and neck cancer, combined postoperative radiotherapy/cisplatin has been shown to improve local–regional control and survival rates for patients with positive microscopic surgical margins and/or extracapsular nodal extension (*412*).

Public health relevance

Head and neck cancer encompasses many site-specific cancers, including oral cavity and oropharyngeal cancers. Studies have estimated the global incidence of all head and neck cancers to be between 400 000 and 600 000 new cases per year, with between 223 000 and 300 000 deaths per year (*413*). Alcohol and tobacco are known risk factors for most head and neck cancers, and incidence rates are found to be higher in regions with high rates of alcohol and tobacco consumption (*414*). During the past few decades, several countries have witnessed a decline in oral cavity cancer incidence that correlates with declining tobacco use. However, despite declining tobacco use since the 1980s, Canada, Denmark, the Netherlands, Norway, Sweden, the United Kingdom and USA have seen increasing rates of oropharyngeal and oral cavity cancers (*413*). Theories that human papillomavirus infection might be an additional risk factor for the development of certain head and neck cancers have emerged and are prompting research; epidemiological information regarding head and neck cancers is thus likely to change with further discoveries (*413*).

Requirements for diagnosis, treatment, and monitoring

Diagnostics

A detailed history and physical examination, including complete head and neck examination with biopsy, are necessary to establish the diagnosis. Examination with a mirror or fibre optic scope is essential in diagnosing and staging lesions involving the larynx and pharynx.

Testing

A panoramic radiograph of the mandible and computerized tomography scan or magnetic resonance imaging of the neck may be done as indicated and are useful to assess the extent and stage of the cancer. A chest X-ray and pretreatment dental evaluation are recommended. For patients with advanced-stage disease who will receive concurrent chemotherapy and radiation, blood counts and blood chemistry may be done to assess critical organ function, including renal and hepatic function.

Administration and care of patients

Despite a lack of randomized comparative trials, both surgery and definitive radiation therapy appear to offer equivalent local tumour control and survival for early-stage head and neck cancers. Choice of treatment is based on various factors, including tumour accessibility, functional outcome, patient's health and preference, and the availability of treatment expertise. Surgery is the preferred treatment modality for early-stage oral cavity cancers and involves resection of the primary tumour, with or without lymph nodal dissection. Patients who are medically inoperable or who refuse surgery can be treated with definitive radiation therapy. Definitive radiation therapy is also the preferred approach for many patients with non-oral cavity tumours, in particular of the hypopharynx and supraglottic and glottic larynx, since it appears to provide a better functional outcome than larynx-sparing surgical approaches. For patients with residual disease after radiation therapy, salvage surgery is recommended; for those managed by surgery, postoperative radiation therapy is indicated in the presence of close or positive margins, lymphovascular or perineural invasion, or when a positive lymph node is identified, upstaging the tumour.

Administration of cisplatin requires intravenous infusion capacity. Adequate intravenous hydration and antiemetics should accompany the infusion of cisplatin, and blood counts and blood chemistry should be serially monitored during the course of treatment.

Concurrent chemotherapy increases the risk for radiation-related adverse effects including mucositis, dysphagia and dermatitis. Patients should be carefully monitored for these and supportive care provided as indicated. Care should be taken to maintain adequate hydration, nutrition and analgesia before, during and

after completion of treatment. Optimal monitoring and supportive care require trained clinicians experienced in the management of these cancers and with access to inpatient care and laboratory services. Late treatment-related toxicities such as xerostomia, dysphagia, speech dysfunction, gastric tube dependence, tracheostomy dependence, neuropathies, depression and cosmetic disfigurement can significantly impact quality of life and psychosocial well-being and therefore need to be identified and addressed.

Overview of regimens

Concurrent radiation and three doses of cisplatin are recommended.

Standard regimen

- **Concomitant chemotherapy–radiation**
  - cisplatin 100 mg/m² IV every 3 weeks (on days 1, 22, 43) x 3 cycles.

The Committee noted that, despite a lack of large, randomized studies and therefore based on phase II trials and centre experience, there are many reports of cisplatin being administered weekly (at 40 mg/ m² IV) in an attempt to reduce the toxicity and increase the tolerability of concomitant chemotherapy and radiation.

Review of benefits and harms

Benefits

Early-stage head and neck cancers are highly curable with either surgery or radiation therapy, but certain high-risk features have been shown to significantly increase the likelihood of recurrence. Two randomized trials have demonstrated improved outcomes following the addition of concomitant cisplatin to postoperative radiation in patients with locally advanced disease or certain adverse risk features. Both studies compared concomitant cisplatin (100 mg/m² on days 1, 22 and 43) and radiotherapy with radiotherapy alone after surgery in patients with advanced-stage cancers of the oral cavity, oropharynx, larynx or hypopharynx.

The RTOG 9501/Intergroup trial randomized 459 patients and showed significant improvement in local–regional control rates and disease-free survival – but not overall survival – in the chemoradiation arm (*415*). The 2-year rate of local and regional control was 82% in the chemoradiation group versus 72% in the radiotherapy group; disease-free survival was significantly longer in the chemoradiation group (hazard ratio (HR) for disease or death, 0.78; 95% CI: 0.61–0.99; $P = 0.04$).

The EORTC 22931 trial randomized 334 patients and showed improved 5-year progression-free survival (47% vs 36%) and overall survival (53% vs 40%)

for the concomitant cisplatin group compared with the radiation group (*416*). The estimated 5-year cumulative incidence of local or regional relapses was 31% with radiation compared with 18% after combined therapy.

A comparative analysis of data pooled from the two trials showed that extracapsular extension and/or microscopically involved surgical margins were the only risk factors for which the impact of concomitant chemoradiation was significant in both trials (*412*). There was also a trend in favour of the combined modality arm in the group of patients who had stage III–IV disease, perineural infiltration, vascular embolisms, and/or clinically enlarged level IV–V lymph nodes secondary to tumours arising in the oral cavity or oropharynx. A 10-year follow up of the RTOG 9501/Intergroup trial confirmed the superiority of the combined arm for local–regional control and disease-free survival in the subgroup of patients with microscopically involved margins and/or extracapsular nodal spread (*417*).

Primary combined chemotherapy with cisplatin and radiation is also the standard for patients with locally advanced, unresectable tumours. In this setting, the addition of cisplatin to radiation improves disease control and overall survival. A meta-analysis of 50 studies showed an absolute benefit of 6.5% in overall survival (HR 0.81; $P < 0.0001$) for patients who received combined chemoradiation (*418*).

In the primary treatment setting, an international phase III study found that cetuximab improved outcomes compared with radiation alone in patients with locally advanced disease (*419*). Radiotherapy plus cetuximab was associated with a median overall survival of 49 months, compared with 29.3 months for patients treated with radiotherapy alone (HR for death 0.74; $P = 0.03$). Progression-free survival was also significantly extended (HR for disease progression or death 0.70; $P = 0.0006$). However, cetuximab has not been shown to be superior to cisplatin and is much more costly. It is therefore neither proposed nor recommended for inclusion on the EML for treatment of HNSCC at this time.

Harms and toxicity considerations

Common

Nausea and vomiting occur in almost all patients treated with cisplatin and is often severe, necessitating the use of antiemetic medications. Major dose-limiting toxicities of cisplatin include renal impairment (28–36%), ototoxicity (40–60% children; 10–31% adults) and myelosuppression (*420*). Ototoxicity usually manifests as tinnitus and high-frequency hearing loss. Myelosuppression can lead to anaemia, leukopenia and thrombocytopenia with associated complications.

In the RTOG 9501 trial, the incidence of acute toxicity of grade 3 or greater was 34% in the radiotherapy group versus 77% in the concomitant cisplatin arm. Similarly, in the EORTC trial, severe adverse effects were more frequent after combined therapy (41%) than after radiotherapy (21%) ($P = 0.001$) (*415*, *417*).

Serious

Renal toxicity caused by cisplatin can be significant and may result in electrolyte abnormalities. Intravenous hydration is needed both before and after administration of cisplatin, particularly in elderly patients and patients with compromised renal function, to reduce the incidence of renal toxicity (*380*). Combining cisplatin chemotherapy with radiation significantly increases the rates of grade 3 and 4 radiation-related toxicity, including dysphagia, dermatitis and mucositis (*415*, *417*).

Recommendations

On the basis of the evidence presented in the application, the Expert Committee recommended the addition of cisplatin to the complementary list of the WHO Model List of Essential Medicines for the treatment, in combination with radiotherapy, of locally advanced head and neck squamous cell carcinoma. Compared with postoperative radiotherapy alone, the Committee considered that the benefits associated with the addition of cisplatin, in terms of local–regional control rates and disease-free survival, progression-free survival and overall survival, were of both clinical and public health relevance.

The Committee also considered that use of primary combined chemotherapy with cisplatin and radiation was associated with a clinical benefit, compared with radiation alone, in patients who have unresectable tumours.

Epithelial ovarian cancer – EML

The application sought endorsement of carboplatin, paclitaxel, doxorubicin and etoposide, already listed on the complementary list of the Essential Medicines List, for the treatment of epithelial ovarian cancer. The application also sought the addition of cisplatin and gemcitabine to the core list of the Model List for the same indication.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Epithelial ovarian cancer is the most common type of ovarian cancer and the most aggressive gynaecological malignancy. Approximately 70% of patients are diagnosed at an advanced stage because of the asymptomatic nature of the disease. Early diagnosis is further hindered by the absence of effective screening tests: serum tumour marker carbohydrate antigen 125 (CA-125), an antigen correlated with breast, lung and gastrointestinal malignancies, cannot adequately be characterized as a screening test because of the overall low incidence of ovarian cancer in the general population and the risk of a false-positive result (*421*). Diagnosis involves gynaecological examination to identify an adnexal mass, combined with ultrasonography and CA-125, but the gold standard for conclusive diagnosis and staging remains surgical excision and further histological examination of the adnexal mass.

Surgery also provides tumour debulking with the ultimate goal of complete macroscopic tumour resection (optimal cytoreduction) (*422*). Epithelial ovarian cancer is one of the most sensitive of all solid tumours to cytotoxic drugs: initial response to standard primary treatment, including surgical cytoreduction and adjuvant platinum-based combined chemotherapy, is approximately 80% (*423*). Five-year survival rate is approximately 43% (*424*).

Public health relevance

Epithelial ovarian cancer is not among the most common human malignancies, but it is a major public health concern because of its disproportionate impact on cancer morbidity and mortality: 238 719 new cases were detected in 2012 (*255*), an increase in morbidity compared with 225 500 new cases in 2008 (*381*). The lifetime risk of epithelial ovarian cancer is approximately 0.67% in sporadic cases across all countries, and is somewhat greater in more developed regions (1.01%) (*255*). Incidence of the disease is lower in developing than in developed countries: the 2012 age-standardized rates in South and North America were 5.8 and 8.1 per 100 000, respectively. The risk of ovarian cancer greatly increases in patients with a familial predisposition (10–40% greater risk than in the

general population). The median age at diagnosis for sporadic cancer is 60 years; predisposed patients may be affected earlier, often in their fifth decade. Age-specific incidence of sporadic disease reaches its peak in women aged 75 years and over.

Despite a statistically significant improvement in treatment results over the last years, ovarian cancer remains the leading cause of gynaecological cancer mortality, with 151 917 ovarian cancer-related deaths registered in 2012 (*255*). Moreover, mortality is much higher in developing countries, probably as a consequence of the high prevalence of advanced-stage cases and lower level of cancer care.

Nulliparous women and those who have not breastfed are at increased risk for developing ovarian cancer; tubal ligation, oral contraception and African race reduce the risk. Endometriosis is associated with a significantly increased risk of clear-cell, low-grade serous and endometrioid invasive ovarian cancer (*425*).

Requirements for diagnosis, treatment, and monitoring

Diagnostics

Surgery remains the gold standard for confirming diagnosis and staging ovarian cancer. Laparotomy serves three main purposes in the management of patients with suspected ovarian cancer:

- to confirm histological type of disease;
- to determine the extent of disease (staging), which is critical in determining whether postoperative treatment will be necessary, and to assess prognosis;
- to permit debulking of tumour since patients with optimal cytoreduction (defined as residual tumour of diameter ≤ 1 cm) have a better prognosis than those with greater amounts of residual disease (*426*).

Laparoscopy may be used to evaluate a pelvic mass although open surgery is usually preferred when there is high suspicion of malignancy. Histological confirmation of the disease should be made on the basis of biopsies of all suspicious sites relevant for staging, such as omentum, mesentery, liver, diaphragm, pelvic and para-aortic lymph nodes (*427*, *428*).

Surgery

As noted above surgery is important in diagnosis, staging and debulking. Debulking surgery is often done at diagnosis, but can also be performed after three or six cycles of cytoreductive chemotherapy.

Testing

The goal of clinical (preoperative) staging is the confirmation of a malignant adnexal mass, exclusion of another primary tumour, assessment of tumour spread and estimation of possible complications of the disease or further treatment.

Computerized tomography (CT) and magnetic resonance imaging (MRI) are standard imaging methods for tumour evaluation and postoperative surveillance. If CT and MRI cannot be used, ultrasonography becomes the method of choice.

The CA-125 serum level should be assessed. Carcinoembryonic antigen (CEA) assessment is optional; it may be useful to distinguish primary serous tumours from primary mucinous tumours or in differentiating ovarian tumours from ovarian metastases of colorectal cancer. Alpha-fetoprotein and beta-chorionic gonadotropin help to exclude germ cell tumours in women younger than 40 years. Other tests that should be done include blood chemistry for the assessment of renal and hepatic functions (liver enzymes, total bilirubin, albumin and creatinine levels) and complete blood count.

Administration and care of patients

Chemotherapy drugs for the treatment of ovarian cancer require peripheral or central venous access. Administration can be performed in either outpatient or inpatient facilities. Antiemetic prophylaxis ideally includes administration of 5HT3-antagonists before the start of chemotherapy. Administration of paclitaxel requires the use of dexamethasone, an H2 blocker, and diphenhydramine to prevent hypersensitivity reactions.

Intravenous vs intraperitoneal chemotherapy

Chemotherapy is most often administered intravenously but certain agents are sometimes administered intraperitoneally. Intraperitoneal administration has been associated with a small improvement in survival outcomes (*429*) but is technically difficult, even in resource-rich settings, and is not generally recommended.

Safety monitoring during chemotherapy requires weekly evaluation of complete blood counts. Patients should regularly visit a medical/general oncologist. Efficacy assessment and follow-up after completion of treatment should be performed using the same methods to evaluate tumour size and spread as were used initially.

Overview of regimens

Ovarian cancer is a chemosensitive disease and chemotherapy is therefore one of the most important components of its systemic treatment.

Standard first-line chemotherapy consists of paclitaxel and carboplatin, both administered intravenously every 3 weeks. Patients with early stage IA–IB disease, with low-grade, or well differentiated, adenocarcinoma after adequate staging, require observation only. In the case of intermediate prognosis (stage IA–IB with moderately well differentiated adenocarcinoma after optimal cytoreduction), four cycles of paclitaxel and carboplatin at 3-week intervals are prescribed.

Standard chemotherapy for advanced ovarian cancer (stage IC–IV) includes six cycles of platinum-based regimens, usually paclitaxel and carboplatin or paclitaxel and cisplatin. The paclitaxel/carboplatin combination is as effective as, but less toxic than, paclitaxel/ cisplatin and less complex to administer (*430*). If taxanes are unavailable, carboplatin or cisplatin can be given as a single agent, but this is not considered optimal therapy.

Standard regimens for first-line therapy

- carboplatin AUC 6 IV infusion on day 1
  paclitaxel 175 mg/m² IV infusion on day 1
- cisplatin 75 mg/m² IV infusion on day 1
  paclitaxel 175 mg/m² IV infusion on day 1

Second-line therapy for patients with recurrent disease after initial chemotherapy

Approximately 80% of patients diagnosed with ovarian epithelial cancer will relapse after first-line platinum- and taxane-based chemotherapy and may benefit from subsequent therapies (*431*). Systemic treatment options for patients with recurrent disease are subdivided into three categories according to the platinum-free interval: platinum-refractory – progressing during therapy; platinum-resistant recurrence – progressing within 6 months after completion of platinum-based chemotherapy; and platinum-sensitive – progressing after more than 6 months after completion of platinum-based chemotherapy.

Therapeutic options for second-line therapy include combinations of a platinum compound with paclitaxel, gemcitabine, etoposide or doxorubicin as listed below. All have similar efficacy and the choice will depend on patient status and drug availability. Six cycles of chemotherapy at 3-week intervals is recommended.

Standard regimens for platinum-sensitive relapse (≥6 months)

- carboplatin AUC 5 IV infusion on day 1
  paclitaxel 175 mg/m² IV infusion on day 1
- cisplatin 75 mg/m² IV infusion on day 1
  paclitaxel 175 mg/m² IV infusion on day 1

- carboplatin AUC 4 IV infusion on day 1
  gemcitabine 1000 mg/m² IV infusion on days 1 and 8
- cisplatin 75 mg/m² IV infusion on day 1
  etoposide 100 mg orally on days 1–7
- carboplatin AUC 5 IV infusion on day 1
  doxorubicin 50 mg/m² IV infusion on day 1

Platinum-refractory and resistant relapse

In patients with platinum-resistant relapse, treatment is focused on quality of life and control of symptoms (*432*). Monotherapy with different non-platinum agents has similar efficacy; agents such as doxorubicin, liposomal doxorubicin, etoposide, gemcitabine, topotecan and bevacizumab-containing regimens can be used in this situation. Some regimens, such as those including bevacizumab, have shown benefit only in terms of progression-free survival with no evidence supporting overall survival benefit. Extension of life is minimal, and these agents are not proposed for addition to the EML for this indication.

Review of benefits and harms

Benefits

For women with stage IC and above ovarian cancer, clear cell histology or other high-risk features, first-line adjuvant chemotherapy with carboplatin and paclitaxel is recommended on the basis of ICON 1 and EORTC ACTION trials (*433*, *434*). Together, these trials involved more than 900 patients and demonstrated a significant improvement in recurrence-free survival (76% vs 65%; $P = 0.001$) and overall survival (82% vs 74%; $P = 0.008$) at 5 years (*435*). Benefit was maintained at 10-year follow-up (*436*). A greater effect of adjuvant chemotherapy was observed in patients who had suboptimal surgery.

A randomized phase III trial compared three and six cycles of adjuvant carboplatin and paclitaxel in early-stage epithelial ovarian carcinoma (*437*). After three years, recurrence rate following six cycles of therapy was 24% lower than that following three cycles (HR 0.761; 95% CI: 0.51–1.13; $P = 0.18$). The estimated probability of recurrence within five years was lower in the six-cycle group (20.1% vs 25.4%). Overall death rate was similar for both regimens.

Administration of platinum-based regimens in first-line chemotherapy has been shown to improve progression-free survival (PFS) to as much as 18 months and overall survival to 44 months. Median overall survival (OS) has improved from 18–24 months two decades ago to 40–60 months; 5-year OS is currently about 44% (*438*). There is no benefit from adding a third chemotherapy agent to standard chemotherapy (*439*).

Patients with platinum-resistant ovarian cancer form a poor-prognosis population, characterized by low response rates (< 10%) with short expected

OS (*432*). Administration of doublet chemotherapy has not been shown to improve PFS but does increase toxicity compared with monotherapy with non-platinum agents.

For platinum-sensitive ovarian cancer, carboplatin doublet chemotherapy with paclitaxel or with gemcitabine is now considered the treatment of choice. Compared with conventional platinum-based chemotherapy, paclitaxel plus platinum chemotherapy improved median OS by 5 months (29 vs 24 months) and median PFS by 3 months (13 vs 10 months) in patients with relapsed platinum-sensitive ovarian cancer in the ICON 4 trial (*440*).

A 2006 inter-group trial (AGO-OVAR, the NCIC CTG, and the EORTC GCG) of 365 patients randomized to receive carboplatin alone or carboplatin with gemcitabine found the doublet regimen significantly improved PFS in patients with platinum-sensitive recurrent ovarian cancer (*441*). With a median follow-up of 17 months, median PFS was 8.6 months (95% CI: 7.9–9.7 months) for the doublet regimen and 5.8 months (95% CI: 5.2–7.1 months) for carboplatin (HR 0.72; 95% CI: 0.58–0.90); $P = 0.0031$). Response rates were 47.2% (95% CI: 39.9–54.5%) for doublet therapy and 30.9% (95% CI: 24.1–37.7%) for carboplatin alone. No significant difference in OS was observed between treatment arms (HR 0.96; 95% CI: 0.75–1.23); however, the trial was not powered to detect improvement in OS.

The Committee noted that doxorubicin and etoposide have also been associated with small improvements in PFS and OS when used for the treatment of patients with platinum-resistant and platinum-sensitive recurrent disease (*442*, *443*). However, the Committee also noted that these medicines are used infrequently in clinical practice and are not considered to be standard of care.

Harms and toxicity considerations

Common

Patients receiving treatment for ovarian cancer experience common drug toxicity reactions. Most patients suffer hematological toxicity from the medication combination including neutropenia, thrombocytopenia, and anemia, all of which are typically rapidly reversible upon discontinuation of agents (*439*, *440*). Paclitaxel can cause hypersensitivity reactions in up to 30% of patients and requires premedication to reduce the risk of these reactions. Paclitaxel frequently causes alopecia and peripheral neuropathy, which is often mild and reversible (*273*, *367*). Cisplatin and carboplatin can cause severe, potentially dose-limiting nausea and vomiting requiring pretreatment with anti-emetics.

Serious

In approximately 10-30% of cases, cisplatin causes nephrotoxicity which may result in electrolyte abnormalities, aggressive IV hydration is necessary to

reduce this risk (*440*). Doxorubicin is associated with the risk of congestive heart failure, although the risk is small (<1%) in patients receiving < 450–500 mg/m² cumulative dose, as in the regimens above (*273*).

Recommendations

The Committee considered that combination therapy with carboplatin and paclitaxel is the preferred first-line treatment for the treatment of epithelial ovarian cancer, as it is associated with less toxicity and is easier to administer than cisplatin and paclitaxel. The Committee endorsed the use of already-listed carboplatin and paclitaxel on the complementary list for this indication.

The Committee did not support the specific addition of cisplatin to the Model List for the treatment of epithelial ovarian cancer but considered that cisplatin may be used in circumstances where carboplatin is unavailable.

On the basis of the available evidence, the Committee also recommended the addition of gemcitabine to the complementary list of the Model List of Essential Medicines.

The Committee did not recommend endorsement of doxorubicin or etoposide on the Model List for treatment of epithelial ovarian cancer, noting that – while there is some evidence of benefit in terms of progression-free and overall survival – these medicines are not widely used in clinical practice for this indication and are not considered the current standard of care.

Ewing sarcoma – EMLc

The application sought the inclusion of medicines used in the treatment of Ewing sarcoma – vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide – on the core list of the Model List of Essential Medicines for Children.

The Committee noted that all of these medicines are currently included in the complementary list of the Model List for adults, and that vincristine, doxorubicin and cyclophosphamide are currently included on the complementary list of the EMLc for other specific indications.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Ewing sarcoma family of tumours (ESFT) is a group of highly malignant diseases with peak incidence in adolescence and early adult life. These tumours arise in either bone or soft tissue and the term ESFT includes the Askin tumour of the chest wall and peripheral primitive neuroectodermal tumours (pPNET). pPNET are related closely to medulloblastoma and intracranial PNET, reflecting the neural differentiating potential of these tumours (*444*). The hallmark of ESFT is a translocation between chromosomes 11 and 22, resulting in a fusion protein referred to commonly as EWS-FLI1 (*445*). The incidence of ESFT is higher among Caucasians than among Africans and Asians, for which a genetic explanation has been proposed (*446*).

Before the introduction of chemotherapy, more than 90% of patients died from tumour spread (*447*). Now, at least 70% of those presenting with apparently localized disease are cured by multimodal treatment (*448*, *449*); however, the outlook for those with evident metastases at diagnosis remains poor, with five-year survival rates of 25–30% (*450*). Other adverse prognostic features include the location (especially in the pelvis) and size (> 8 cm) of the tumour (*451*). Outcomes may be better for patients with extra-osseous primary tumours (*452*).

Since the early 1970s, the core of chemotherapeutic strategies in both North America and western Europe, has been the combination of vincristine, doxorubicin and cyclophosphamide (VDC). The addition of ifosfamide and etoposide (IE) was pioneered by the U.S. National Cancer Institute (*453*). The VDC-IE combination is now the standard of care in the United States and forms the basis of various protocols in Europe (*451*). Studies by the Children's Oncology Group demonstrated that dose intensification offered no advantage and gave rise to a predictably greater burden of toxicity (*449*), but that chemotherapy intensification through interval compression offered benefit in terms of survival, without increasing toxicity, in patients with localized extradural disease (*454*).

Public health relevance

Primary bone tumours account for 5% of all cancers in childhood, and Ewing sarcoma is the second most common bone tumour in this age group. The incidence of ESFT in the USA between 1973 and 2004 was estimated to be approximately 3 per 1 000 000 (*448*).

Requirements for diagnosis, treatment, and monitoring

Diagnostics

A definitive diagnosis is almost always made on biopsied material. Incisional rather than needle core biopsy is necessary to provide sufficient material for pathological interpretation and for biological studies. Frozen sections may be used to determine whether the biopsy has provided lesional tissue but should not be the basis for a final diagnosis. It is strongly recommended that the biopsy be obtained by the orthopaedic surgeon who will perform the operation to achieve local tumour control, adhering to the principles of surgical oncology (*455*). At the time of tumour resection, a histological response to neoadjuvant chemotherapy has prognostic implications (*456*). Bone marrow biopsies appear to be unnecessary in patients who have seemingly localized disease after comprehensive radiological assessment (*457*).

Testing

Determination of the extent of disease is critical to selection of appropriate therapy and initial assessment of prognosis. Plain radiographs of the primary site are complemented by: computerized tomography (CT) scans, including scans of the chest to look for pulmonary metastases; magnetic resonance imaging (MRI), particularly of the primary site, to provide anatomical detail of value to both radiation and surgical oncologists; radioisotopic bone scan to detect osseous metastases; and positron emission tomography (PET) scan to confirm findings and identify other sites of occult disease (*458*). PET scans are also of value in assessing response to therapy (*455*).

Institutions caring for patients with ESFT should be able to detect the EWS-FLI1 related translocation by one of various techniques or expression of CD99 by immunohistochemical methods. However, CD99 expression, while a highly sensitive marker for ESFT, has low specificity, being found in other "small round blue cell" tumours of childhood. Standard blood tests to assess organ function and a baseline echocardiogram are required. For very large tumour volumes, biochemical monitoring for tumour lysis syndrome is valuable. Serum lactate dehydrogenase is a surrogate marker of tumour volume (*455*).

Administration and care of patients

Chemotherapy for ESFT consists of multiple agents given intravenously. This requires careful management of fluid and electrolyte balance, as well as prophylactic antiemetic therapy and other supportive care measures, e.g. mesna to offset bladder toxicity from cyclophosphamide and ifosfamide. Since all of this is usually accomplished through a central venous catheter, it should be undertaken only in a specialized cancer centre.

Local control of ESFT demands careful consideration of and planning for radiotherapy and surgery, which may involve limb conservation procedures.

In the short term, the side-effects of chemotherapy include nausea, vomiting, anorexia, mucositis, pancytopenia, electrolyte imbalance, peripheral neuropathy and haematuria. In the long term, survivors are at risk for infertility (notably from cyclophosphamide), cardiomyopathy (especially from doxorubicin) and second cancers (particularly leukaemia from etoposide and solid tumours in the radiation fields).

Overview of regimens

The following sections include basic information on administration and dosing of standard regimens; no details are given of ancillary medications pertaining to the management of adverse events.

Standard regimens (of equivalent efficacy)

- **AEWS 1031 (11 cycles)**
  - vincristine 1.5 mg/m² (max. 2 mg/m²) IV push, approx. weekly intervals x 18 doses
  - doxorubicin 37.5 mg/m² IV infusion, approx. monthly intervals x 5 doses
  - cyclophosphamide 1200 mg/m² IV infusion, approx. monthly intervals x 9 doses
  - ifosfamide[7] 1800 mg/m² IV infusion, approx. monthly intervals x 8 doses
  - etoposide 100 mg/m² IV infusion, approx. monthly intervals x 8 doses
- **Euro-EWING 99 (6 cycles)**
  - vincristine 1.5 mg/m² (max. 2 mg/m²) IV push, every 1 week x 6 doses

[7] Administration of ifosfamide requires the accompanying drug, mesna.

- ifosfamide 3000 mg/m² IV infusion, daily x 3 days per cycle = 18 doses
- doxorubicin 20 mg/m² IV infusions, daily x 3 days per cycle = 18 doses
- etoposide 150 mg/m² IV infusion, daily x 3 days per cycle = 18 doses

Review of benefits and harms

Benefits

For patients with localized disease, several studies have shown that the strategy of neoadjuvant multi-agent chemotherapy with vincristine, doxorubicin and cyclophosphamide, alternating with ifosfamide and etoposide, followed by local control (surgery/radiotherapy) then further chemotherapy is associated with 5-year survival rates of around 70% (*448*, *449*, *453*, *459*).

A randomized controlled trial conducted by the Children's Cancer Group and the Pediatric Oncology Group investigated the effect of the combination of ifosfamide and etoposide, alternated with standard chemotherapy with doxorubicin, vincristine, cyclophosphamide and dactinomycin (used in combination) in 518 patients with Ewing sarcoma, PNET of bone or primitive sarcoma of bone (*453*). In patients without metastatic disease ($n = 398$), 5-year event-free survival was higher in the group receiving alternating therapy with ifosfamide/etoposide than in the standard chemotherapy group (69% vs 54%); 5-year overall survival rate was also greater in the ifosfamide/etoposide group (72% vs 61%).

A randomized controlled trial of 568 patients with Ewing sarcoma tested whether intensification through interval compression improved outcomes of chemotherapy with alternating vincristine/doxorubicin/cyclophosphamide and ifosfamide/etoposide cycles (*454*). The results for the primary end-point of event-free survival at 5 years were 65% in the standard treatment arm (21-day interval) and 73% in the intensified treatment arm (15-day interval). Toxicity of the two regimens was similar.

A second treatment intensification strategy is high-dose chemotherapy with autologous haematopoietic stem cell rescue (*460–462*). Because of the considerable toxicity of this approach, most studies investigate high-dose chemotherapy for very high-risk patients, most commonly those with primary disseminated multifocal diagnosis, or following recurrence. In the European Ewing Tumour Initiative of National Groups (Euro-EWING 99), treatment consisted of six cycles of vincristine, ifosfamide, doxorubicin and etoposide, one cycle of vincristine, dactinomycin and ifosfamide, local treatment (surgery and/or radiotherapy), and high-dose busulfan–melphalan followed by autologous stem-cell transplantation. After a median follow-up of 3.8 years, event-free

survival (EFS) and overall survival (OS) at 3 years for all 281 patients were 27% and 34%, respectively (*463*). High-dose regimens caused profound grade 4 aplasia in 93% of patients, but with acceptable grade 3 and 4 infection rates. The protocol was associated with six transplant-associated deaths.

Treatment with conventional chemotherapy regimens using cyclophosphamide, doxorubicin, vincristine and dactinomycin with radiation and/or surgery among patients with metastatic disease at diagnosis has been associated with high rates of complete response at metastatic sites and local control (*464*). However, OS remains poor, with about one quarter of patients surviving: relapse-free survival has increased from less than 15% to 20–30% using more recent regimens, including increased doses of alkylating agents and anthracyclines. Age is a prognostic factor, with outcomes being age-dependent: in two intergroup Ewing's sarcoma studies, 5-year OS for patients aged 10 years or less was 40%, compared with 20% for patients aged over 10 years (*465*). Prognosis is also worse for patients with pelvic primary, marrow diseases or multiple sites of disease. Studies incorporating intensive therapy followed by stem-cell infusion have not shown clear benefit (*466*).

Harms and toxicity considerations

Vincristine commonly causes neurotoxicity, including sensory and motor neuropathies, which is typically dose-related. The neurotoxicity is usually reversible, although recovery may be gradual. Vincristine also causes constipation, which can be severe, and patients should receive appropriate prophylaxis (*274*).

Anthracyclines including doxorubicin are associated with a risk of cardiotoxicity. Development of severe heart failure is uncommon but myocardial dysfunction may appear during long-term follow-up. In paediatric patients, the risk of heart failure and pericardial disease increases with cumulative doses ≥ 250 mg/m² (*273*).

Patients treated with cyclophosphamide have a high risk of bladder toxicity and possibly haemorrhagic cystitis due to the accumulation of active metabolites in urine. Patients should be suprahydrated (at least 2 L/m² per day), need to void frequently and/or should receive mesna prophylaxis to reduce the incidence of haemorrhagic cystitis (*467*). Cyclophosphamide also commonly causes alopecia, mucositis and stomatitis and may result in infertility (*468*).

Ifosfamide can also cause bladder toxicity, and administration should be managed as for cyclophosphamide. Ifosfamide also causes alopecia and myelosuppression in most patients.

The most frequent dose-limiting toxicity for etoposide is myelosuppression, primarily leukopenia, which can be grade 3–4 in more than 10% of patients. A small percentage (up to 2%) of patients experience hypersensitivity reactions to intravenous etoposide, which may include angioedema, bronchospasm and/or

chest discomfort (*368*). Etoposide also causes reversible alopecia in up to 60% of patients (*469*). The use of etoposide has been associated with an increased risk of a second cancer.

One long-term follow-up study found that the risk of developing a second malignancy in patients treated for ESFT was as high as 9% and apparently highest among patients receiving radiation (*470*).

Recommendations

On the basis of the evidence presented in the application, the Expert Committee recommended that vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide be included on the complementary list of the EMLc for the treatment of Ewing sarcoma. The Committee also recommended the inclusion of mesna for this indication, to counter the bladder toxicity associated with cyclophosphamide and ifosfamide.

The Committee noted the availability of a 500-mg vial of ifosfamide powder for injection, which it considered would represent a less expensive option than the 2-g vial currently listed on the EML for treatment of paediatric patients. The Committee recommended this formulation be included on the EMLc.

The Committee also considered it appropriate to include these medicines in the complementary list of the EML for treatment of Ewing sarcoma, noting that the peak incidence of this disease is in the second decade of life.

Follicular lymphoma – EML

The application sought inclusion of medicines used in the treatment of follicular lymphoma in the core list of the Essential Medicines List. In addition, the application sought the addition of rituximab and bendamustine and the Expert Committee's endorsement of cyclophosphamide, vincristine, prednisone and doxorubicin, which are currently included in the complementary list, for use in this indication.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Follicular lymphoma (FL) is the most common indolent lymphoma and the second most common non-Hodgkin lymphoma – accounting for about 10–20% of all lymphomas in developed countries. The incidence of FL, as of other non-Hodgkin lymphomas, is rising, although it varies between geographical regions and ethnic groups; incidence is lower in Asian and sub-Saharan African countries than in western regions, probably as a result of both genetic and environmental factors (*471*, *472*).

The initial symptoms of FL include painless swelling in one or more lymph nodes, particularly in the cervical, axillary, inguinal and femoral regions. The median age at diagnosis is 55–60 years and there is a slight preponderance in women. The progression of FL varies, in terms of the speed of the tumour's growth and the involvement of other organs. Some people diagnosed with FL will have no symptoms for many years and need no treatment. Approximately 45% of cases (3% of FL patients per year) eventually transform – or progress – to an aggressive disease that resembles diffuse large B-cell lymphoma. Transformation severely worsens outcomes and 10-year survival drops from 75% to 36% for patients with transformed FL (*473*).

Although prognosis has improved substantially over the past two decades, a cure for FL has remained elusive. Treatment therefore depends upon a person's symptoms, tumour grade, age and general health (*474*). Most people with FL have widespread disease when first diagnosed; bone marrow involvement is common and present in more than 50% of patients. The vast majority of patients present with advanced (stage III–IV) disease but are often asymptomatic. The disease is usually characterized by an indolent course, response to initial therapy with frequent relapses and shorter duration of response to salvage therapy (*475*). Because cure is not possible and early treatment does not improve overall survival, treatment should be started on the basis of symptoms associated with tumour burden as determined using Group d'Etude des Lymphomes Folliculaires (GELF) criteria or the Follicular Lymphoma International Prognostic Index (FLIPI), or if there is rapid lymphoma progression.

The standard of care for the treatment of symptomatic disease in high-income countries is combination chemotherapy plus immunotherapy with the humanized monoclonal anti-CD20 antibody, rituximab (R). Chemotherapy is often based on a combination of cyclophosphamide, vincristine and prednisone (CVP); the cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) combination is sometimes used, particularly in patients with large tumour burden or high-grade disease. All cases of grade 1–3a disease are treated with R-CVP or bendamustine–rituximab (B-R), according to the paradigms for FL and other indolent lymphomas; grade 3b FL is treated as an aggressive B-cell non-Hodgkin lymphoma and may be cured with R-CHOP. For patients with grade 1–3a disease, CHOP offers no advantage over CVP, and has the added toxicity of an anthracycline. Recently, B-R has been shown to be as good as, or superior to, R-CVP. While rituximab is more costly than the drugs of the CVP combination and is more difficult to administer, its availability has been partly responsible for improved median overall survival in patients with FL (*476*).

Public health relevance

Epidemiological data pertaining to low-grade follicular lymphomas are limited. However, the incidence of general follicular lymphomas is known to account for about one third of non-Hodgkin lymphomas (NHLs) (*477*). Epidemiological information for NHLs serves as an approximation for follicular lymphomas.

GLOBOCAN estimates global incidence of total NHLs in 2012 to be 385 741 (age-standardized rate (ASR) of 5.0 per 100 000) (*255*). The incidence of NHLs in more developed regions (190 403 with an ASR of 8.6 per 100 000) was more than twice that in less developed regions (190 811 with an ASR of 3.6 per 100 000). According to GLOBOCAN, NHLs seem to affect North America, South Africa and the United Kingdom more than other regions. The 2012 prevalence of NHLs in men and women was 463 300 and 162 200 respectively. Global mortality rate due to all NHLs in 2012 was estimated to be 199 670 (ASR of 2.5 per 100 000).

Requirements for diagnosis, treatment, and monitoring

Diagnostics

An accurate diagnosis of lymphoma is paramount. Excisional lymph node or tissue biopsies are needed for definitive histopathological diagnosis. Although FL has characteristic morphological features, diagnosis requires immunohistochemical stains. This requires a histological specimen (haematoxylin and eosin stain), immunostaining for B-cell markers CD79a and CD20, the T-cell marker CD3 and the proliferative marker Ki67. Immunohistochemical detection of CD20 antigen on malignant B-lymphocytes is required where treatment with R-CHOP

is possible. Further immunostaining for CD5, CD23, CD10, cyclin D1 and CD21 allows differentiation of low-grade lymphomas into FL, mantle-cell NHL, marginal-zone lymphoma and small-cell lymphocytic lymphoma.

Grading of FL can be helpful in determining prognosis and optimal therapy. Grading is based on the number of centroblasts per high-powered field (grade 1, 0–5; grade 2, 6–15; grade 3, >15; in grade 3a, centrocytes are also present but in grade 3b there are sheets of centroblasts. This is important because all cases of grade 1–3a FL are treated according to the paradigms for FL and other indolent lymphomas, whereas grade 3b FL is treated as an aggressive B-cell NHL.

Testing

Staging of FL is done in accordance with the Ann Arbor staging system. Contrast computerized tomography is the basic imaging technique required for staging; 18F-FDG (fludeoxyglucose) positron emission tomography is not required, except for excluding distant involvement in apparent stage I or II FL, and is not routinely recommended. If the patient is considered to have stage I or II disease and local radiation is considered, a bone marrow biopsy is required to rule out stage IV disease.

Full blood count, biochemistry and lactate dehydrogenase (LDH) are required to assess tumour load, bone marrow function, and critical organ function, including renal and hepatic function. The role of pretreatment cardiac function assessment with echocardiography or nuclear imaging is controversial and probably unnecessary.

Administration and care of patients

Administration requires intravenous infusion capacity, and the patient must have regular access to clinical care. In developed countries, administration of chemotherapy is usually performed in outpatient facilities, although patients may be treated as inpatients in other settings. Antiemetics should be given to all patients being treated with CVP, R-CVP, CHOP, R-CHOP and B-R. Intravenous hydration is required for the cyclophosphamide-containing regimens. Care should be taken to avoid extravasation of both doxorubicin and vincristine, which may cause severe soft tissue injury and necrosis. Rituximab can cause allergic reactions and anaphylaxis and must be given slowly, with close monitoring and supportive medicines readily available, including adrenaline, steroids and antihistamines. Premedication with paracetamol 650 mg orally, hydrocortisone 100 mg IV, and diphenhydramine 25–50 mg IV 30–60 minutes before rituximab (at least before the first rituximab dose) is recommended and can be scaled back if there is no reaction to the first dose. If the patient has evidence of hepatitis B or C infection, this should be monitored since

administration of rituximab can reactivate either of these infections. Given the severe consequences associated with reactivated infection, screening and prophylaxis against hepatitis B is recommended.

Monitoring requires that clinicians have access to laboratory facilities, as well as the ability to recognize and address potential adverse events related to the effects of FL and to the treatment, including bone marrow suppression, infection, allergic reactions to rituximab, and gastrointestinal toxicity. Social and financial well-being can be affected by the side-effects of treatment and should also be monitored and addressed.

Overview of regimens

The following includes basic information on administration and dosing for rituximab, B-R, R-CVP and R-CHOP; no details are given of ancillary medications pertaining to the management of adverse events. Where rituximab is administered as monotherapy for asymptomatic advanced disease, it is given weekly for 4 weeks. For both CHOP and R-CHOP, six cycles of therapy are recommended.

- **Local disease (stage I or contiguous stage II)**
  - involved-field radiotherapy (RT) 30–36 Gy
- **Advanced asymptomatic disease**
  - observation ("watch-and-wait")

  or, for advanced disease with low tumour burden:
  - rituximab 375 mg/m² IV on day 1 (if available/affordable)

  or
  - bendamustine 90 mg/m² IV on days 1 and 2
  - rituximab 375 mg/m² IV on day 1 (if available/affordable)

The Expert Committee noted, however, that in elderly, frail or pretreated patients, the dosage of bendamustine should be reduced to 70–80 mg/m² in order to avoid haemotoxicity.

Standard regimen for advanced symptomatic disease, grades 1–3a

- **R-CVP (every 3 weeks x 6 cycles)**
  - rituximab 375 mg/m² IV on day 1 (if available/affordable)
  - cyclophosphamide 750 mg/m² IV on day 1
  - vincristine 1.4 mg/m² IV on day 1 (capped at 2 mg total dose)
  - prednisone 100 mg/day orally on days 1–5

Standard regimen for advanced symptomatic disease, high-grade disease 3b (should be treated similarly to diffuse large B-cell lymphoma)

- **R-CHOP (every 3 weeks x 6 cycles)**
  - rituximab 375 mg/m² IV on day 1 (if available/affordable)
  - cyclophosphamide 750 mg/m² IV on day 1
  - doxorubicin 50 mg/m² IV on day 1
  - vincristine 1.4 mg/m² IV on day1 (capped at 2 mg total dose)
  - prednisone 100 mg/day orally on days 1–5

Review of benefits and harms

Benefits

Limited-stage FL

Approximately 10–20% of patients with FL present with limited (stage I and contiguous stage II) disease. In these patients, involved-field or extended-field radiotherapy (RT) with 30–36 Gy without additional chemotherapy is highly effective and will achieve durable long-term remission in more than 50% of cases. In a large study of 6568 patients with stage I or II disease diagnosed between 1973 and 2004, patients who received RT had better 5-year (90% vs 81%), 10-year (79% vs 66%) and 20-year (63% vs 51%) disease-specific survival rates and 5-year (81% vs 71%), 10-year (61% vs 48%) and 20-year (35% vs 23%) overall survival rates compared with those treated with other therapeutic approaches (*478*). Involved-field radiotherapy is therefore the standard of care for most patients with limited-stage FL, with systemic treatment (as given to patients with advanced-stage disease) considered only for patients with a high tumour burden and those who do not respond to initial radiotherapy.

In selected patients with stable, low-bulk stage I and II disease, deferred therapy may also be an acceptable approach to initial management. In a retrospective analysis from Stanford University, more than half of patients remained untreated at a median of 6 or more years, and survival was comparable to that observed in patients given immediate treatment (*479*). The Committee noted that other data suggest that there is no difference in overall survival between radiotherapy and observation and considered that observation should also be considered as a standard treatment for limited-stage disease.

Advanced-stage FL

The majority of patients have advanced disease at diagnosis but most are asymptomatic. Since cure of FL is generally not possible, the main reason for starting treatment is to improve symptoms and/or avoid complications. Selection

of patients for treatment, as opposed to observation, is therefore often made on the basis of certain features of active disease, including progressive enlargement of lymph nodes, B symptoms (fever, weight loss or night sweats) or bone marrow failure and/or on the basis of an assessment of tumour burden. The tumour burden in FL can be defined in different ways but is often defined using the GELF criteria or FLIPI (*480*).

This approach is supported by a number of randomized controlled trials (RCTs) comparing observation with "watch and wait" versus immediate treatment, which showed that immediate treatment does not yield longer survival. A study by Ardeshna et al. demonstrated clearly that, when compared with patients treated with oral chlorambucil – an alkylating agent – survival among patients in the "watch and wait" cohort was at least as long (*481*). More recently, Ardeshna and colleagues investigated the use of rituximab monotherapy in FL patients with low tumour burden (*482*). This RCT showed that, compared with watchful waiting, the immediate use of rituximab significantly prolonged time to initiation of new therapy and improved mental adjustment to illness and coping; however, it had no impact on quality of life or overall survival. Thus, while rituximab therapy for patients with newly diagnosed disease without GELF criteria may be an option in resource-rich environments where this approach is subsidized, a "watch and wait" strategy remains the most common approach for most patients with advanced asymptomatic FL.

There is no debate about the need for treatment in patients with symptomatic advanced FL. Such patients have traditionally been treated with combination chemotherapy (CHOP or CVP), but the benefit of adding rituximab to this treatment has been clearly established in recent RCTs, all of which demonstrated improvements in response rates, time to progression and overall survival (*483–485*). A systematic review and meta-analysis of all relevant trials from 1990–2005 that compared rituximab with non-rituximab-containing regimens in patients with newly diagnosed or relapsed indolent lymphoma established that R-chemotherapy was associated with superior response rates and duration of response and with a 65% reduction in the risk of death due to lymphoma (*486*). In an effort to establish which chemotherapy regimen is best, the Fondazione Italiana Linfomi conducted the FOLL05 trial, comparing R-CVP, R-CHOP and R-FM (fludarabine and mitoxantrone) in 534 patients with stage II–IV FL (*487*). Results showed that R-CVP was associated with an inferior time-to-treatment failure (TTF) (47%) compared with R-FM (60%) and R-CHOP (57%). The anti-lymphoma activity of R-CHOP was similar to that of R-FM, but R-CHOP had a better toxicity profile and was associated with less risk of second malignancy. Generally, R-CVP is considered to be the standard of care for patients with grade 1–3a disease and R-CHOP for patients with grade 3b disease.

Data on the effectiveness and safety of rituximab confirm an overall survival advantage, irrespective of choice of chemotherapy regimen. In absolute terms, this corresponds to 28 patients who would need to be treated with R-chemotherapy to prevent one additional death in two years (95% CI: 21–50).

In recent years evidence has begun to emerge that bendamustine plus rituximab (B-R) may offer better results than R-CHOP in patients with advanced FL, mantle-cell and other indolent lymphomas. Complete response (CR) rates were higher with B-R (40% vs 30%, $P = 0.021$), progression-free survival longer (55 months vs 35 months, $P < 0.01$) and the toxicity profile better (grade 3–4 neutropenia 2.25 times less frequent with B-R than with R-CHOP) (*488*). The comparable effectiveness of B-R to that of R-CHOP on surrogate outcomes (i.e. overall response) was confirmed in a second large, multi-centre RCT, again with a favourable safety profile (*489*). Median overall survival data were not yet mature because patients were still being followed up. Although the B-R regimen was associated with a significantly higher incidence of drug hypersensitivity, vomiting and nausea than the R-CVP regimen, it offered a different toxicity profile. In a disease that affects mostly elderly individuals, the toxic effects of CHOP and CVP regimens are a particular concern because existing comorbidities or impaired organ function can compromise the ability to tolerate cytotoxic chemotherapy. Even considering that results for the R-CHOP regimen were inferior compared with those noted in other studies, the effectiveness of bendamustine was clinically highly relevant, confirming the favourable and unique safety profile of bendamustine, and the equivalent efficacy to CHOP and CVP chemotherapies.

Recent trials have investigated the role of rituximab maintenance after first-line therapy, and in patients with relapsed or refractory FL, in increasing progression-free survival, time to treatment failure and overall survival. The PRIMA trial compared 2 years of maintenance rituximab every 8 weeks with observation in patients with previously untreated FL who had received immunochemotherapy induction. Progression-free survival at 36 months was longer in the rituximab maintenance group (74.9% vs 57.6%), but there was no difference in overall survival. Patients who received maintenance therapy were also more likely to be in remission at the end of maintenance therapy but had more grade 2–4 infections (*490*). The lowered risk of disease progression after responding to induction is likely to be preferred by patients with FL, but this preference should be balanced with the constraints and costs associated with several years of rituximab maintenance.

An RCT that aims to assess the addition of rituximab maintenance after B-R induction (i.e. StiL NHL (MAINTAIN) ClinicalTrials.gov Identifier: NCT00877214) is in process and no data are yet available.

The addition of bendamustine to rituximab has been explored only in single-arm trials. Results have confirmed the promising clinical activity

of bendamustine, with acceptable toxicity, in patients with indolent B-cell, rituximab-refractory lymphoma.

The Committee noted the outcomes of the recently published RESORT trial in which patients with low-burden FL were randomized either to maintenance rituximab or to rituximab only at relapse. With a median follow-up of 4–5 years, there was no difference in median time to treatment failure between the two treatment arms (*491*).

The vast majority of patients with FL will ultimately relapse. In these situations, salvage immunochemotherapy will often offer disease control. In resource-rich countries, autologous stem cell transplantation may be used to consolidate remission in patients with relapsed FL, achieving long-lasting remissions and a plateau in long-term survival curves in patients with all grades of FL (*492*).

Harms and toxicity considerations

Common

Patients receiving CHOP and R-CHOP will experience alopecia and blood count suppression, particularly neutropenia, which increases the risk of infection. In spite of this, the incidence of serious infection in these patients is low (≤ 5%) (*483*, *487*, *488*). Vincristine may cause peripheral and autonomic neuropathy, particularly in older patients, but this is usually mild and reversible.

The CVP and R-CVP regimens have a similar toxicity profile to CHOP regimens, but adverse effects are generally milder. Peripheral neuropathy from vincristine and gastrointestinal toxicity are the most common adverse effects of CVP regimens; patients do not experience alopecia (*493*).

Because rituximab can cause significant systemic allergic reactions during administration, special precautions must be taken, particularly during the first infusion. It is important that rituximab is administered slowly and that appropriate medicines are available both for premedication and to treat allergic reactions as necessary.

Bendamustine causes severe (grade 3–4) lymphocytopenia in most patients; neutropenia and thrombocytopenia are also common (*488*). Patients may experience dermatological effects, including rash and pruritus, although these are typically mild (*494*).

Serious

Doxorubicin is associated with a risk of congestive heart failure. The risk is dose-dependent and, at the doses delivered with 6 cycles of CHOP or R-CHOP (300 mg/m²), small and is considered to be outweighed by the potential benefits of treatment.

Rituximab may also cause neutropenia and, infrequently, viral infection or reactivation of latent viral infection, including viral hepatitis and JC virus, resulting in progressive multifocal leukoencephalopathy (*495*).

The risk of long-term bone marrow damage or secondary malignancies is small (less than 1%) but significant and is similar across the treatment regimens detailed above (*487*, *488*).

Recommendations

The Expert Committee acknowledged that systemic treatment of FL is considered only for patients with high tumour burden, for those who do not respond to initial radiotherapy, and for patients with symptomatic-stage FL. The Committee also acknowledged that diagnosis, staging, grading, treatment and monitoring of FL require access to clinical care with laboratory, imaging and intravenous infusion capacity and considered that there is a public health need to add to existing CHOP or CVP regimens for patients with advancing FL. Therefore, and on the basis of the available evidence, the Committee made the following recommendations in relation to treatment for advanced symptomatic follicular lymphoma with the goal of achieving remission:

- that rituximab and bendamustine be added to the complementary list;
- that cyclophosphamide, doxorubicin, vincristine and prednisone, currently on the complementary list, should be specifically endorsed for this indication.

The Committee noted that maintenance therapy with rituximab has not been shown to be associated with a relevant clinical benefit over rituximab treatment at relapse. The Committee therefore did not recommend inclusion of rituximab on the EML for use in maintenance treatment of FL.

Gastrointestinal stromal tumour (GIST) – EML

The application sought the addition of imatinib to the core list of the Model List of Essential Medicines for the treatment of gastrointestinal stromal tumour (GIST).

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Gastrointestinal stromal tumours (GISTs) account for some 80% of primary mesenchymal tumours of the gastrointestinal tract (*496*) and represent 5% of all sarcomas (*497*). Incidence has been estimated in a Swedish study at 14.5 per million and prevalence at 129 per million (*498*); there are 5000–6000 new cases per year in the United States (*499*). Median age at diagnosis is 60 years and men and women are affected equally. There are rare cases of paediatric disease, and rare reports of familial cases, but the vast majority of cases are sporadic and no risk factors are known. Data on worldwide incidence of the disease are limited; such data as are available (based mostly on European populations) indicate an incidence of 10–20 per million.

In the past 15 years, tremendous progress has been made in understanding and treating the underlying pathophysiology of GIST. Most GISTs (about 80%) have a mutation in *c-KIT* and 5–10% have a mutation in *PDGFRA*. *c-KIT* and *PDGFRA* mutations are mutually exclusive. The mutations activate similar signal transduction pathways, which facilitate GIST oncogenesis. *c-KIT* and *PDGFRA* mutations are associated with response to targeted treatment with small-molecule tyrosine kinase inhibitors (TKIs). Effective use of these targeted agents relies on being able to demonstrate the specific mutation in a patient's cancer cells. Depending on histological phenotype and site of mutations, TKIs represent an important therapeutic option for improving the prognosis of molecular GIST subsets.

Metastatic GIST represents 15–47% of diagnosed disease. Before the use of TKIs for treatment, metastatic GIST was characterized by poor response to cytotoxic chemotherapy and poor prognosis: median overall survival on chemotherapy was 17 months and the chances of survival for more than 2 years were very slim (*500*). With imatinib as first-line therapy, there have been significant improvements in both progression-free survival (median PFS approximately 2 years) and overall survival (median OS 57 months) (*501*). Sunitinib has shown efficacy as second-line treatment in imatinib-refractory disease and patients intolerant of imatinib, with median PFS of 27–34 weeks versus 6 weeks for placebo (*502–504*). In disease that has progressed on imatinib and sunitinib, regorafenib as third-line therapy has demonstrated activity, with improved median PFS of 4.8 months compared with 0.9 months in the placebo

group (*505*). The application proposed the inclusion of imatinib. Although sunitinib adds benefit to PFS, it was not included in the current application because of the reported poor quality of life associated with the drug and its unclear benefits for overall survival. Regorafenib, as a third-line drug, was also excluded from the application.

Treatment of localized GIST consists of primary resection, followed by adjuvant treatment with imatinib for patients with high-risk disease. Roughly 60% of patients are cured with surgery alone and are not candidates for adjuvant therapy (*506*). Risk stratification is determined by tumour size, mitotic count and tumour site. Tumours larger than 10 cm are associated with increased risk of recurrence and metastasis despite clean surgical margins. Additionally, tumour rupture and multi-organ involvement can also necessitate use of adjuvant therapy. Adjuvant therapy with imatinib reduces rates of recurrence by approximately 65% (*507*) and is associated with an increase in 5-year OS from 82% to 92% (*508*).

Public health relevance

Epidemiological data regarding the global incidence and prevalence of GISTs are limited because of such factors as inconsistencies in nomenclature and in diagnostic criteria (*509*). However, one study estimated GIST incidence in USA to be 1458 cases between 1992 and 2000, with an overall age-standardized rate of 0.68 per 100 000 person–years, and determined that incidence rates of GIST increased with increasing age (*509*). Another study estimated the annual incidence of clinically detected GIST in western Sweden in 2005 to be 14.5 cases per million and the prevalence to be 129 per million inhabitants (*498*). It is possible that both global and national incidence rates of GIST, and prevalence figures, will increase over the next few years as the availability of c-KIT immunoreactivity will improve the detection of GIST, facilitating the diagnosis of high-risk and malignant forms. Indeed, GIST may affect much larger numbers of people than previously thought.

Requirements for diagnosis, treatment, and monitoring

Diagnostics

Pathological laboratory analysis of surgically excised tissue or core-needle biopsies is necessary for diagnosis, including immunohistochemistry (CD117 and/or DOG1), which is present in around 90% of cases. Additional CD117-negative cases can be diagnosed with mutational analysis for mutations involving *KIT* and *PDGFRA* genes, but these are rare cases and the critical aspects of diagnosis remain pathological review of lesional tissue and immunohistochemistry.

Mutational analysis also has prognostic and predictive value for response to targeted therapy. Specifically, *c-KIT* mutation with exon 9 involvement (the second most common) has shown poor response to the standard dose of imatinib and improved response to a higher dose. However, routine mutational testing may not be available worldwide and an acceptable practice would be treat all patients with unresectable and/or metastatic GIST with the standard imatinib dose of 400 mg/day, and to consider dose escalation only in cases of poor response.

Testing

Radiological imaging is important to distinguish resectable disease from unresectable and metastatic disease. Computerized tomography (CT) of the abdomen and pelvis is acceptable for this purpose. If CT imaging is not available, abdominal ultrasound may be considered.

Administration and care of patients

Adjuvant therapy

Routine follow-up with laboratory tests, examination, and monitoring of side-effects of treatment are necessary throughout the 3 years of treatment although their frequency can be moderated over time. Restaging scans should be done every 3–6 months for the first 3 years, every 3 months for the following 2 years (at the end of adjuvant therapy), every 6 months for the next 3 years, then yearly thereafter (*510*): the vast majority of recurrences arise within the first 5 years and within the first few years after the discontinuation of adjuvant therapy.

Metastatic disease

Routine follow-up with laboratory tests, examination, and monitoring of side-effects of treatment are necessary for dose adjustments and interruptions. The frequency of these can be moderated over time, from weekly initially to every 3–6 months eventually. Restaging scans to detect disease recurrence or progression should be done every 3–6 months (or more frequently in the event of development of symptoms).

Overview of regimens

The following sections include basic information on administration and dosing for imatinib; no details are given of ancillary medications pertaining to the management of side-effects. For the therapeutic regimens considered, continued therapy is recommended until there is evidence of disease progression or of the therapy no longer being tolerated in metastatic disease; treatment is for up to three years in the adjuvant setting.

Standard first-line regimen for adjuvant therapy

- **Imatinib: minimum 3 years' treatment for patients with resected high-risk GIST**
  - imatinib 400 mg/day orally

Standard first-line regimen for treatment of metastatic disease

- **Imatinib: continuing until progression or intolerance**
  - imatinib 400 mg/day orally (consider 400 mg twice daily, i.e. total 800 mg daily)

Patients with metastatic or unresectable disease who achieve a response to treatment at an imatinib dose of 400 mg/day should be continued at this dose and assessed for response at regular intervals; for patients who fail to achieve a response to 400 mg/day, the dose may be increased to 600 mg/day. Doses higher than 600 mg/day do not show incremental benefit in terms of overall survival (*501*).

For patients with advanced disease, interruption of imatinib therapy results in rapid progression and should not be tried unless there is significant toxicity.

Review of benefits and harms

Benefits

Complete surgical resection with negative margins offers the only definitive chance for cure in patients with GISTs. Surgery is also indicated in symptomatic patients with locally advanced or metastatic disease. Partial or complete removal of large lesions is helpful, in combination with therapy with imatinib mesylate if available and possible.

In 2002, Demetri et al. randomly assigned patients with metastatic or unresectable KIT-positive GIST to imatinib at a daily dose of either 400 mg or 600 mg. Imatinib induced an objective response in more than half of the patients (*511*). The median duration of response had not been reached after follow-up of a median of 24 weeks after the onset of response, indicating a sustained objective response in advanced GIST resistant to conventional chemotherapy. In contrast, treatment with standard chemotherapy (dacarbazine, mitomycin, doxorubicin and cisplatin) has been associated with median overall survival of 16.7 months (*500*).

A systematic review (*512*) of one randomized controlled trial (RCT) (*507*), three phase II studies, three cohort studies and nine case reports of imatinib in the adjuvant setting found that the results of the RCT were supported by the observational studies: recurrence-free survival was improved with imatinib

400 mg/day compared with placebo in adult patients with completely resected GIST. Estimated 1-year recurrence-free survival was 98% in the imatinib group versus 83% in the placebo group (hazard ratio (HR) 0.35; 95% CI: 0.22–0.53), corresponding to a 65% reduction in the risk of disease recurrence.

In patients with operable GIST but at high risk for disease recurrence after surgery, two schedules of imatinib at 400 mg/day were compared: 12 months or 36 months, started within 12 weeks of surgery (*508*). At median follow-up of 54 months, imatinib for 36 months significantly improved 5-year overall survival compared with the 12-month course: 92.0% vs 81.7%, respectively (HR 0.45; 95% CI: 0.22–0.89; $P = 0.02$).

Results from a randomized phase II trial of standard (400 mg daily) versus higher-dose (600 mg daily) imatinib in patients with unresectable or metastatic GIST showed response rates, median PFS and median OS to be essentially identical in both treatment arms (*501*). Median time to progression was 24 months overall, while estimated median OS was 57 months for the total population, with no significant differences observed between treatment arms.

Results from a randomized phase III trial of imatinib 400 mg daily versus 400 mg twice daily in 694 patients with unresectable or metastatic GIST showed no statistically significant differences in objective response rates, PFS or OS between the treatment arms (*513*). With median follow-up of 4.5 years, PFS was 18 months and 20 months in the standard and high-dose arms, respectively, while OS was 55 months and 51 months.

Neoadjuvant administration can result in unresectable or borderline resectable disease becoming resectable.

Harms and toxicity considerations

Imatinib is generally well-tolerated. Patients may experience mild adverse effects including diarrhoea, oedema, fatigue or muscle cramps (*511*).

Recommendations

On the basis of the available evidence, the Expert Committee recommended the addition of imatinib to the complementary list of the Model List of Essential Medicines for the treatment of gastrointestinal stromal tumour.

While noting the high cost of imatinib, the Committee considered that the improvement in overall survival associated with imatinib treatment in the metastatic setting, and the reduction in the rate of disease progression and improved 5-year overall survival (in patients at high risk of recurrence) associated with imatinib in the adjuvant setting were clinically relevant and important. The Committee also noted that the cost was likely to reduce with generic brands of imatinib entering the market in some countries.

Gestational trophoblastic neoplasia (GTN) – EML

The application sought specific endorsement of the following medicines, currently included on the complementary list of the Model List of Essential Medicines, for the treatment of gestational trophoblastic neoplasia: methotrexate, calcium folinate, dactinomycin, etoposide, cyclophosphamide and vincristine.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Gestational trophoblastic disease (GTD) is a range of pregnancy-related premalignant and malignant disorders; the malignant forms are termed gestational trophoblastic neoplasia (GTN). The most common form of this disease is the hydatidiform mole, which occurs in 1–3 of every 1000 pregnancies and more frequently in Asia than in Europe or North America (*514*). Five clinicopathological forms make up this entity. Hydatidiform mole – partial or complete – is the benign form. About 10% of hydatidiform moles transform into one of the malignant forms: invasive hydatidiform mole (IHM), choriocarcinoma (CCA), placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT) (*515*). Each of these conditions can perforate the uterine wall, metastasize and lead to death if left untreated. Approximately 50% of cases of GTN arise from molar pregnancy, 25% from miscarriage or tubal pregnancy, and 25% from term or preterm pregnancy. Invasive mole and choriocarcinoma, which make up the vast majority of these tumours, always produce substantial amounts of human chorionic gonadotropin (hCG) and are highly responsive to chemotherapy; overall cure rate exceeds 90% and it is usually possible to preserve fertility while achieving cure (*516*). This success is due to the unique sensitivity of these two trophoblastic neoplasms to chemotherapy and the use of hCG as a tumour marker for diagnosis, monitoring treatment and follow-up. In contrast, PSTT and ETT, which occur only rarely, produce scant amounts of hCG and are relatively resistant to chemotherapy (*514*).

In 2002, the International Federation of Gynecology and Obstetrics adopted a combined anatomical staging and modified WHO risk-factor scoring system for GTN (see Tables 7 and 8). Treatment is based on the total score, which signifies the risk of the patient developing single-agent drug resistance. Patients with non-metastatic disease (stage I) and low-risk metastatic GTN (stages II and III, score < 7) can be treated initially with single-agent chemotherapy – either methotrexate or dactinomycin – with cure rates approaching 80–90%. Patients classified as having high-risk metastatic disease (stage IV, and stages II–III with scores > 6) require a multidrug chemotherapy regimen, preferably with etoposide, methotrexate, dactinomycin, cyclophosphamide, and vincristine (EMA/CO),

possibly with adjuvant radiation and/or surgery to achieve similar cure rates (*517*). There is growing evidence that patients with low-risk GTN and prognostic scores of 5 or 6 are at increased risk of initial single-agent drug resistance and may require multi-agent chemotherapy (*514*). The use of the FIGO staging/scoring system has become the accepted basis for determining the optimal initial therapy, achieving the best outcome with the least morbidity.

Table 7
FIGO staging of GTN

Stage	Organ involvement
I	Disease localized to uterus
II	Disease localized to the pelvis and adnexa
III	Pulmonary metastases
IV	Distant organ involvement (liver, brain, kidney, gastrointestinal tract, spleen, etc.)

Table 8
Modified WHO prognostic scoring system

Prognostic factor	Score			
	0	1	2	4
Age (years)	< 40	≥ 40	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval months from index pregnancy	< 4	4–6	7–12	> 12
Pretreatment serum hCG (IU/L)	$< 10^3$	10^3–10^4	10^4–10^5	$> 10^5$
Largest tumour size (including uterus)	< 3	3–4 cm	≥ 5 cm	–
Site of metastases	Lung	Spleen, kidney	Gastrointestinal	Liver, brain
Number of metastases	–	1–4	5–8	> 8
Previous failed chemotherapy	–	–	Single drug	≥ 2 drugs

Public health relevance

Global epidemiological data pertaining to gestational trophoblastic neoplasia are limited. Epidemiological characteristics of GTD and GTN are difficult to determine because of the rarity of the conditions, the inconsistencies in case definitions, and the lack of centralized databases (*518*).

Certain studies have shown a higher incidence of GTD in Asia than in North America or Europe. In the United Kingdom, all patients are included on a national register, with central pathology review; the incidence of partial and complete hydatidiform mole is around 4 per 1000 pregnancies and GTN is diagnosed in 15% of patients with complete hydatidiform mole and 0.5–1% with partial hydatidiform mole (*514*). A review published in the American Journal of Obstetrics and Gynecology in 2010 indicates that choriocarcinoma, a subset of GTN, affects 1 in 40 000 pregnancies in Europe and North America compared with 9.2 in 40 000 pregnancies in south-east Asia and Japan (*518*). A seminar in The Lancet in 2010 estimated CCA to occur in 1 in 50 000 deliveries in the United Kingdom (*514*). The same seminar found that placental-site trophoblastic tumour accounted for about 0.2% of cases of gestational trophoblastic disease in the United Kingdom in 2010.

Requirements for diagnosis, treatment, and monitoring

Diagnostics

- Pathology laboratory analysis of surgically excised specimens.
- Clinical laboratory facilities to perform the routine haematological and chemical analyses required for monitoring the effects of chemotherapy.
- Facilities for performing radioimmunoassay of hCG which serves as a tumour marker for GTN. The measurement of hCG requires trained technicians and a laboratory with automated equipment and reagents designed for radioimmunoassay procedures. The serial quantitative measurement of hCG is essential for diagnosis, monitoring the efficacy of treatment, and follow-up of patients with GTN. After evacuation of a molar pregnancy, hCG levels usually become undetectable within 8–10 weeks (compared with 3–6 weeks after normal delivery or miscarriage). Persistence of hCG levels indicates local or metastatic disease, which allows for early detection and timely intervention. During treatment, hCG response is used as a guide for deciding whether to continue treatment with a particular agent or switch to another. After treatment, hCG monitoring allows identification of patients who relapse and require additional therapy.

Testing

Once it is determined that a patient has an elevated and rising hCG level, a thorough evaluation is required to determine the extent of disease, including blood tests to assess renal and hepatic function, peripheral blood counts, and baseline serum hCG levels. A speculum examination should be performed to identify vaginal metastases, which may cause heavy bleeding. Radiological evaluation should include a pelvic ultrasound, both to look for retained trophoblastic tissue and to evaluate local spread. Chest imaging is also required as the lungs are the most common site of metastases. In the absence of pulmonary and vaginal involvement, brain and liver metastases are rare and further radiological testing may not be needed. However, magnetic resonance imaging of the brain with contrast is important in women with metastases and in all patients with a pathological diagnosis of CCA. It is usually not recommended to obtain a histological diagnosis because of the high vascularity of the tumour and the risk of haemorrhage.

Administration and care of patients

Administration of chemotherapy requires intravenous infusion capacity, and the patient must have regular access to clinical care. Methotrexate can be administered either intramuscularly or intravenously. Dactinomycin is a vesicant and requires careful administration through a freely running infusion. All other chemotherapeutic agents are also administered intravenously. Antiemetics and intravenous hydration should accompany the administration of most agents.

Monitoring requires that clinicians have access to laboratory facilities, as well as the ability to recognize and address potential toxicities caused by the treatment itself, including but not limited to bone marrow suppression, infection, allergic reactions, and gastrointestinal toxicity.

hCG follow-up and relapse

All patients with GTN are followed with weekly hCG values until levels are undetectable for 3 consecutive weeks, and then monthly until undetectable for 12 months. The use of effective contraception must be encouraged during the entire period of monitoring. Relapse rates range from 3% to 9% percent for stages I to IV and the mean time to recurrence from the last non-detectable hCG level is 6 months (*517*).

Subsequent pregnancy after treatment for GTN

Patients who have been successfully treated for GTN with chemotherapy can expect normal future reproductive function with no increased risk of congenital anomalies (*517*).

Psychosocial issues

Women with GTN can experience significant mood disturbance, marital and sexual problems, and concerns about future fertility. They may therefore need emotional support and counselling during and after treatment.

Overview of regimens

Standard regimens

- **Single-agent regimens for low-risk gestational trophoblastic neoplasms**

Methotrexate (MTX) regimens	*Primary remission rates (%)*
MTX: 0.4-0.5 mg/kg IV or IM daily for 5 days	87–93
MTX: 30–50 mg/m² IM weekly	49–74
MTX/calcium folinate	74–90
MTX 1 mg/kg IM or IV on days 1, 3, 5, 7	
Calcium folinate 15 mg orally on days 2, 4, 6, 8	
High-dose IV MTX/calcium folinate	69–90
MTX 100 mg/m² IV bolus	
MTX 200 mg/m² 12-hour infusion	
Calcium folinate 15 mg every 12 hours in 4 doses IM or orally beginning 24 hours after starting MTX	

Dactinomycin regimens	*Primary remission rates (%)*
Dactinomycin 10–12 μg/kg IV push daily for 5 days	77–94
Dactinomycin 1.25 mg/m² IV push every 2 weeks	69–90

- **EMA/CO regimen for resistant low-risk GTN or as primary therapy for high-risk GTN**

Day	*Drug*	*Dose*
1	Etoposide	100 mg/m² by infusion in 200 ml normal saline over 30 min
	Dactinomycin	0.5 mg IV push
	MTX	100 mg/m² IV push; 200 mg/m² by infusion over 12 hours

2	Etoposide	100 mg/m² by infusion in 200 ml normal saline over 30 min
	Dactinomycin	0.5 mg IV push
	Calcium folinate	15 mg every12 hours x 4 doses IM or orally beginning 24 hours after starting MTX
8	Cyclophosphamide	600 mg/m² by infusion in normal saline over 30 min
	Vincristine	1 mg/m² IV

Review of benefits and harms

Benefits

Women with GTN are classified as having low- or high-risk GTN using the FIGO scoring system. After undergoing dilatation and curettage of the womb, the absolute majority (>90%) of women with low-risk GTN are cured by treatment with chemotherapy. Methotrexate and dactinomycin are the two most commonly used drugs for first-line treatment of low-risk GTN. A Cochrane systematic review of five randomized controlled trials comparing single-agent chemotherapy with methotrexate and dactinomycin in women with low-risk GTN found that, overall, dactinomycin was associated with higher rates of primary cure than methotrexate (risk ratio RR 0.64; 95% CI: 0.54–0.76), while methotrexate was associated with significantly more treatment failure than dactinomycin (RR 3.81; 95% CI: 1.64–8.86) (moderate-quality evidence) (*519*). If the first-line treatment fails to cure the disease or is associated with adverse events that require it be discontinued, a secondary treatment has to be used. If methotrexate is the first drug used, dactinomycin is usually the secondary treatment, and vice versa.

High-risk tumours are treated with combination chemotherapy (e.g. EMA/CO), with or without adjuvant radiotherapy and surgery. Various drug combinations may be used for high-risk tumours; however, no experimental studies comparing different chemotherapy regimens are available and the comparative efficacy and safety of these regimens is unknown. The EMA/CO regimen has been widely adopted because of its efficacy and easily manageable short-term toxicity. In cohort studies five-year overall survival has been reported to range from 75% to 90% (*520–522*).

Harms and toxicity considerations

Common

Chemotherapy regimens for GTN are associated with well-recognized toxicities including bone marrow suppression, increased risk of infection, hair loss,

stomatitis, nausea and vomiting, neuropathy, and alterations in hepatic and renal function. Toxic side-effects are more likely to occur when chemotherapy agents are used in combination.

Specifically, dactinomycin is a highly emetogenic agent requiring prophylaxis with antiemetics to reduce the severity of nausea and vomiting. Patients treated with dactinomycin also commonly suffer reversible alopecia. Methotrexate regimens are associated with a higher incidence of diarrhoea and stomatitis (*523*).

The EMA/CO regimen can cause predictable, and generally easily manageable, adverse effects including reversible alopecia and myelosuppression, occasionally with severe neutropenia and anaemia (*514*, *523*, *524*).

Serious

The use of etoposide in this patient population has also been associated with a small but increased risk of secondary cancers in <2% of patients, particularly leukaemia (*523*, *525*). The risk of etoposide-induced acute myeloid leukaemia is increased when the cumulative drug dose is high or when etoposide is used with concomitant radiotherapy or high-dose platinum agents (*526*).

Recommendations

The Expert Committee acknowledged that gestational trophoblastic neoplasia is a rare, but highly curable, malignancy. On the basis of the evidence presented in the application, the Committee recommended endorsement of the following medicines for the treatment of GTN on the complementary list of the Model List of Essential Medicines: dactinomycin, methotrexate, calcium folinate, etoposide, cyclophosphamide and vincristine. However, the Committee noted that availability of dactinomycin is poor.

The Committee noted that the treatments are highly effective and the benefit is clinically obvious – high cure rates (greater than 90%) and preservation of fertility in the majority of patients.

Granulocyte colony stimulating factor (G-CSF) (addition) – EML and EMLc

The application requested the inclusion of granulocyte-colony stimulating factor (G-CSF) on the EML and EMLc as supportive treatment alongside myelosuppressive chemotherapy regimens for numerous cancers.

Many antineoplastic agents are cytotoxic to bone marrow and prevent development of the granulocytes necessary to fight infection, resulting in neutropenia. Fever may be the only sign of infection in neutropenic patients, and infection may progress rapidly to sepsis and death if empirical antibiotics are not given. Febrile neutropenia is a medical emergency that gives rise to a substantial increase in morbidity, mortality, hospitalizations and cost of care. In the absence of medicines to stimulate proliferation of granulocytes, physicians must reduce the dose or delay the timing of chemotherapy.

G-CSF is a glycoprotein that stimulates the bone marrow to produce granulocytes and promotes granulocyte survival, proliferation and differentiation. When used as primary prophylaxis (initiated early in the first cycle of chemotherapy and continued through subsequent cycles), G-CSF has been shown to reduce the risk of febrile neutropenia and of infection-related and early all-cause mortality, while also reducing the need for dose reduction or delays in treatment delivery (*527*, *528*).

The Expert Committee noted that American Society of Clinical Oncology (ASCO) guidelines, reviewed and updated in 2005, recommend G-CSF for primary prophylaxis when the risk of febrile neutropenia, secondary to a recommended chemotherapy regimen, is approximately 20% and no alternative, but equal, chemotherapy regimen that does not require G-CSF is available (*529*).

Because of the high cost, the Expert Committee agreed that use of G-CSF is justified only in patients deemed to be at high risk for developing febrile neutropenia. A patient's risk is based both on risks inherent in the myelosuppression induced by specific chemotherapy regimens and on individual health factors. The following clinical factors are associated with a higher risk of developing severe complications from prolonged neutropenia (*529*):

- age greater than 65 years
- poor performance status
- prior episodes of febrile neutropenia
- extensive prior treatment, including large radiation ports
- administration of combined chemotherapy
- cytopenias due to bone marrow involvement by tumour
- poor nutritional status
- presence of open wounds or active infections

- more advanced cancer
- other serious comorbidities.

The Committee accepted that the prevalence of some of these factors may be increased in low-resource settings, when the consequences of febrile neutropenia may be even more striking.

Kuderer et al. conducted a systematic review of 17 randomized controlled trials comparing primary G-CSF prophylaxis with placebo or untreated controls in 3493 adult patients with solid tumours and malignant lymphoma (*527*). The review found that, compared with controls, patients treated with G-CSF had a 45% lower risk of infection-related mortality (relative risk (RR) 0.55; 95% CI: 0.33– 0.90; $P = 0.018$). Similarly, G-CSF treated patients had a 40% lower risk for all-cause mortality during the chemotherapy period (RR = 0.60; 95% CI: 0.43–0.83; $P = 0.002$) and a 46% lower risk of febrile neutropenia (RR 0.54; 95% CI: 0.43–0.67; $P < 0.01$). Significant reductions in febrile neutropenia were also observed in studies that allowed secondary G-CSF prophylaxis in controls.

In the secondary prophylaxis setting, the Expert Committee noted that, for patients who have experienced neutropenic complications from a prior cycle of chemotherapy, and for whom dose reduction or delay might result in adverse treatment outcomes, the ASCO guidelines recommend routine use of G-CSF in subsequent cycles (*529*).

When treating cancer with curative intent, dose-density of chemotherapy has been shown to have an impact on long-term survival in certain circumstances. For example, randomized controlled trials in breast cancer, non-Hodgkin lymphoma and Ewing sarcoma have demonstrated improvements in clinical outcomes (e.g. event- and disease-free survival) following use of dose-dense regimens compared with standard regimens (*454*, *530*, *531*). While these data cannot be extrapolated to all disease settings and chemotherapy regimens, the Committee considered that use of G-CSF to enable administration of dose-dense regimens may be appropriate where there is evidence that such regimens produce superior clinical outcomes.

In most cases, patients treated with palliative intent should not be treated with intensive regimens that require G-CSF. For most patients with most diseases in this situation, intensive therapies have not been shown to improve overall survival, nor have dose-dense therapies been associated with gains in quality of life. Dose reduction or dose delay is an appropriate treatment strategy in the palliative setting (*529*).

With regard to dosage and administration, G-CSF for primary prophylaxis should generally be given 24–72 hours after the administration of myelotoxic chemotherapy. A dose of 5 mg/kg per day should be continued until a target absolute neutrophil count of at least 2 or 3×10^9 cells/L is reached. G-CSF has a short half-life and daily subcutaneous injections are required.

Several studies have shown the comparability in effectiveness and patient outcomes of daily filgrastim and once per cycle pegfilgrastim (*532–534*). A meta-analysis in 2007, analysing outcomes among patients with different types of cancer (and different chemotherapy regimens), concluded that pegfilgrastim produced moderately better outcomes than filgrastim (*535*). In general, however, the choice between filgrastim and pegfilgrastim largely concerns individual clinical preference, ease of administration and the difference in cost; pegfilgrastim is much more expensive than filgrastim. Additionally, biosimilars are available for filgrastim, allowing for comparable clinical efficacy at lower cost. Guidelines are generally accepting of both options, depending on patient circumstances and cost considerations within the health system concerned (*536*).

The Expert Committee noted that G-CSF has not been associated with clinical benefit in patients with afebrile neutropenia or as a treatment for most patients who have already developed febrile neutropenia. Use of G-CSF in these circumstances is not routinely recommended (*529*).

The Expert Committee acknowledged that avoidance of febrile neutropenia is a meaningful goal of holistic care of patients with cancer undergoing myelosuppressive chemotherapy. On the basis of the available evidence, the Committee recommended addition of filgrastim to the EML and EMLc for use in the following circumstances:

- as primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy;
- as secondary prophylaxis in patients who have experienced neutropenia following prior myelotoxic chemotherapy;
- to facilitate administration of dose-dense chemotherapy regimens.

Hodgkin lymphoma (adult) – EML

The application sought the endorsement of medicines already included in the complementary list of Essential Medicines for treatment of Hodgkin lymphoma in adults. The proposed medicines are those in the treatment regimens ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) and BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone). The application also sought addition to the core list of granulocyte colony-stimulating factor (G-CSF) for use with the BEACOPP regimen.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Hodgkin lymphoma is a lymphoid malignancy of B-cell origin occurring more frequently in young people between the ages of 20 and 35 years. It is classified as either nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) or classical Hodgkin lymphoma (cHL) in accordance with the 2008 WHO classification. Although they have characteristics in common, these two disease entities differ in their clinical features and behaviour as well as their cellular properties. cHL accounts for 95% of all Hodgkin lymphomas and can be further subdivided into four histological subtypes: lymphocyte-rich (LR), nodular sclerosis (NS), mixed cellularity (MC), and lymphocyte-depleted (LD) (*537*).

Hodgkin lymphoma is an uncommon neoplasm with an estimated 65 950 cases globally; incidence varies significantly by age, sex, ethnicity, geographical location and socioeconomic status (*255*).

Incidence rates are higher in more developed regions and among males and lower in Asia (*538*). However, Hodgkin lymphoma accounts for 15% of all cancers in young adults globally, with a high impact on quality of life (*538*). Up to the 1960s, the 5-year survival rate was less than 10% worldwide (*539*). Since then, the outcome has progressively improved, and the current 5-year overall survival (OS) rate has reached 80% for patients with advanced disease and more than 90% for those with limited-stage disease (*540*). This success may be attributed to improved chemotherapy and radiation therapy approaches. Among the regimens developed to treat Hodgkin lymphoma, the ABVD regimen is recommended as the standard; the BEACOPP regimen is considered an acceptable alternative for high-risk patients.

Public health relevance

GLOBOCAN estimates for 2012 were 65 950 cases of Hodgkin lymphoma worldwide, with 25 469 deaths (*255*). Of these cases, 28 852 occurred in more developed regions and 37 098 in less developed regions. The age-standardized

rate (ASR) of Hodgkin lymphoma is 2.1 per 100 000 in more developed regions and 0.6 in less developed regions. Regions most affected by Hodgkin lymphoma include the Americas (ASR 1.5 per 100 000), the eastern Mediterranean region (ASR 1.5 per 100 000), and Europe (ASR 2.0 per 100 000). The highest age-standardized mortality rate, 1.0 per 100 000, is found in the eastern Mediterranean region. Men (ASR 1.1 per 100 000) are slightly more at risk of developing Hodgkin lymphoma than women (ASR 0.7 per 100 000). The disease is most often diagnosed between the ages of 15 and 30 years and in populations older than 55 (*541*). Risk factors for developing Hodgkin lymphoma include previous exposure to an Epstein–Barr viral infection and infection with immunocompromising conditions such as HIV/AIDS (*541*).

Requirements for diagnosis, treatment, and monitoring

Diagnostics

Pathology laboratory analysis of surgically excised lymph node, lymph node core or extranodal tissue is required. In cHL, the presence of Hodgkin and Reed–Sternberg (HRS) cells is disease-defining, while the detection of lymphocyte-predominant (LP) cells is required for the diagnosis of NLPHL. The immunophenotype of the malignant cells in cHL and NLPHL differs significantly. In contrast to HRS cells, which stain consistently positive for CD30 and CD15, occasionally positive for CD20 and negative for CD45, LP cells are characterized by the expression of CD20 and CD45 but lack CD15 and CD30 (*537*).

Testing

It has been recommended that pretreatment tests include staging, using contrast-enhanced computerized tomography (CT) scan, and blood counts and blood chemistry to assess critical organ function, including renal and hepatic function, and determine prognosis. Several groups have developed scoring systems to predict survival of patients and guide decisions on therapy. Most consider the presence of constitutional symptoms and bulky mediastinal disease to be unfavourable features in limited-stage disease (stage I/II); stage III/IV disease is considered to be advanced-stage disease (*537*). Whenever it is available, baseline positron emission tomography (PET) should also be carried out according to the recommendations for staging and response assessment in lymphoma (*542*, *543*). The PET-CT scan can be performed after two cycles of ABVD; complete response is associated with better prognosis and can result in a patient needing fewer cycles of ABVD overall. If a PET-CT is performed, bone marrow biopsy is no longer indicated for Hodgkin lymphoma (*543*). To identify those at increased risk for acute and/or long-term complications, pulmonary function tests should be performed in older patients. Since chemotherapy and radiotherapy can potentially cause permanent fertility damage, reproductive counselling must be offered to young patients of both sexes before treatment (*544*).

Administration and care of patients

Administration requires intravenous infusion capacity and regular patient access to clinical care. A central venous catheter such as a Hickman or PICC (peripherally inserted central catheter) aids in minimizing the pain associated with peripheral administration of ABVD. In developed countries, administration is usually performed in outpatient facilities; in other settings, patients may be treated in inpatient facilities. Intravenous hydration and antiemetics should accompany administration of ABVD. Careful monitoring is mandatory to prevent soft tissue extravasation, which can cause severe local reactions and necrosis, especially with dacarbazine.

Monitoring requires that clinicians have access to laboratory facilities, as well as the ability to recognize and address potential adverse events caused by the treatment itself, including bone marrow suppression, infection, mucositis, nausea and vomiting (*545*). Special attention is needed for acute reactions to bleomycin, including fever, and anaphylactoid reactions (*545*). Bleomycin-induced pulmonary toxicity (BPT) may occur in 20–30% of patients, while on therapy or up to 6 months after treatment; patients should be carefully assessed for signs and symptoms of BPT before each bleomycin dose. A history of new or worsening dyspnoea or pulmonary crackles should lead to bleomycin being stopped until an alternative cause is identified (*544*). Among patients who develop BPT, omission of bleomycin does not compromise the efficacy of therapy, but a diagnosis of BPT itself could potentially compromise outcomes (*546*). Clinicians should be sensitive to aspects of fatigue and related (emotional) symptoms in their patients and encourage them to seek further support if needed (*547*).

Overview of regimens

Management of Hodgkin lymphoma (both cHL and NLPHL) relies on multimodality treatment with standard chemotherapy, radiation therapy, and autologous or allogeneic stem cell transplantation in cases of relapsed disease (20–30% of advanced cases) (*548*).

In many countries ABVD is considered to be the standard of care for Hodgkin lymphoma. Over the past decade, however, other regimens have been developed for patients with advanced (stage III/IV) disease, to improve efficacy or reduce toxicity (*548*). Dose-escalated BEACOPP, was developed by the German Hodgkin Study Group (GHSG) to improve efficacy; it has emerged as a very effective regimen.

The following provides information on administration and dosing for ABVD and BEACOPP; no details are given of ancillary medications pertaining to the management of adverse events.

Standard regimen (ABVD) (*549*)

ABVD: 2–4 cycles for limited disease, 6–8 cycles for advanced disease (repeated every 28 days)

- doxorubicin 25 mg/m² IV infusion on days 1 and 15
- bleomycin 10 000 IU/m² IV infusion on days 1 and 15
- vinblastine 6 mg/m² IV infusion on days 1 and 15
- dacarbazine 375 mg/m² IV infusion on days 1 and 15

Alternative regimen (dose-escalated BEACOPP) (*550*)

Dose-escalated BEACOPP: 6–8 cycles (repeated every 21 days)

- bleomycin 10 000 IU/m² IV infusion on day 8
- etoposide 200 mg/m² IV infusion on days 1–3
- doxorubicin 35 mg/m² IV infusion on day 1
- cyclophosphamide 1250 mg/m² IV infusion on day 1
- vincristine 1.4 mg/m² (max 2 mg) IV infusion on day 8
- procarbazine 100 mg/m² orally on days 1–7
- prednisone 40 mg/m² orally on days 1–14
- G-CSF subcutaneous injection starting on day 8

Review of benefits and harms

Benefits

Chemotherapy has transformed Hodgkin lymphoma from a disease that was uniformly fatal a few decades ago to a largely curable disease nowadays. The study by Canellos and colleagues established ABVD as more efficient and less toxic than other combinations (*549*). In 1992, the Cancer and Leukemia Group B (CALGB) reported the results of a prospective three-group randomized trial involving 359 patients with Hodgkin lymphoma. This trial compared the following regimens: ABVD for 6–8 months; mechlorethamine, vincristine, procarbazine and prednisone (MOPP) for 6–8 months; and MOPP alternating with ABVD for 12 months. The trial was limited to patients with advanced disease (clinical stages III and IV). No radiotherapy was administered. The results indicated an event-free survival (EFS) advantage of ABVD over MOPP but no differences in overall survival (OS) between the ABVD and MOPP groups. However, the toxicity profile was remarkably better with ABVD. These findings were confirmed in a follow-up study of the data published in 2002, and later at a median follow-up of 20 years (*551*).

Most patients (more than 90–95%) with limited-stage disease, usually defined as non-bulky (largest tumour diameter < 10 cm) stage IA or IIA disease, can be cured with 2–4 cycles of ABVD followed by involved-field radiation therapy (IFRT) (*552*). GHSG recently reported results for their four-group trial (HD13) in which 1502 patients with early-stage favourable-risk Hodgkin lymphoma were randomly assigned to two cycles of either standard ABVD chemotherapy or one of three experimental treatments, omitting either dacarbazine (ABV) or bleomycin (AVD) or both, all followed by 30-Gy IFRT (*553*). GHSG aimed to investigate whether omission of one or both of dacarbazine and bleomycin reduced the efficacy of this regimen in the treatment of Hodgkin lymphoma. With respect to the predefined non-inferiority margin, neither dacarbazine nor bleomycin could be omitted from ABVD without a substantial loss of efficacy. The standard of care for patients with early-stage favourable Hodgkin lymphoma should remain ABVD followed by IFRT.

An alternative to ABVD as the standard of care for patients with advanced Hodgkin lymphoma is the intensive BEACOPP regimen, which has shown superior activity to ABVD in terms of improving EFS and OS. However, it is associated with significant short- and long-term toxic effects. Moreover, given the direct medical costs of inpatient stays, chemotherapy drugs and G-CSF, dose-escalated BEACOPP therapy is more expensive than ABVD. Nevertheless, the incremental cost–effectiveness ratio with respect to the absolute gain in OS appears to be favourable (*554*).

The absolute majority of patients with Hodgkin lymphoma are cured with ABVD. A meta-analysis of five randomized trials examining the efficacy of BEACOPP compared with ABVD for first-line treatment of Hodgkin lymphoma demonstrated the positive impact of BEACOPP on EFS but not OS (*555*).

A subsequent network meta-analysis identified 14 trials comparing various BEACOPP regimens with ABVD-based regimens in 10 042 patients and demonstrated 7% OS advantage over 5 years, strongly supports the use of six cycles of dose-escalated BEACOPP or eight cycles of BEACOPP-14 (baseline-dose BEACOPP, repeated every 14 days) as initial treatment for patients with advanced-stage Hodgkin lymphoma (*556*). Random-effects meta-regression of absolute OS rates estimated a 5-year OS rate of 88% (95% CI: 84–91%) for ABVD. An additional 7% (95% credibility interval (CrI): 3–10%) benefit was estimated for 5-year OS for dose-escalated BEACOPP, and a 7% (95% CrI: 2–9%) benefit for BEACOPP-14, resulting in 95% 5-year overall survival for both BEACOPP regimens.

European Society for Medical Oncology clinical practice guidelines endorse ABVD as standard regimen for patients with all stages of Hodgkin lymphoma, especially fit patients over 60 years of age. For advanced stages, they emphasize the need for appropriate supportive care and close surveillance if BEACOPP is used, to control short- and long-term toxicities (*537*).

A similar recommendation was made by the British Committee for Standards in Haematology, the Italian Society of Haematology and the Italian Society of Experimental Haematology, and the Spanish Society of Haematology (*544*, *557*, *558*).

Harms and toxicity considerations

Common

Patients receiving chemotherapy for Hodgkin lymphoma will suffer from temporary alopecia and myelosuppression, including suppression of the neutrophil count, increasing the risk of infection (although infection incidence remains low at 2%). The dose-escalated BEACOPP regimen caused more haematological toxicities and infections than ABVD, with subsequently higher risk for transplant-related mortality, especially among those with poor performance status and patients older than 60 years (*555*, *556*).

Serious

Patients should be monitored for symptoms indicating the existence of long-term toxicity, particularly of heart and lung. Treatment with bleomycin may result in late BPT, particularly when combined with mediastinal irradiation. Toxicity may occur in up to 20–30% of patients and fatal pulmonary complications have occurred (*546*, *549*, *559*). There may be a significant decline in median forced vital capacity and diffusing capacity (*560*). A high index of suspicion is therefore warranted, to allow omission of bleomycin as early as possible when toxicity occurs.

Doxorubicin can lead to long-term cardiomyopathy when cumulative doses exceed 450 mg/m². However, ABVD provides cumulative doxorubicin doses of 300–400 mg/m² and therefore is uncommonly associated with cardiomyopathy.

Escalated BEACOPP regimens are associated with higher risk for gonadal toxicity, especially among women (*561*, *562*). Additionally, the BEACOPP regimen can lead to secondary malignancy in 0–2% of patients, including acute leukaemia and myelodysplasia (*563*, *564*). The ABVD regimen may have lower leukaemogenicity than BEACOPP. Finally, with respect to fatal toxicity, acute treatment-related mortality (TRM) is a matter of concern with BEACOPP (*565*). TRM occurred in about 2% of patients in the BEACOPP group in the GHSG HD9 trial, caused mainly (87.5%) by neutropenic infections (*566*).

Recommendations

On the basis of the evidence presented in the application, the Expert Committee endorsed the inclusion on the complementary list of the Essential Medicines List of medicines in the ABVD regimen for treatment of Hodgkin lymphoma

in adult patients – doxorubicin, bleomycin, vinblastine and dacarbazine. The Committee did not endorse inclusion in the EML of medicines used in the BEACOPP regimen for this indication, noting that while there was comparable survival associated with the BEACOPP and ABVD regimens, BEACOPP was associated with greater toxicities, including infertility, myelosuppression and secondary malignancies.

The Committee recognized that the procarbazine currently on the list has no indication and could be considered for future deletion.

Further, as empirical use of G-CSF has not been shown to be necessary during treatment with ABVD, the Committee did not recommend the addition of G-CSF to the EML for this indication.

Hodgkin lymphoma (paediatric) – EMLc

The application sought the addition of vincristine, doxorubicin, cyclophosphamide, prednisone, etoposide, bleomycin and dacarbazine to the core list of Essential Medicines for Children (EMLc) for the treatment of Hodgkin lymphoma in paediatric patients. The Committee noted that vincristine, doxorubicin and cyclophosphamide are currently included on the complementary list of the EMLc for other indications.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Hodgkin lymphoma (HL) is the most common malignancy among adolescents aged 15–19 years (*567*). It is one of the most curable forms of cancer in young people, with estimated 5-year survival rates exceeding 98%, yet long-term overall survival declines primarily as a result of the delayed effects of therapy (*568*). Various strategies have been developed – often quite different from those used for adults with HL – that aim to identify the optimal balance between maintaining overall survival and avoiding the long-term consequences of therapy. The regimens described here apply to children, adolescents and young adults, without specific age categories. Chemotherapeutic strategies include combinations of vincristine, doxorubicin, cyclophosphamide and prednisone, and variations that incorporate bleomycin, etoposide, and dacarbazine across North America and western Europe (*569–578*). Assignment of radiotherapy on the basis of early response to chemotherapy has become a standard across the different treatment approaches.

For standard-risk patients, the application proposed AVPC: (including doxorubicin, vincristine, prednisone, cyclophosphamide) or OEPA: (including vincristine, etoposide, prednisone, doxorubicin). For patients with intermediate- or high-risk disease, the application proposed ABVE-PC (including doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide), or OEPA/COPDac (including vincristine, etoposide, prednisone, cyclophosphamide, doxorubicin, dacarbazine).

Public health relevance

Hodgkin lymphoma is diagnosed in approximately 1100 children and adolescents under the age of 20 years in the USA each year, accounting for 6% of overall childhood cancer diagnoses. The disease ranks as the most common malignancy among adolescents aged 15–19 years (*567*). In developing countries, there is an early peak before adolescence (*579*). There is a strong male predominance among children younger than 5 years, while the male-to-female ratio is more balanced in children aged 15–19 years (*580*). A family history of Hodgkin lymphoma in a sibling or a parent is associated with an increased risk of this disease (*581*).

Requirements for diagnosis, treatment, and monitoring

Diagnostics

Pathological laboratory analysis of surgically excised lymph node, lymph node core or extranodal tissue is required. In classical HL (cHL), the presence of Hodgkin and Reed–Sternberg (HRS) cells is disease-defining; the detection of lymphocyte-predominant (LP) cells is required for the diagnosis of the more uncommon type of HL – nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). The immunophenotype of the malignant cells in cHL and NLPHL differs significantly. In contrast to HRS cells, which stain consistently positive for CD30 and CD15, occasionally positive for CD20 and negative for CD45, LP cells are characterized by the expression of CD20 and CD45 but lack CD15 and CD30 (*537*).

Testing

Physical examination and diagnostic imaging evaluations (upright posteroanterior and lateral thoracic radiographs; computerized tomography (CT) scans of the neck, chest, abdomen and pelvis, with intravenous and oral contrast; and functional nuclear imaging studies with fludeoxyglucose positron emission tomography (FDG-PET)) are used to designate a clinical stage. Data from retrospective studies suggest that FDG-PET may replace the need for bone marrow biopsies in patients with clinical stage III–IV disease or B symptoms (fever, night sweats, weight loss) (*582*), but this has not been validated prospectively. Staging laparotomy is rarely appropriate with the imaging modalities currently available, but biopsy of specific sites with equivocal findings by clinical staging should be considered when results will alter therapy. Interim assessment of response by FDG-PET is incorporated into contemporary treatment approaches. However, the optimum time point for assessment and the criteria for response have not been defined. Continued FDG-PET surveillance for relapse within the post-treatment period is not recommended, because of its low positive predictive value.

Administration and care of patients

Chemotherapy for HL consists of multiple agents given intravenously and orally. This requires careful management of fluid and electrolyte balance as well as prophylactic antiemetic therapy and other supportive care measures. IV administration is usually accomplished through a central venous catheter and so should be undertaken only in a specialized cancer centre. Radiotherapy also requires special expertise to minimize exposure of normal tissue.

In the short term, the side-effects of chemotherapy include nausea, vomiting, mucositis, pancytopenia and peripheral neuropathy. In the long term, survivors are at risk for infertility (notably from cyclophosphamide or

procarbazine), cardiomyopathy (especially from doxorubicin and radiotherapy), restrictive pneumonitis (especially from bleomycin and radiotherapy), hypothyroidism (from radiotherapy) and second cancers (particularly leukaemia from etoposide and solid tumours in the radiation fields).

Overview of regimens

The following includes basic information on administration and dosing for the Children's Oncology Group and European Consortium regimens; no details are given of ancillary medications pertaining to the management of adverse events.

Standard regimens for standard-risk patients

- **AVPC (COG AHOD03P1): three 21-day cycles** (*578*)
  - doxorubicin 50 mg/m² IV infusion
  - vincristine 1.4 mg/m² (max. 2.8 mg) IV push
  - prednisone 20 mg/m² orally twice daily on days 1–7
  - cyclophosphamide 800 mg/m² IV infusion

or

- **OEPA (GPOH 2002): two 28-day cycles** (*572*)
  - vincristine 1.5 mg/m² (max. 2 mg) IV push on days 1, 8 and 15
  - etoposide 125 mg/m² IV infusion on days 2–6
  - prednisone 30 mg/m² orally twice daily on days 1–15
  - doxorubicin 40 mg/m² IV infusion on days 1 and 15

Standard regimens for intermediate- or high-risk patients

- **ABVE-PC (COG AHOD0031** (*569*)**; P9425** (*575*)**: four (intermediate risk) or five (high risk) 21-day cycles**
  - doxorubicin 25 mg/m² IV infusion on days 1 and 2
  - bleomycin IV infusion 5 units/m² on day 1, 10 units/m² on day 8
  - vincristine 1.4 mg/m² (max. 2.8 mg) IV push on days 1 and 8
  - etoposide 125 mg/m² IV infusion on days 1–3
  - prednisone 20 mg/m² orally twice daily on days 1–7
  - cyclophosphamide 800 mg/m² IV infusion on day 1

or

- **OEPA/COPDac (GPOH 2002** (*572*))

  Two 28-day cycles:
  - vincristine 1.5 mg/m² (max. 2 mg) IV push on days 1, 8 and 15

– etoposide 125 mg/m² IV infusion on days 2–6
– prednisone 30 mg/m² orally twice daily on days 1–15
– doxorubicin 40 mg/m² IV infusion on days 1 and 15

Two (intermediate risk) or four (high risk) 28-day cycles:

– cyclophosphamide 500 mg/m² IV infusion on days 1 and 8
– vincristine 1.5 mg/m² (max. 2 mg) IV push on days 1 and 8
– prednisone 40 mg/m² orally on days 1–15
– dacarbazine 250 mg/m² IV infusion on days 1–3

Review of benefits and harms

Survival benefits

Special consideration is given to treatment of paediatric patients with HL in relation to the late effects of high cumulative doses of chemotherapy and high doses of irradiation: increased risk of second malignancies and risk of infertility and cardiomyopathy. Paediatric regimens for HL reduce dose and volume of radiation and reduce exposure to anthracyclines and alkylating agents compared with adult regimens.

Radiotherapy usage varies considerably. The Children's Oncology Group recently reported that radiotherapy may be safely omitted in intermediate-risk patients in whom CT scans reveal a rapid reduction in tumour dimensions after two cycles of chemotherapy (*569*). The European Consortium has omitted radiotherapy for low-risk patients achieving a complete remission after two cycles of OEPA (*572*). In general, paediatric radiotherapy approaches use lower doses (15–25 Gy) and smaller fields (involved-field or nodes) than adult radiotherapy.

For treatment of cHL, the application identified numerous trials that have used different chemotherapy regimens of varying dose intensity and that have significantly different criteria for omission of radiotherapy.

The GPOH-HD-2002 study investigated OEPA (vincristine, etoposide, prednisone, doxorubicin) for treatment of low-risk patients, and OEPA with COPDac (cyclophosphamide, vincristine, prednisone, dacarbazine) for treatment of intermediate- and high-risk patient groups (*572*). This study enrolled 573 paediatric patients who received two courses of either OEPA (boys) or OPPA (vincristine, procarbazine, prednisone and doxorubicin) (girls) as induction therapy. Patients with intermediate-stage (TG-2) and advanced-stage (TG-3) disease received a further two or four cycles of COPP (cyclophosphamide, vincristine, procarbazine and prednisone) (girls) or COPDac (boys) respectively. With the exception of patients with early-stage (TG-1) disease in complete remission following chemotherapy, all patients received involved-field radiation after induction chemotherapy.

After 5 years, the overall survival (OS) rate (± standard error) was 97.4% (± 0.7%) and the event-free survival (EFS) rate was 89.0% (± 1.4%) (*572*). In TG-1, overall EFS was 92.0% ± 2.0%. In patients who received no irradiation EFS (93.2% ± 3.3%) was similar to that in irradiated patients (91.7% ± 2.5%). In TG-2 and TG-3, EFS did not differ significantly between boys and girls (90.2% ± 2.3 vs 84.7% ± 2.7, respectively; $P = 0.12$).

Similar results were observed in the GPOH-HD-95 study of 1018 children and adolescents with HL (*583*). In this study, TG-1 disease was treated with two cycles of OPPA (girls) or OEPA (boys); TG-2 and TG-3 disease was treated with two cycles of OPPA or OEPA followed by an additional two or four cycles of COPP, for TG-2 and TG-3 stage disease respectively. Patients achieving complete remission did not receive radiation; all other patients received local radiotherapy to the initially involved sites, with the dose depending on the tumour response. After 5 years, the probability of EFS was 0.88 and the probability of OS was 0.97. There was no difference in the probability of disease-free survival between irradiated and non-irradiated TG-1 patients (0.97 vs 0.94). In the other treatment groups, disease-free survival was significantly worse for non-irradiated patients than for those who received radiation.

The Children's Oncology Group protocol AHOD0431 investigated the rate of induction of complete response after three cycles of AVPC (doxorubicin, vincristine, prednisone, cyclophosphamide) in a single-arm study of 287 subjects aged 21 years or less with newly diagnosed low-risk HL (*570*). At 2 years, EFS was 84% and OS was 100%. Similar results were observed in a prospective trial of 180 patients with lymphocyte predominant HL (LPHL) (*578*). Of the 137 patients who received three cycles of AVPC, 4-year EFS was 86.6%; OS at 4 years for the entire cohort was 100%. Surgery alone could be considered for completely resected stage I LPHL.

The benefit of early chemotherapy was demonstrated in AHOD0031 a large randomized phase III study that evaluated the role of early chemotherapy response in tailoring subsequent therapy in 1712 paediatric patients with intermediate-risk HL (*569*). Response following two cycles of ABVE-PC was evaluated. Rapid early responders received two additional cycles of the same chemotherapy, followed by evaluation for complete response. Patients achieving a complete response were then randomly assigned to radiation or no additional therapy. All patients achieving less than a complete response received radiation. Slow early responders received two additional cycles of ABVE-PC with or without two cycles of DECA (dexamethasone, etoposide, cisplatin and cytarabine), followed by radiation. Four-year EFS and OS were 85% and 97.8%, respectively. Among slow early responders, EFS and OS for those receiving DECA were similar to those in patients who did not receive DECA (OS: DECA 96.5% (95% CI: 91.7–98.5%); non-DECA 94.3% (95% CI: 88.9–97.1%; $P = 0.16$). This trial demonstrated that early response assessment supported chemotherapeutic

titration, augmenting chemotherapy in selected slow early responders with PET-positive disease.

Radiation can probably be restricted to those patients with a less than complete response after three cycles of chemotherapy. This approach eliminates the requirement for radiation for more than 90% of patients.

For intermediate- and high-risk disease, the Children's Oncology Group has primarily evaluated ABVE-PC and its derivatives across the risk groups (*575*, *576*, *578*). In the P9425 study (*575*), 216 patients aged less than 22 years with intermediate- or high-risk HL were given ABVE-PC every 21 days for three cycles. Rapid early responders received radiation therapy, while slow early responders received an additional two cycles of ABVE-PC and then radiation. Five-year EFS was 86% for rapid early responders and 83% for slow early responders. Five-year OS was 95%. In the P9426 study, patients received two cycles of chemotherapy consisting of doxorubicin, bleomycin, vincristine, and etoposide (*576*). Rapid early responders received radiation therapy, while patients with partial response or stable disease received two more cycles of chemotherapy and radiation therapy. Rapid-responding patients had the same outcome as slower-responding patients despite receiving half as much chemotherapy.

The efficacy of AV-PC (doxorubicin, vincristine, prednisone, cyclophosphamide) was also studied in low-risk NLPHL (*578*). Patients were treated with limited (three cycles) chemotherapy and those with less than complete response also received radiation therapy. Four-year EFS for the entire cohort of 180 patients was 86.2% and the OS 100%. Again, the majority of patients could avoid radiotherapy, limiting salvage therapy to the few relapsing cases.

The overall 5-year relative survival for 2002–2008 from the SEER database was 84.7%. Children and adolescents have significantly better HL-specific survival than adults (5-year survival rate 96% ± 0.4% vs. 88% ± 0.3%, $P < 0.001$) (*568*).

Harms and toxicity considerations

Common

Paediatric patients receiving combination chemotherapy for HL will experience significant haematotoxicity, including severe neutropenia – increasing the risk of infection – and high incidences of anaemia and thrombocytopenia. The incidence of serious infection, including sepsis, is relatively high, occurring in 8–17% of patients (*569*, *575*). Many patients also experience stomatitis and mucositis from combined therapy.

Vincristine commonly causes neurotoxicity, including sensory and motor neuropathies, which is typically dose-related. Neurotoxicity is usually reversible and in the regimens described above is typically mild. A small percentage (up to 2%) of patients experience hypersensitivity reactions to intravenous etoposide, which may include angioedema, bronchospasm and/or chest discomfort (*469*).

Serious

Patients should be monitored for symptoms that indicate the existence of long-term toxicity, particularly of heart and lung, as well as secondary malignancy. Treatment with bleomycin may result in late bleomycin-related pulmonary toxicity; a high index of suspicion is therefore warranted, to allow omission of this drug as early as possible when toxicity occurs.

Doxorubicin is associated with a risk of cardiotoxicity. Development of severe heart failure is uncommon, but myocardial dysfunction may appear in long-term follow-up. In paediatric patients, the risk of heart failure and pericardial disease increases with cumulative doses ≥ 250 mg/m² (*273*).

Survivors are also at risk of secondary malignancy, associated most commonly with etoposide and dacarbazine in the regimens described above. Although the risk remains small (< 3% in the paediatric HL trials listed), patients should be closely monitored for this development (*569*, *575*). Survivors are also at risk for infertility, most notably from cyclophosphamide.

Recommendations

On the basis of the evidence presented in the application, the Expert Committee recommended the addition of vincristine, doxorubicin, cyclophosphamide, prednisolone, etoposide, bleomycin and dacarbazine to the complementary list of the EMLc for the treatment of paediatric patients with Hodgkin lymphoma.

The Committee noted that regimens using these medicines are highly effective but also considered that the alternative regimen of ABVD (considered by the Committee and recommended for EML inclusion in adult patients) is also effective in paediatric patients, and may be more suitable for use in developing countries where therapies of shorter duration may be beneficial and where facilities for management of acute toxicities may be less readily available. The Committee therefore also endorsed the inclusion in the EMLc of vinblastine for the indication of Hodgkin lymphoma.

The Committee also considered it appropriate to include these medicines in the adult EML for HL for the treatment of adolescents over 12 years because the evidence supporting use of these regimens is from trials that included patients up to 21 years of age. This requires endorsement of vincristine, cyclophosphamide, etoposide and prednisolone for this condition on the EML.

Kaposi sarcoma – EML

The application sought the inclusion on the WHO Model List of Essential Medicines of bleomycin, doxorubicin, paclitaxel, vinblastine and vincristine for the treatment of Kaposi sarcoma.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Kaposi sarcoma is a vascular tumour that arises in multifocal sites. The skin is most commonly involved, although almost any organ, except perhaps the brain, can be involved. It exists in four forms, based on varying clinical characteristics and risk factors – classic; endemic African; secondary to iatrogenic immunosuppression; and HIV/AIDS-related (*584*).

Classic Kaposi sarcoma affects elderly, immunocompetent individuals of Mediterranean or eastern European descent. It is a slow-progressing and relatively benign form of the cancer. Endemic or African Kaposi sarcoma is most common in central and eastern Africa and affects adults primarily. Iatrogenic Kaposi sarcoma is found in populations with compromised immune systems, primarily patients who have received organ transplants. HIV/AIDS-related Kaposi sarcoma (AIDS-KS) develops in populations infected with HIV-AIDS; in developed countries, it is most commonly found in HIV-infected men who have sex with men.

Kaposi sarcoma (KS) is the most common tumour in HIV-infected individuals in Africa (*585*). It was relatively common in central Africa before the HIV/AIDS epidemic, with an estimated incidence of more than 6 per 1000 individuals in Uganda, United Republic of Tanzania and Zaire (now the Democratic Republic of the Congo) (*586*). After the advent of HIV/AIDS, the incidence increased dramatically (*587*). A study by Onyango et al. showed that mucocutaneous KS diagnosed from 1968 to 1997 at Kenyatta National Hospital, Nairobi, represented 2–5% of all malignancies (*588*). In certain African countries with high rates of HIV, AIDS-KS affects men and women equally, and there is also a high incidence in children (*584*).

Patients with aggressive forms of KS are commonly treated with paclitaxel, or doxorubicin (or liposomal doxorubicin), bleomycin and vinblastine (or vincristine) (ABV). The ABV regimen has been shown to give better response rates than BV (bleomycin + vinblastine/vincristine) alone (*589*, *590*); however, this regimen was unpopular because of toxicity (*589*).

Paclitaxel, with response rates ranging from 59% to 71% when given without HAART (highly active antiretroviral therapy) (*591*, *592*), is considered the most attractive agent since it is both effective and tolerable over long-term

administration, especially when combined with growth factors (*591*, *593*). For this reason, the application requested that paclitaxel be added to the EML.

Liposomal daunorubicin and pegylated liposomal doxorubicin are popular in high-income countries because of their better toxicity profile and their efficacy, which is similar to that of ABV. However, no studies support the superiority of these agents when compared with ABV or doxorubicin (*589*, *594*). Moreover, they are more costly and, without clear, proved incremental benefit over other regimens, they are not proposed for inclusion in the EML.

It has been noted that HAART alone improves the outcome of HIV-KS (*595*, *596*). In South Africa, addition of chemotherapy to HAART has achieved better KS response over 12 months compared with HAART alone (*590*).

Public health relevance

KS is a relatively rare cancer worldwide. GLOBOCAN estimated 44 247 new cases and 26 974 deaths worldwide in 2012 (*255*). Data for 2012 data show 40 874 new cases in less developed regions and 3373 new cases in more developed regions. The African continent is disproportionately affected: 85% of all cases occur here. The risk for men of developing KS is approximately twice that for women worldwide. In classic KS, however, the male:female ratio is about 10:1.

Requirements for diagnosis, treatment, and monitoring

Diagnostics

The principal diagnostic feature of KS is erythematous, violaceous cutaneous lesions, which can be macular, patch, plaque, nodular or exophytic. The lesions can be solitary, localized or disseminated. Against a background of HIV/AIDS, this should alert the physician to the diagnosis of KS. The presence of local/regional lymphoedema supports the diagnosis. However, tissue confirmation is mandatory before any form of therapy is instituted.

Skin biopsy by local punch biopsy or, rarely, excision biopsy is recommended. Lymph node excision can also be done in predominantly nodal lesions. Endoscopic biopsies may be required for lesions presenting solely in visceral lumens. Pathological examination of tissues should be carried out by an experienced histopathologist.

Testing

Any patient with a diagnosis of KS must be tested for HIV. Positive cases must have differential lymphocyte counts and where possible HIV viral load assessment performed. Patients are often anaemic, thrombocytopenic or neutropenic, and complete blood counts must be performed. Renal function studies must be carried out, because there may be various forms of kidney

injury. Liver function tests and coagulation assays are also essential. Cardiac function should be assessed because the anthracycline doxorubicin, pegylated or not, which is a key agent in the management of KS, carries an attendant risk of cardiotoxicity.

Patients with HIV/AIDS commonly have concurrent opportunistic infections including tuberculosis and opportunistic tumours including aggressive subtypes of B-cell lymphomas. Concurrent diseases have significant implications for the treatment approaches, and appropriate imaging should therefore be carried out.

Solitary, asymptomatic, nonulcerated patch lesions can be managed simply with appropriate combination antiretroviral therapy. Surgical excision may have a role if lesions are raised and/or symptomatic, although this is controversial, since there is a tendency for new lesions to spring up from the excision wound edges. Locoregional lesions can be appropriately managed with radiation.

Administration and care of patients

Clinical needs include the ability to manage patients with HIV who are on antiretroviral therapy and deal with the various issues associated with that treatment. Facilities need to be capable of providing additional services for HIV-positive patients, including monitoring of CD4 counts and organ function, and management of HIV-related infectious complications. Management of cytopenias related to HIV and cytotoxic agents is paramount.

Treatment with the regimens described requires safe and effective ordering, preparation and administration of parenteral chemotherapy. Care and skill in the administration of vesicants such as vincristine and doxorubicin is needed. Specifically, the capacity for clinical and laboratory assessment is required, as well as the infrastructure to deliver parenteral chemotherapy and to manage potential allergic reactions to taxanes, bleomycin and other drugs. Skills in management of potential lung toxicity from bleomycin and of potential neurotoxicity from vincristine and taxanes are needed.

Overview of regimens

The following provides basic information on administration and dosing of standard and alternative chemotherapy regimens for KS; no details are given of ancillary medications pertaining to the management of adverse events. Treatment duration is based on clinical judgement.

The addition of liposomal doxorubicin preparations is acceptable for treatment of KS, and in some patients the toxicity profile is favourable; however, efficacy is no greater than that of the other regimens described (*597*), and the cost is considerably higher. These preparations were therefore not proposed as

standard of care at the time of the application, nor were they recommended for inclusion in the EML.

Standard regimen

- **Paclitaxel**
  - paclitaxel 100 mg/m² IV infusion every 2 weeks
  - paclitaxel 135 mg/m² IV infusion every 3 weeks

Alternative regimens (if paclitaxel is unavailable or not tolerated)

- **Vincristine: 6 cycles**
  - vincristine 1.4 mg/m² IV bolus every 2 weeks
- **Vincristine/bleomycin: 6 cycles**
  - vincristine 1.4 mg/m² IV bolus every 2 weeks
  - bleomycin 10 IU/m² IV bolus every 2 weeks
- **ABV for HIV-positive patients: 6 cycles**
  - vinblastine 6 mg/m² IV bolus every 2 weeks
  - bleomycin 10 IU/m² IV bolus every 2 weeks
  - doxorubicin 25 mg/m² IV infusion every 2 weeks
- **ABV for HIV-negative patients: 6 cycles**
  - vinblastine 6 mg/m² IV bolus every 3 weeks
  - bleomycin 10 IU/m² IV bolus every 3 weeks
  - doxorubicin 50 mg/m² IV infusion every 3 weeks

Review of benefits and harms

Benefits

The treatment of HIV-KS is basically palliative – complete remission is not a realistic goal. Various treatment regimens are available, with differing response rates and toxicity profiles.

In high-income countries, where patients with HIV-KS are likely to present with disease that is not widespread, response rates ranging between 22% and 80% have been reported with combined antiretroviral therapy alone (*595*, *598*, *599*). The same is highly unlikely to be true of low-income countries, where patients present with bulky, advanced disease (*590*). Krown and colleagues noted that it was extremely rare for patients with extensive KS and poor prognosis to respond to HAART alone (*600*).

HAART plus chemotherapy may be beneficial in reducing disease progression compared with HAART alone in patients with severe or progressive KS. A Cochrane systematic review of six randomized controlled trials and three observational studies compared HAART plus chemotherapy with HAART alone in patients with severe KS (*597*). The review found that HAART plus chemotherapy was associated with reduced disease progression compared with HAART alone. Chemotherapy regimens used included medicines proposed for inclusion on the EML. For example, the comparison by Mosam et al. demonstrated a significant reduction in progressive disease in patients treated with HAART plus ABV compared with those given HAART alone (risk ratio (RR) 0.10; 95% CI: 0.01–0.75) (*590*). However, no statistically significant reduction in mortality or difference in adverse events was observed. With regard to different chemotherapy regimens for patients on HAART with severe KS, there was no large observed difference between liposomal doxorubicin, liposomal daunorubicin and paclitaxel (*597*).

Paclitaxel, with complete or partial response rates ranging from 59% to 71% when given without HAART in patients with previously treated severe KS (*591*, *592*), could be considered an attractive option. It is effective and tolerable over prolonged administration, especially when haematopoietic growth factor support is incorporated (*591*, *593*).

Harms and toxicity considerations

Common

Vinca alkaloids, including vincristine and vinblastine, are associated with a high incidence of neurotoxicity, typically manifesting as sensory neuropathy, which is usually reversible (*274*). This neuropathy also reduces gastrointestinal transit time and, specifically with vincristine and vinblastine, leads to constipation, which may warrant prophylaxis (*396*).

Patients with KS treated with paclitaxel commonly experience alopecia, myelosuppression including neutropenia, anaemia and thrombocytopenia, and mild peripheral neuropathy (*591*). Paclitaxel administration requires premedication with glucocorticoids and antihistamines to reduce the risk of infusion reactions.

Serious

Myelosuppression with paclitaxel, pegylated liposomal doxorubicin and/or vinblastine can be severe and may lead to an increased risk of opportunistic or other serious infections (*591*, *594*).

Bleomycin is associated with rare but potentially serious cases of pulmonary fibrosis (*594*, *601*). The risk of toxicity is dose-dependent, increasing

with cumulative doses above 400 IU; at the doses used in the regimens detailed above, therefore, bleomycin carries very little risk of this adverse event.

Doxorubicin can lead to long-term cardiomyopathy when cumulative doses exceed 450 mg/m². This risk is dose-dependent, however, and at the doses delivered in the regimens detailed above (< 300 mg/m²), the risk is small (*273*, *594*).

Recommendations

The Expert Committee noted that all medicines proposed in the application for treatment of Kaposi sarcoma are currently listed on the complementary list of the Model List of Essential Medicines. On the basis of the evidence presented, the Committee recommended that paclitaxel, vincristine, vinblastine, bleomycin and doxorubicin be specifically endorsed on the Model List for the treatment of Kaposi sarcoma.

The Committee also noted that chemotherapy in combination with HAART is associated with improved outcomes for patients with Kaposi sarcoma, and considered that combination therapy should be used whenever clinically appropriate and possible.

Metastatic breast cancer – EML

For the treatment of metastatic breast cancer, the application sought inclusion on the core list of the Model List of Essential Medicines of chemotherapy regimens utilizing cyclophosphamide, doxorubicin, paclitaxel or docetaxel, vinorelbine, capecitabine and gemcitabine administered as single agents, sequentially, for treatment of HER2-negative disease, trastuzumab (in combination with a taxane, vinorelbine or capecitabine) for patients with HER2-positive disease, and hormone therapies tamoxifen and anastrozole (as representative of the pharmacological class of aromatase inhibitors) for patients with hormone receptor-positive disease.

Cyclophosphamide, doxorubicin, paclitaxel, docetaxel and tamoxifen are currently included in the complementary list of the Model List. Vinorelbine, capecitabine, gemcitabine, trastuzumab and anastrozole were proposed for addition.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Metastatic breast cancer is defined as disease beyond the breast and regional lymph nodes. Breast cancer can metastasize to any site in the body, including bones, liver, lung, serosal surfaces and brain. Although metastatic breast cancer is generally incurable, survival is highly variable: treatment is almost always indicated and patients can be treated and given palliative support with hormonal therapy, chemotherapy and/or targeted agents (*602*, *603*).

Breast cancer is no longer viewed as a single disease but rather as a series of diseases defined by biological characteristics. Hormone receptor (HR) positive tumours demonstrate positivity for either estrogen receptors or progesterone receptors. Human epidermal growth factor receptor 2 (HER2) positive tumours overexpress the receptor HER2. Patients with HER2-positive disease typically have a worse prognosis.

Breast cancer can be viewed as four subtypes, as follows:

1. HR-positive/HER2-negative
2. HR-positive/HER2-positive
3. HR-negative/HER2-positive
4. HR-negative/HER2-negative.

These biological subtypes help predict which therapies are likely to be efficacious. Hormone therapy is beneficial only for patients with HR-positive tumours, and trastuzumab and similar HER2-targeted therapies are helpful only in patients with HER2-positive cancers.

Public health relevance

Breast cancer comprises one-quarter of all new cancer cases worldwide including women and men, with an estimated 1.67 million cases in 2012 alone according to GLOBOCAN 2012, the database of the International Agency for Research on Cancer. Although highly treatable with systemic therapy, surgery and radiation therapy, breast cancer was the cause of death of approximately half a million women worldwide in 2012 (*255*). In sub-Saharan Africa alone, it is believed that nearly 50 000 women died from the disease during that one year. The ratio of incidence to mortality in high-, middle- and low-income countries varies dramatically, reflecting disparities in access to resources, clinical knowledge and medicines (as is the case for all cancers). According to one study in 2010, the 5-year survival rate for breast cancer ranged from 12% in Gambia, an extremely poor country, to 79% in the Republic of Korea, a high-income country (*354*). It has been noted that women suffering from breast cancer in the developing world are more likely to present to health facilities at later stages because of structural barriers to care, absence of treatment options, or inadequate information being disseminated to the public (*604*). Women who receive treatment for early-stage breast cancer have a significantly higher chance of survival than those treated for metastatic disease. Even in less developed regions of the world, overall survival at 5 years for women treated for localized disease was 73.6% on average, compared with 47.4% for regional disease (*354*).

Requirements for diagnosis, treatment, and monitoring

Diagnostics

The treatment of breast cancer should always be determined by pathological evaluation of the primary cancer. It is recommended that biopsy be performed by ultrasound-guided core needle technique, which will generally yield adequate tissue for histological and marker studies. Fine-needle aspiration can play a role but does not allow a distinction between in-situ and invasive cancer and often does not give adequate material for immunohistochemistry. Surgical excision should be required only rarely, if needle biopsy is technically not feasible. Evaluation of the biopsy by an experienced pathologist will yield the histological subtype and grade of the cancer. Immunohistochemistry (IHC) analysis for estrogen receptors, and in some cases progesterone receptors, is critical since this will determine prognosis and whether the cancer is potentially sensitive to hormone therapy. HER2 can be assessed by either IHC or by fluorescence in situ hybridization if IHC is equivocal.

Testing

Staging should be performed to assess the extent of disease. Computerized tomography (CT) scans and bone scans can delineate the extent of metastatic

disease. In more resource-constrained settings, a chest X-ray, liver ultrasound and plain films of bones that are painful are acceptable.

Administration and care of patients

Hormone therapies (tamoxifen and aromatase inhibitors) are largely administered orally. No special testing or administrative resources are necessary for the use of these drugs, although a reliable supply is important.

Cytotoxic chemotherapy requires the ability to administer intravenous chemotherapy, with particular consideration of avoidance of extravasation with doxorubicin and of allergic reactions with taxanes. Chemotherapy can be administered in an outpatient infusion setting or an inpatient setting. Intravenous fluids and antiemetics, as well as hypersensitivity medications, are required. Monitoring of complete blood count, renal function, electrolytes and liver functions tests are required.

Trastuzumab and similar anti-HER2 targeted therapies are generally administered intravenously. Administration is relatively straightforward and is usually done in outpatient infusion facilities.

Cardiac monitoring is recommended for patients receiving trastuzumab or an anthracycline, although the incidence of serious cardiac toxicity is low – especially if anthracycline doses remain below cumulatively toxic levels – and the potential benefit in disease control is substantial.

As with all cancer treatment, social support, clean water and adequate nutrition are essential.

Overview of regimens

The following provides basic information on administration and dosing for the four biological subtypes of breast cancer, followed by specific regimens.

HR-positive/HER2-negative tumours

Premenopausal patients should be treated initially with hormonal therapy, preferably tamoxifen, unless they were on tamoxifen at the time of the development of metastatic disease. Patients who are tolerating tamoxifen should be treated until there are clear signs of tumour progression. Stable disease is an indication to continue tamoxifen therapy. Aromatase inhibitors are not recommended for premenopausal women who should undergo either oophorectomy or ovarian suppression with a luteinizing hormone-releasing hormone agonist.

Women who are postmenopausal (naturally, surgically or chemically) can be treated with tamoxifen or an aromatase inhibitor. If they were on tamoxifen at the time of development of metastatic disease, they should be treated with an aromatase inhibitor. Treatment should continue until there is clear evidence of tumour progression, at which time the patient should be

converted to the other agent (from tamoxifen to an aromatase inhibitor or vice versa). Stable disease is an indication to continue hormone therapy.

At the time of tumour progression, sequential single-agent chemotherapy should be used, unless there is rapidly progressive disease or high disease burden that requires a rapid response, in which case combination chemotherapy can be used (*602*). Patients who were treated in the adjuvant setting with chemotherapy 12 months or less from the time of developing metastatic disease should be treated with chemotherapy agents other than those received in the adjuvant setting.

HR-positive/HER2-positive tumours

As above, hormone therapy should always be a component of the therapy for these patients; the factors that determine choice of therapy are the same as for patients with HR-positive/HER2-negative tumours.

Chemotherapy and trastuzumab should be initiated concurrently with hormone therapy. Typically trastuzumab is given concurrently with a taxane and not given concurrently with an anthracycline; however, trastuzumab can be given concurrently with other cytotoxic agents, such as vinorelbine.

HR-negative/HER2-positive tumours

Hormone therapy is not indicated. Trastuzumab chemotherapy combinations as described above for patients with HR-positive/HER2-positive tumours are indicated.

HR-negative/HER2-negative tumours

Hormone therapies and trastuzumab-containing regimens are not indicated for these patients. Sequential single-agent chemotherapy should be used, unless there is need for rapid control of disease due to visceral crisis or very high tumour burden (*602*, *605*). The application stated that choice among recommended chemotherapeutic agents is arbitrary – there are no data to suggest that initial treatment with one agent is more efficacious than another. The only exception is that patients who were treated in the adjuvant setting with chemotherapy 12 months or less from the time of developing metastatic disease should be treated with agents other than those received in the adjuvant setting.

Standard chemotherapy regimens (non-trastuzumab regimens)

- **Doxorubicin, for subtypes 1 and 4 (and 2 and 3 if trastuzumab is unavailable)**
  - doxorubicin 60 mg/m² IV every 3 weeks

  Note: Cumulative dose of doxorubicin should not exceed 450 mg/m² because of the increased likelihood of severe cardiomyopathy with increasing dose.

- **Paclitaxel, for subtypes 1 and 4 (and 2 and 3 if trastuzumab is unavailable)**
  - paclitaxel 175 mg/m² IV every 3 weeks[8]

  or
  - paclitaxel 80 mg/m² IV weekly

Standard regimens including trastuzumab, for HER2-positive disease

- **Paclitaxel and trastuzumab, for subtypes 2 and 3**
  - paclitaxel 80 mg/m² IV weekly
  - trastuzumab 2 mg/kg IV weekly (following loading dose of 4 mg/kg)
- **Docetaxel and trastuzumab, for subtypes 2 and 3**
  - docetaxel 60–75 mg/m² IV every 3 weeks
  - trastuzumab 6 mg/kg IV every 3 weeks (following loading dose of 8 mg/kg)

Single-agent chemotherapy regimens, for HER2-negative disease

The application stated that capecitabine, vinorelbine and gemcitabine have all been shown to have activity for patients with metastatic breast cancer, and can be supported to be given as single agents for patients with HER2-negative breast cancer. For patients with HER2-positive breast cancer trastuzumab has also been given with vinorelbine, successfully. These regimens are listed below.

- **Capecitabine (single agent)**
  - capecitabine 2000 mg/m² per day orally in two divided doses on days 1–14 of 21-day cycle
- **Vinorelbine (single agent)**
  - vinorelbine 25 mg/m² IV weekly
- **Gemcitabine (single agent)**
  - gemcitabine 1000 mg/m² IV on days 1 and 8 of 21-day cycle
- **Cyclophosphamide (single agent)**
  - cyclophosphamide 1000 mg/m² IV on day 1 of a 21-day cycle

[8] Weekly paclitaxel is the more efficacious option but requires more frequent visits.

Capecitabine is an alternative to paclitaxel in patients for whom anthracycline treatment has failed and for elderly patients or women wishing to avoid the adverse effects associated with cyclophosphamide, methotrexate and fluorouracil (*606*). Compared indirectly with vinorelbine, capecitabine was associated with lower costs and improved patient outcomes (*607*). Vinorelbine has a similar efficacy and toxicity profile to standard first-line chemotherapy with anthracyclines and other non-taxane-containing regimens (*608*).

Single-agent chemotherapy regimens, for HER2-positive disease

- **Vinorelbine (with trastuzumab)**
  - vinorelbine 25 mg/m² IV weekly

  with either
  - trastuzumab 2 mg/kg IV weekly (following loading dose of 4 mg/kg)

  or
  - trastuzumab 6 mg/kg IV every 3 weeks (following loading dose of 8 mg/kg)

Standard hormone regimens

- tamoxifen 20 mg/day orally until tumour progression

or

- anastrozole 1 mg/day orally until tumour progression

Aromatase inhibitors should be used only in postmenopausal women (natural or surgical) or premenopausal women who are receiving ovarian suppression.

Premenopausal women should receive tamoxifen, in addition to ovarian ablation (surgical) or ovarian suppression, until tumour progression. Postmenopausal women can be treated with either tamoxifen or an aromatase inhibitor, but not both concurrently. If there is tumour progression during treatment with one of these agents, that agent should be stopped and the other initiated. Sequential use of these agents results in increased survival and improved quality of life: delay in time to tumour progression results in increased time until use of chemotherapy becomes necessary (*609*).

Review of benefits and harms

Benefits

Hormone therapy will yield clinical benefit for approximately half of the patients who have tumours that are estrogen- and/or progesterone-receptor-positive.

Clinical benefit is defined by either reduction in tumour size or disease stability for at least several months. Patients who experience clinical benefit generally have a reduction in symptoms, improved quality of life and prolonged survival.

For about one third of patients who have had progressive disease on hormone therapy or have estrogen- and/or progesterone-receptor-negative disease, chemotherapy can lead to a reduction in tumour burden. Patients who benefit from chemotherapy have a reduction in symptoms, improved quality of life and a modest prolongation of survival.

A 2013 Cochrane systematic review of 12 trials comparing combination with sequential single-agent chemotherapy for metastatic breast cancer found there to be no difference in overall survival between the two groups (hazard ratio (HR) 1.04; 95% CI: 0.93–1.16; $P = 0.45$). The review also found some evidence of a higher risk of progression in the combination arm (HR 1.11; 95% CI: 0.99–1.25; $P = 0.08$). Overall tumour response rates were higher in the combination arm (RR 1.16; 95% CI: 1.06–1.28; $P = 0.001$), as was the risk of febrile neutropenia (risk ratio (RR) 1.32; 95% CI: 1.06–1.65; $P = 0.01$). The authors concluded that the findings supported recommendations in international guidelines for the use of sequential monotherapy unless there is rapid disease progression (*605*).

The Expert Committee considered that the evidence showed that gemcitabine is not a highly effective treatment for metastatic breast cancer. A meta-analysis of nine randomized controlled trials (2651 patients) revealed that, compared with gemcitabine-free chemotherapy, gemcitabine-based therapy offered no improvement in terms of time to progression (HR 0.91; 95% CI: 0.72–1.15; $P = 0.44$) or overall survival (HR 1.05; 95% CI: 0.88–1.25; $P = 0.60$) (*610*). The rates of grade 3 and 4 anaemia (HR 2.02; 95% CI: 1.35–3.02; $P = 0.006$), neutropenia (HR 2.33; 95% CI: 1.37–3.63; $P = 0.01$) and thrombocytopenia (HR 8.31; 95% CI: 5.00–13.82; $P < 0.0001$) were significantly higher in the gemcitabine-based arm. The authors concluded that gemcitabine-based chemotherapy was as effective as gemcitabine-free chemotherapy in patients with metastatic breast cancer but with increased haematological toxicity.

For patients with HER2-positive disease, the addition of trastuzumab to chemotherapy dramatically increases the response rate and overall survival. Typically, trastuzumab is given concurrently with a taxane, but patients may be treated with trastuzumab and vinorelbine or capecitabine (*602*).

A Cochrane systematic review of seven randomized controlled trials comparing trastuzumab alone or in combination with chemotherapy, hormonal therapy or targeted agents against the same regimen without trastuzumab (control) in 1497 women with HER2-positive metastatic breast cancer reported that adjuvant trastuzumab as first-line treatment improves survival but may increase the risk of heart failure (*611*). Trastuzumab-containing regimens were favoured for overall survival and progression-free survival (HR 0.82;

95% CI: 0.71–0.94, $P = 0.004$; and HR 0.61; 95% CI: 0.54–0.70, $P < 0.00001$, respectively; moderate-quality evidence). Trastuzumab was associated with increasing rates of heart failure (RR 3.49; 90% CI: 1.88–6.47, $P = 0.0009$; moderate-quality evidence) and left ventricular ejection fraction decline (RR 2.65; 90% CI: 1.48–4.74; $P = 0.006$). The authors concluded that studies that administered trastuzumab as first-line treatment, or along with a taxane-based regimen, improved mortality outcomes. The evidence to support the use of trastuzumab beyond progression is limited.

The Committee noted that, since submission of the application, final results of the CLEOPATRA study have been published (*612*). This study compared the efficacy and safety of pertuzumab, trastuzumab and docetaxel versus placebo, trastuzumab and docetaxel as first-line treatments in patients with HER2-positive metastatic breast cancer. Deaths were reported in 168/402 patients (41.8%) in the pertuzumab group and in 221/406 patients (54.4%) patients in the control group (HR favouring the pertuzumab group, 0.68; 95% CI: 0.56–0.84; $P < 0.001$). The difference in median overall survival between the two groups was 15.7 months: 56.5 months (95% CI: 49.3 to not reached) in the pertuzumab group and 40.8 months (95% CI: 35.8–48.3) in the placebo group (HR favouring the pertuzumab group 0.68; 95% CI: 0.56–0.84; $P < 0.001$). The Expert Committee considered that the CLEOPATRA results are notable for their clinical relevance, but further efficacy and safety data from clinical trials other than single sponsor-driven trials are needed. In particular, the Committee considered that additional evidence is needed in women previously exposed to trastuzumab in the adjuvant setting. Pertuzumab was neither proposed nor recommended for inclusion in the EML at this time.

Harms and toxicity considerations

Common

Risks of treatment include common short-term toxicities such as alopecia, neutropenia, fever and infection, and neuropathy (affecting 15–60% of patients) from taxanes. Paclitaxel and trastuzumab are both associated with infusion reactions in up to 30–40% of patients; most infusion reactions are mild and easily managed (*367*, *368*).

Tamoxifen can cause hot flushes, mood changes and, rarely, thromboembolic disease and endometrial cancer; it generally has a positive effect on bone density. Aromatase inhibitors can cause hot flushes, mood changes, musculoskeletal complaints and bone loss.

Vinorelbine often causes severe neutropenia and granulocytopenia, which increase patients' risk of infection. Like other vinca alkaloids, vinorelbine also frequently causes constipation. It is a strong vesicant, and care must be taken to avoid extravasation and associated tissue damage (*613*).

Palmar–plantar erythrodysaesthesia (hand–foot syndrome) is associated with capecitabine, with an increased incidence of up to 60% in patients treated with capecitabine. This adverse effect typically resolves following interruption of treatment (*397*).

Gemcitabine frequently causes myelosuppression with dose-limiting thrombocytopenia and leukopenia with associated risk of infection. Gemcitabine is also associated with increased hepatic transaminases, which may lead to more severe hepatotoxicity in up to 10% of patients. Many patients experience oedema and dyspnoea (*614*).

Serious

Cardiac muscle suppression or cardiac damage can occur after therapy with anthracyclines and trastuzumab, and administration of both agents together increases the risk. For the regimens described above, the risk of congestive heart failure is small and reversible upon discontinuation in most cases (*273*, *357*, *369*). Rare incidences of bone marrow damage, myelodysplastic syndrome and acute leukaemia can occur after therapy with doxorubicin. Diarrhoea occurs in up to 50% of patients treated with capecitabine. Diarrhoea can be severe, may require hospital admission for intravenous fluid replacement and is often dose-limiting (*396*).

Recommendations

On the basis of the evidence presented in the application, the Committee made the following recommendations in relation to treatments for metastatic breast cancer:

- Trastuzumab should be added to the complementary list of the EML for the treatment of HER2-positive metastatic breast cancer.
- Capecitabine and intravenous vinorelbine should be added to the complementary list of the EML for the treatment of metastatic breast cancer. The Committee noted that orally administered vinorelbine is better tolerated but is more costly, so recommended inclusion only of the intravenous formulation of vinorelbine at this time.
- Doxorubicin, paclitaxel, docetaxel and cyclophosphamide, currently on the complementary list, should be endorsed for use in the treatment of metastatic breast cancer.
- Tamoxifen should be specifically endorsed for treatment of HR-positive metastatic breast cancer.

- Anastrozole should be added to the complementary Model List for treatment of HR- positive metastatic breast cancer, with a square box symbol as representative of the therapeutic class of aromatase inhibitors.
- Inclusion of gemcitabine on the Model List is not recommended at this time, as the available evidence did not support an advantage of gemcitabine-based therapy over gemcitabine-free therapy in terms of time to progression and overall survival.

Metastatic colorectal cancer – EML

The application sought endorsement of calcium folinate and fluorouracil, already listed on the complementary list of the Model List of Essential Medicines, for the treatment of metastatic colorectal cancer. The application also sought the addition of oxaliplatin, irinotecan and capecitabine to the core list of the Model List for the same indication.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Metastatic colorectal cancer (mCRC) is, with a few exceptions, an incurable illness. Palliative chemotherapy significantly improves survival and provides relief of symptoms in settings with sufficient resources to administer and handle the toxicities of treatment. Multiple chemotherapy regimens are effective. The least costly regimen shown to increase survival is 5-fluorouracil (5-FU)/calcium folinate. The efficacy of 5-FU/calcium folinate is improved, in a usually cost–effective manner, by combining it with oxaliplatin (FOLFOX regimen) or irinotecan (FOLFIRI). It is also thought that first and second lines of treatment should be seen as complementary for reaching maximum benefit from currently available palliative chemotherapy agents. Survival can be further improved, albeit to a small degree, by the first-line use of biological agents such as bevacizumab, cetuximab or panitumumab, followed by other newer agents such as ziv-aflibercept or regorafenib. However, these agents are not usually considered to be cost–effective.

Public health relevance

It has been estimated that worldwide there are 1.2 million new cases of colorectal cancer a year (*381*). Globally, colorectal cancer is the fourth most common cause of cancer-related deaths in men and the third in women, causing the deaths of an estimated 320 600 men and 288 100 women annually (*381*).

In the developed world, the death rate from colorectal cancer has been falling, largely as a result of colonoscopy screening, which enables both the removal of precancerous polyps and the detection of early-stage, curable disease. Because 90% of colon cancers occur in patients who are at least 50 years old, the recommendation in countries that are able to afford colonoscopy is for screening of the general population to begin at age 50 (*382*).

Because of the expense of colonoscopy, population-based screening programmes are usually not feasible in many parts of the world. With poor access to health care added to that, patients in low- and middle-income countries often present with more advanced stages of colorectal cancer.

In the United States, 40% of colorectal cancer patients have localized disease (stage I and II), 36% are regionally advanced (stage III) and 20% have metastases at presentation (*383*).

Requirements for diagnosis, treatment, and monitoring

Diagnostics and testing

The primary mass in colorectal cancer can be diagnosed by rectal examination, sigmoidoscopy or colonoscopy. A biopsy can be performed during endoscopy so that the diagnosis of cancer can be confirmed pathologically.

A critical aspect of evaluating patients with colorectal cancer is establishing whether they have metastatic disease. In high-resource health systems, computerized tomography scan of the chest, abdomen and pelvis is performed routinely. In resource-constrained settings systemic evaluation with less costly abdominal and pelvic ultrasound and a chest X-ray is commonly employed. Preoperative rectal cancer staging, which evaluates the T and N stage of the tumour, is also important in establishing the degree of loco-regional invasiveness of the tumour. Where available, it is performed by either rectal magnetic resonance imaging or endoscopic ultrasound – complex and highly specialized techniques with limited availability in resource-constrained settings.

When chemotherapy is employed, laboratory evaluations play an important role in monitoring patient safety. A complete blood count (CBC) with differential assesses whether patients are myelosuppressed and neutropenic. A comprehensive metabolic panel monitors renal and hepatic function as well as electrolyte imbalances.

Treatment

Palliative chemotherapy for mCRC has improved in stepwise fashion over the past several decades. Fluorouracil (5-FU) was the first cytotoxic chemotherapeutic agent shown to be effective in mCRC and arguably remains the most efficacious and cost–effective drug against colorectal cancer. Several clinical trials have tested the importance of combining calcium folinate, a reduced form of folate, with 5-FU. A meta-analysis showed that the response rate for 5-FU/calcium folinate is double that for 5-FU alone and also increases survival (*615*).

An integrated efficacy analysis of two large phase III trials of patients with mCRC showed the oral fluoropyrimidine capecitabine to be equivalent to intravenous 5-FU/calcium folinate in terms of time to disease progression and overall survival (OS) (*616*).

Subsequent cytotoxic chemotherapeutic agents, irinotecan and oxaliplatin, showed considerable efficacy when added to the 5-FU/calcium folinate backbone. Irinotecan, a type I topoisomerase inhibitor, is combined with 5-FU/

calcium folinate in the FOLFIRI regimen. Oxaliplatin, a third-generation platinum compound, is combined with 5-FU/calcium folinate in the FOLFOX (infusional) or FLOX (bolus) regimens or with capecitabine in the CapeOx scheme (also known as XELOX). Multiple clinical trials have shown that the FOLFIRI and FOLFOX or CapeOx regimens are equivalent in terms of efficacy (*617*, *618*). Oncologists typically use one regimen as first-line therapy and then the other as second-line therapy.

Systemic chemotherapy in mCRC is usually not curative. In countries that do not have sufficient resources to administer and handle the toxicities of chemotherapy, it is appropriate to forgo chemotherapy and focus instead on palliative care. It must also be noted that, where available, multidisciplinary treatment and resection of oligometastatic disease associated with systemic treatment may cure mCRC in some patients.

Administration and care of patients

Administration requires intravenous infusion capacity and regular patient access to clinical care. In developed countries, administration is usually performed in outpatient facilities; in other settings, patients may be treated in inpatient facilities. Antiemetics need to be available. Monitoring requires that clinicians have access to laboratory facilities, as well as the ability to recognize and address potential adverse events caused by the treatment itself. Importantly, inpatient facilities capable of supporting patients with severe infections and dehydration need to be readily available. Social and financial well-being can be impacted by treatment side-effects and should also be monitored and addressed.

Overview of regimens

Standard regimens

Standard chemotherapy regimens for mCRC are used until disease progression or unacceptable toxicity occurs.

- **Modified de-Gramont (2-week cycle)**
  - calcium folinate 400 mg/m² IV on day 1 of each 14-day cycle
  - 5-FU 400 mg/m² IV bolus on day 1 of each 14-day cycle
  - 5-FU 1200 mg/m² continuous IV infusion over 46 hours (days 1– 2 of each 14-day cycle)
- **FOLFOX-6 (2-week cycle)**
  - calcium folinate 400 mg/m² IV on day 1 of each 14-day cycle
  - 5-FU 400 mg/m² IV bolus on day 1 of each 14-day cycle

  - 5-FU 1200 mg/m² continuous IV infusion over 46 hours (days 1– 2 of each 14-day cycle)
  - oxaliplatin 85 mg/m² IV on day 1 of each 14-day cycle

- **FOLFIRI (2-week cycle)**
  - calcium folinate 400 mg/m² IV on day 1 of each 14-day cycle
  - 5-FU 400 mg/m² IV bolus on day 1 of each 14-day cycle
  - 5-FU 1200 mg/m² continuous IV infusion over 46 hours (days 1–2 of each 14-day cycle)
  - irinotecan 180 mg/m² IV on day 1 of each 14-day cycle

- **CapeOx (3-week cycle)**
  - capecitabine 850–1000 mg/m² orally twice daily on days 1–14 of each 21-day cycle
  - oxaliplatin 130 mg/m² over 2 hours on day 1 of each 21-day cycle

  Note: Low-dose calcium folinate, i.e. 20 mg/m², may be used instead of higher doses (*384*). Fixed-dose (50 mg) calcium folinate is also an option.

Alternative regimens

Where administration of 5-FU by continuous infusion or oral capecitabine is not feasible, an alternative regimen is first-line FLOX (using bolus 5-FU) followed by irinotecan on a two- or three-weekly basis as second-line treatment.

- **FLOX (8-week cycle)**
  - 5-FU 400 mg/m² IV bolus weekly for first 6 weeks of 8-week cycle
  - calcium folinate 500 mg/m² IV weekly for first 6 weeks of each 8-week cycle
  - oxaliplatin 85 mg/m² IV on day 1 of weeks 1, 3, 5 of each 8-week cycle

  Note: Low-dose calcium folinate, i.e. 20 mg/m², may be used instead of higher doses (*384*). Fixed-dose (50 mg) calcium folinate is also an option.

- **Irinotecan, single-agent**
  - Schedule 1: 135 mg/m² on days 1 and 8 of each 21-day cycle
  - Schedule 2: 180 mg/m² on day 1 of each 14-day cycle
  - Schedule 3: 300–350 mg/m² on day 1 of each 21-day cycle (this is the least preferred schedule because of toxicity)

Review of benefits and harms

Benefits

Fluoropyrimidines alone

As in the adjuvant setting, fluoropyrimidines form the cornerstone of chemotherapy for advanced disease. Compared with a monthly schedule of low-dose calcium folinate and bolus 5-FU, the modified de Gramont regimen is associated with superior response rates (32% vs. 14%; $P = 0.0004$) and median progression-free survival (PFS) (28 vs 22 weeks; $P = 0.0012$); median OS is increased slightly (62 vs 57 weeks; $P = 0.067$). Grade 3–4 toxic effects were less frequent with the modified de Gramont regimen (11% vs 24%; $P = 0.0004$) (*385*).

Similarly, oral fluoropyrimidines such as capecitabine have been compared with 5-FU regimens in several trials, most of which show non-inferiority of oral fluoropyrimidines and, typically, a superior toxicity profile (*389*, *616*).

The choice of fluoropyrimidine (5-FU bolus or infusion or oral capecitabine) should be based on local practice, experience and the availability of infusional capabilities and other supportive treatment. In general, a fluoropyrimidine alone as initial treatment for advanced colorectal cancer should be reserved for patients who are not candidates for more intensive therapy. If a fluoropyrimidine alone is selected, infusional 5-FU or an oral fluoropyrimidine is preferred to bolus 5-FU regimens because of reduced toxic effects and possibly slightly superior outcomes.

Fluoropyrimidine doublets

Oxaliplatin and irinotecan are typically combined with a fluoropyrimidine (irinotecan has single-agent activity, oxaliplatin does not) and have shown good efficacy.

A randomized controlled trial of 387 patients with advanced colorectal cancer compared treatment with 5-FU/calcium folinate with and without irinotecan (the FOLFIRI regimen) (*619*). Patients in the irinotecan group had a significantly higher response rate than those given 5 FU/calcium folinate alone (49% vs 31%, $P < 0.001$ for evaluable patients; 35% vs 22%, $P < 0.005$ by intention to treat). Similarly, both time to progression (TTP) and OS were greater in the irinotecan group (median TTP 6.7 vs 4.4 months, $P < 0.001$; median OS 17.4 vs 14.1 months, $P = 0.031$).

The FOLFOX regimen (5-FU/calcium folinate plus oxaliplatin) has also been shown to improve response rates and median PFS and OS in patients with advanced colorectal cancer. In the US Intergroup 9741 study – a randomized controlled trial of 5-FU/calcium folinate, irinotecan and oxaliplatin combinations in patients with previously untreated mCRC (*620*) – 795 patients were randomly assigned to receive irinotecan and bolus 5-FU/calcium folinate (IFL), FOLFOX, or irinotecan and oxaliplatin (IROX). Superiority of FOLFOX over the IFL regimen was noted. A median time to progression of 8.7 months, response rate of 45%,

and median survival time of 19.5 months were observed for FOLFOX. These results were significantly superior to those observed for IFL for all end-points (6.9 months, 31%, and 15.0 months, respectively, for OS: $P = 0.0001$; hazard ratio, 0.66) and for IROX (6.5 months, 35%, and 17.4 months, respectively). Significantly lower rates of severe nausea, vomiting, diarrhoea, febrile neutropenia and dehydration were seen with the FOLFOX regimen. Sensory neuropathy and neutropenia were more common with the regimens containing oxaliplatin.

Comparisons of FOLFIRI and FOLFOX have shown similar results for both regimens, in either sequence. A randomized phase III Groupe Coopérateur Multidisciplinaire en Oncologie (GERCOR) trial showed median survival was 21.5 months in patients treated with FOLFIRI followed by FOLFOX, and 20.6 months in patients treated with FOLFOX followed by FOLFIRI (*617*). Median second PFS (time from randomization to disease progression after the second line of chemotherapy) was 14.2 months in the FOLFIRI then FOLFOX arm versus 10.9 in the FOLFOX then FOLFIRI arm. In first-line therapy, FOLFIRI achieved 56% response rate and 8.5 months median PFS; FOLFOX achieved 54% response rate and 8.0 months median PFS. Second-line FOLFIRI achieved 4% response rate and 2.5 months median PFS, compared with 15% response rate and 4.2 months PFS for FOLFOX.

A phase III randomized trial comparing FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer observed no difference in overall response rates (31% vs 34%), median time to disease progression (7 months in each arm) or overall survival (14 vs 15 months) between the two treatment groups (*618*). The authors concluded that both therapies are effective first-line treatments for advanced colorectal cancer and that the main differences between the two regimens lie in their toxicity profiles.

Substitution of capecitabine for 5-FU has been assessed for regimens containing either irinotecan or oxaliplatin. Non-inferiority of CapeOx over FOLFOX has been noted, with a comparable but different toxicity profile. FOLFOX is associated with more grade 3–4 neutropenia and neutropenic fever, whereas CapeOx causes more grade 3 diarrhoea and hand–foot syndrome.

The FLOX regimen may be used in settings where capecitabine and the ability to administer infusional 5-FU are unavailable, even though it has not been assessed in phase III trials outside the adjuvant setting. Survival is comparable between FOLFIRI and FOLFOX.

Chemotherapy and targeted treatments

Targeted treatments have been investigated extensively in advanced colorectal cancer. Currently, five targeted agents are approved in different jurisdictions for advanced disease: bevacizumab, ziv-aflibercept and regorafenib, which target angiogenesis; and cetuximab and panitumumab, which target the epidermal

growth factor receptor . These agents have shown only a small increase in overall survival. For example, in a pooled analysis of seven randomized clinical trials, bevacizumab combined with chemotherapy was shown to increase overall survival by only 2.2 months compared with chemotherapy alone (19.8 months vs 17.6 months) when used in the first-line setting (*621*). Targeted agents are more expensive than older chemotherapy agents and have not usually been considered to be cost–effective. Therefore, they were not proposed for inclusion in the EML at this time. One set of resource-stratified guidelines, for instance, suggests that 5-FU costs less than US$ 1000 per life-year saved, oxaliplatin or irinotecan can cost up to US$ 40 000 (but probably less nowadays, with the use of generics), and the targeted agents often cost more than US$ 200 000 (*390*).

Harms and toxicity considerations

Common

Frequent adverse effects of 5-FU/calcium folinate combination therapy are diarrhoea and associated dehydration, neutropenia (uncommonly leading to infection in <2% of patients), anaemia, nausea and vomiting, and mucositis (*392*). Notably, both FOLFOX and FOLFIRI cause increased myelosuppression and nausea compared with 5-FU/calcium folinate alone.

Palmar–plantar erythrodysaesthesia (hand–foot syndrome) is also common with 5-FU and capecitabine regimens, with an increased incidence of up to 60% in patients treated with capecitabine. This adverse effect typically resolves following interruption of treatment (*397*). Irinotecan can cause asthenia or weakness and is associated with a cholinergic syndrome characterized by rhinitis, increased salivation, lacrimation, diaphoresis and flushing, although symptoms are typically low-grade.

Serious

Oxaliplatin-containing regimens can cause significant neuropathy, with approximately 18% of patients developing grade 3 neuropathy (*408*). Irinotecan may cause severe diarrhoea, with approximately 13% of patients developing grade 3–4 events (*619*). Diarrhoea can be severe with any of the above regimens and may require hospital admission for intravenous fluid replacement. It can be early or late onset and is often dose-limiting (*392*, *396*, *619*).

Recommendations

On the basis of the evidence presented in the application, the Expert Committee recommended addition of oxaliplatin, irinotecan and capecitabine to the complementary list of the Model List of Essential Medicines for the treatment of metastatic colorectal cancer. The Committee also endorsed calcium folinate and fluorouracil (already currently included on the complementary list) for use in this indication.

Metastatic prostate cancer – EML

The application sought endorsement of medicines already listed on the Model List of Essential Medicines for the treatment of metastatic prostate cancer: docetaxel, dexamethasone, calcium and vitamin D. The application also sought the addition of leuprorelin (as representative of the class of luteinizing hormone-releasing hormone (LHRH) agonists), bicalutamide and diethylstilbestrol to the core list of the Model List for the same indication.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Prostate cancer is the second most common cancer among men globally, with an estimated 1.1 million new cases and more than 300 000 deaths annually (*255*). Although the majority of patients in resource-abundant regions are diagnosed with localized (and potentially curable) disease, patients in resource-limited regions typically present with advanced disease.

Androgen suppression, via either surgical or medical castration, is the mainstay for advanced disease. Both options are equally efficacious; multiple randomized trials have documented improvements in disease progression with the use of androgen suppression (*622*). Androgen suppression reduces tumour volume, improves symptoms and delays progression; however, it poses serious limitations since it is a palliative therapy and may reduce quality of life. Surgical castration, via bilateral orchiectomy, is a more cost–effective option and overcomes the problems of medication non-compliance and poor access to healthcare (*622*). For patients whose quality of life would diminish substantially if they underwent orchiectomy, medical castration may represent a reasonable alternative. The primary forms of medical castration are gonadotropin-releasing hormone (GnRH) agonists, administered either alone or in combination with an antiandrogen (complete androgen blockade) (*623*).

The effect of androgen suppression on prostate cancer progression is finite and the disease will eventually progress from "castration-sensitive" to "castration-resistant". Despite initial response rates of 80–90%, nearly all men eventually develop progressive disease following androgen suppression. Castration-resistant prostate cancer, potentially treated with the addition of chemotherapy, is characterized by a median overall survival of between 1 and 2 years.

Public health relevance

Prostate cancer is known to be the sixth most common cancer in the world and the third most common among men (*624*). Prevalence varies hugely with geography and ethnicity, which may be attributed to differences in genetic susceptibility or

external factors, such as environment and differences in health care. Unfortunately, only limited information is available on the specific epidemiology of metastatic prostate cancer. The mean age of men with prostate cancer is 72–74 years (*624*).

Requirements for diagnosis, treatment, and monitoring

Diagnostics

The diagnosis of prostate cancer is most often made by histological examination of a biopsy of the primary tumour/prostate gland (common) or metastasis (less common) using haematoxylin–eosin staining (*625*). Core needle biopsy of the prostate is often performed with imaging assistance (e.g. transrectal ultrasound); a minimum of 12 cores are typically obtained to reduce sampling error. In advanced disease, however, a biopsy of a distant metastatic site can confirm extraprostatic disease. A surgeon usually performs the prostate biopsy under local anaesthesia. In addition to a morphological description, the pathologist should grade the cancer using the Gleason grading system, which not only characterizes the architecture of the prostate cancer but also provides prognostic information (*626*).

Serum prostate-specific antigen (PSA) serves as a sensitive but not specific tumour marker, providing both diagnostic and prognostic information. If PSA is elevated, imaging studies (plain X-rays, ultrasound, radionuclide bone scan and/or computerized tomography scan, or magnetic resonance imaging) can clarify potential sites of distant disease. A rise in PSA during treatment indicates the need for further testing and/or treatment. Imaging studies should also be directed toward symptomatic areas (e.g. back pain, bone pain) and again can confirm the presence of metastatic disease.

Metastatic disease is further classified depending on the site of disease (e.g. regional lymph node involvement, non-regional lymph node involvement, involvement of bone, or involvement of another site).

On occasion, a presumptive diagnosis of metastatic prostate cancer can be reasonably made on the basis of concurrent findings of widespread metastatic disease in an expected distribution (e.g. bones, lymph nodes) along with a markedly elevated PSA (hundreds to thousands range), particularly if a biopsy cannot be performed or reasonably evaluated by an experienced individual.

Testing

Once the diagnosis of metastatic prostate cancer has been established, the following investigations should be carried out: PSA, comprehensive metabolic panel to assess renal and hepatic function, and complete blood count. For patients actively undergoing therapy with androgen deprivation, PSA is monitored every 3–6 months. If PSA is rising, a serum testosterone should be obtained to determine whether therapy is suppressing testosterone into the

castrated range. Rising PSA despite castrated levels of testosterone reflects the development of castration-resistant prostate cancer, the lethal form of advanced prostate cancer.

Administration and care of patients

Given the role of testosterone in the pathogenesis of prostate cancer, the initial treatment for patients with castration-sensitive metastatic disease is androgen deprivation therapy (ADT). Androgen deprivation can be induced either medically or surgically (i.e. orchidectomy) with equivalent efficacy, although bilateral orchiectomy is the more cost–effective option (*627*, *628*).

Bilateral surgical orchiectomy – the removal of both testicles via a scrotal incision – should be performed by a trained surgeon under sterile operating conditions. This procedure, performed as an outpatient operation, immediately reduces testosterone level and may be particularly useful when testosterone reduction is needed urgently.

GnRH agonists are the mainstay of medical castration and achieve a reduction in serum testosterone similar to that achieved by surgical orchiectomy (*629*, *630*). Administration of GnRH agonists results in the down-regulation of luteinizing and follicular-stimulating hormones; however, initiation of treatment with GnRH agonists may cause a surge of testosterone (*629*). Consequently, a short course of an oral antiandrogen, such as bicalutamide, is recommended at the start of therapy to prevent transient worsening of cancer-related symptoms, such as urinary retention or pain, which are considered as "flare" responses (*627*, *631*). GnRH agonists are administered either intramuscularly or subcutaneously and the duration of effect (typically 1–6 months) varies with formulation. Patients should be monitored for local reactions (including allergic skin reactions) as well as adverse effects secondary to androgen suppression. Importantly, patients should be monitored for the behavioural and neurological effects of ADT, including depression.

PSA should be measured every 3–6 months. Although most patients will respond to ADT, the effect of ADT is finite and the cancer will subsequently progress as evinced by PSA, imaging or worsening of cancer-related symptoms despite castrate levels of testosterone (castration-resistant prostate cancer).

Additional treatment options for castration-resistant prostate cancer include therapies that target the androgen pathway (abiraterone and enzalutamide), immunotherapy (sipuleucel-T), and radiopharmaceuticals (radium-223). However, these agents are still in development and thus far have provided a relatively small benefit; moreover, current costs limit the use of these agents, which are therefore not proposed to for addition to the EML at this time.

A phase II trial and other small series have shown a benefit of using low-dose conjugated estrogens (diethylstilbestrol or fosfestrol), together with

warfarin therapy, with PSA responses of up to 79% (*632*, *633*). This has been recommended as an alternative second-line approach in resource-deprived regions that do not have access to other standard medications (*634*, *635*).

Overview of regimens

The following provides basic information on administration and dosing for ADT with surgical orchiectomy and LHRH agonists.

Surgical option for castration-sensitive metastatic prostate cancer when LHRH agonists are not available or affordable

- **ADT: bilateral orchiectomy and supportive measures**
  - surgical orchiectomy
  - calcium 1000 mg orally daily
  - vitamin D 2000 IU orally daily

Standard regimens for castration-sensitive metastatic prostate cancer

- **ADT: LHRH agonist (when bicalutamide is not available)**
  - leuprorelin 7.5–22.5 mg IM every 1–3 months
  - calcium 1000 mg orally daily
  - vitamin D 2000 IU orally daily
- **ADT: LHRH agonist**
  - leuprorelin 7.5–22.5 mg IM every 1–3 months
  - bicalutamide 50 mg orally daily
  - calcium 1000 mg orally daily
  - vitamin D 2000 IU orally daily

  Note: Leuprorelin is proposed to be added to the EML as a class agent, to include similar LHRH agonists.

Regimen for castration-sensitive metastatic prostate cancer with high volume of disease (visceral metastases and/or four or more bone metastases)

- **ADT plus docetaxel**
  - leuprorelin 22.5 mg IM every 3 months
  - bicalutamide 50 mg orally every day
  - docetaxel 75 mg/m² IV every 3 weeks x 6–9 cycles
  - dexamethasone 8 mg orally twice daily for 3 days, beginning the day before docetaxel for patients not receiving prednisone

- calcium 1000 mg orally daily
- vitamin D 2000 IU orally daily

Alternative regimen for use when LHRH agonists are not available or affordable

- diethylstilbestrol 1–3 mg orally daily (in conjunction with warfarin therapy)

Review of benefits and harms

Benefits

Androgen suppression, initially performed via orchiectomy, has been a recognized treatment for prostate cancer for approximately 75 years since the role of testosterone in the pathogenesis of prostate cancer was elucidated.

Orchiectomy: Data from the Veterans Affairs Research Service Cooperative Urological Research Group revealed that progression from extraprostatic extension to distant metastases within 10 years was significantly improved in men receiving orchiectomy (32%) versus placebo (62%) (*636*, *637*). The Group also found an increased 5 year overall survival among patients in the treatment arm (32%) versus placebo (20%) (*638*). The benefits of surgical treatment over medical androgen deprivation include cost and patient adherence.

LHRH agonists: Multiple studies have compared LHRH agonists with surgical orchiectomy. A systematic review covering 10 randomized trials and nearly 2000 men found no difference between LHRH agonists and surgical orchiectomy (hazard ratio, 1.13; 95% CI: 0.92–1.39) (*628*). LHRH agonists are often the first line of therapy as they are greatly preferred by patients to surgical castration (*639*).

An overview of randomized controlled trials and meta-analysis explored whether early ADT improves outcomes compared with deferred therapy (*640*). The early initiation of androgen suppression reduced prostate cancer-related mortality but did not improve overall survival. Early therapy is associated with higher costs and greater frequency of treatment-related adverse effects (*641*). Deferred treatment risks the development of hormone independence in the tumour as well as serious complications such as spinal cord compression. In fact, immediate treatment with either surgical orchiectomy or LHRH agonists was associated with reduced risk of pathological fracture, spinal cord compression and ureteric obstruction (*642*). For these reasons, androgen suppression is often initiated early.

Docetaxel in combination with prednisone is still considered the reference systemic therapy for patients with metastatic hormone-refractory prostate cancer, and studies of combination therapy with docetaxel and other chemotherapeutic agents have been disappointing (*643*, *644*). Docetaxel plus

prednisone achieved statistically significantly higher overall survival than mitoxantrone plus prednisone. Docetaxel was also associated with improved response rate, quality of life, pain response and PSA decline, with statistically significant benefits for all outcomes except response rate.

Harms and toxicity considerations

Adverse effects of ADT include sexual dysfunction, vasomotor symptoms (e.g. hot flushes), anaemia, behavioural and neurological effects, diabetes, cardiovascular disease and decreased bone density. Given the risk of osteoporosis and pathological fracture, a baseline measurement of bone density is recommended, as are calcium and vitamin D supplementation and exercise (*645*). Anaemia is typically mild and does not usually necessitate specific therapy. Vasomotor symptoms can be treated supportively. In order to minimize the side-effects of ADT, researchers attempted to compare intermittent with continuous androgen deprivation. The results were inconclusive and continuous therapy remains the standard of care (*646*).

Among ADT agents, diethylstilbestrol is known to be cardiotoxic at high doses. An intermediate dose (3 mg/day) seems to be as effective as orchiectomy and may have an acceptable adverse effect profile. However, the need to monitor patients for contemporary cardiac risk makes it a weak alternative.

Other than the adverse effects of ADT described above, risks of surgical orchiectomy include blood loss, haematoma and infection. Patients typically recover fully from surgery in 2–4 weeks.

Patients receiving docetaxel frequently experience dose-limiting neutropenia. Docetaxel is also associated with fluid retention, ranging from mild peripheral oedema to severe fluid retention and pleural effusion. To reduce this risk, patients should be treated with a corticosteroid before and after docetaxel doses (*647*). Hypersensitivity reactions to docetaxel occur frequently but incidence is reduced to < 5% with corticosteroid premedication (*367*). Patients may also experience sensory neuropathy, although this is generally mild and reversible.

Recommendations

On the basis of the evidence presented in the application, the Expert Committee recommended the addition of bicalutamide and leuprorelin to the complementary list of the Model List of Essential Medicines for the treatment of metastatic prostate cancer. The Committee recommended listing of bicalutamide and leuprorelin each with a square box symbol as representative of the wider class of peripheral androgen blockers and GnRH agonists, respectively. In addition, the Committee endorsed the use of the already listed docetaxel for this indication.

The addition of diethylstilbestrol to the Model List was not supported because of its being associated with an increased risk of cardiovascular death and providing no advantage compared with surgical orchiectomy or other ADT in terms of overall survival.

Nasopharyngeal carcinoma – EML

The application sought the addition of cisplatin and oxaliplatin to the core list of the Essential Medicines List for the treatment of nasopharyngeal carcinoma. The application also sought endorsement of carboplatin, fluorouracil and paclitaxel (currently included on the complementary list) specifically for use in this indication.

The application, amended to include details of the Expert Committee's consideration and decision, is presented in this section.

Introduction

Globally, nasopharyngeal carcinoma (NPC) is an uncommon cancer; approximately 80 000 new cases are reported per year and NPC accounts for 0.7% of all cancers. In North America and Europe, the incidence rate is less than 1 case per 100 000 population, but in endemic areas such as southern China (e.g. Hong Kong Special Administrative Region) and south-east Asia, the annual age-standardized incidence rates in men and women are as high as 20–30 and 8–15 cases per 100 000 population respectively (*255*).

Historically, NPC has been classified into different histological subtypes: type 1 (I) squamous cell carcinoma; type 2a (II) keratinizing undifferentiated carcinoma; and type 2b (III) non-keratinizing undifferentiated carcinoma. The WHO III subtype is the commonest form of NPC in endemic areas and differs from the squamous cell subtype in its association with the Epstein–Barr virus and sensitivity to chemotherapy and radiotherapy. Staging of NPC is based on the depth of invasion of the soft tissue, cranial nerves and bony structures at and near the nasopharynx by the primary tumour, the involvement of local and regional lymph nodes of the head and neck, and the presence of distant metastases. In Hong Kong SAR, the stage distribution at presentation is: stage I, 7%; stage IIA–B, 41%; stage III, 25%; stage IVA–C, 28%. The age-adjusted mortality rate of NPC is 3.9 per 100 000 persons; 5-year overall survival (OS) in stage I and II NPC is now approaching 90%, and in non-metastatic stage III and IV it is around 60%.

The standard of care for the treatment of stage I NPC is radiotherapy (RT); non-metastatic stage II–IV NPC is treated with concurrent chemoradiotherapy, with or without adjuvant chemotherapy. A total RT dose of 70 Gy is needed for eradication of gross tumour and either 50–60 Gy or 46–60 Gy for elective treatment of sites at potential risk. Three-dimensional RT is the minimum requirement, while intensity-modulated radiation therapy is the preferred approach in expert centres. Neoadjuvant chemotherapy is sometimes used to down-stage those locally advanced NPCs that cannot be encompassed readily within the radiation field without incurring significant risks to adjacent normal tissues. For metastatic NPC, the standard first-line therapy is a platinum-based

doublet that commonly consists of cisplatin or carboplatin in combination with one of the following drugs: fluorouracil (5-FU), gemcitabine, paclitaxel, docetaxel. Other drugs such as capecitabine, irinotecan, doxorubicin, vinorelbine and oxaliplatin can also be used, alone or in combination. For locally recurrent NPC, the options are individualized on the basis of the patient's condition, prior oncological treatment and disease stage at recurrence; these may include re-irradiation, surgery or palliative chemotherapy.

Public health relevance

Although NPC is the most common malignant tumour of the nasopharynx, it constitutes only 0.7% of cancers worldwide. According to GLOBOCAN, the age-standardized incidence for both sexes in many countries is 1 per 100 000 people per year. Globally, there are 80 000 new cases per year, making NPC the 23rd most common of all new cancers worldwide. GLOBOCAN estimates that men are 2–3 times more likely than women to develop NPC. Geographically, south-east Asia, southern China and north African countries have the highest prevalence of NPC (*255*). The stark difference in geographical distribution suggests that genetic factors play a large role in NPC susceptibility.

Requirements for diagnosis, treatment, and monitoring

Diagnostics

Diagnosis is based on histological examination. Immunohistochemical detection for Epstein–Barr virus-encoded small RNA expression may be useful for distinguishing inflammatory atypia from non-keratinizing NPC.

Testing

Staging of NPC is based on the staging system of the Union for International Cancer Control and the American Joint Committee on Cancer. Routine staging procedures include history, physical examination (including cranial nerve examination), complete blood cell count, serum biochemistry (including liver function test), chest X-ray, nasopharyngoscopy, computerized tomography (CT) scan or magnetic resonance imaging (MRI) of nasopharynx and base of skull and neck. Although MRI is generally preferred if available, each centre will choose the best imaging technique according to its usual clinical practice and experience. Imaging for distant metastases, including isotope bone scan and CT scan of chest and upper abdomen, could be considered for at-risk subsets (node-positive, especially N3 stage) and for those patients in whom clinical or biochemical abnormalities have been detected. The use of positron emission tomography-computerized tomography(PET-CT) and plasma/serum load of Epstein–Barr viral DNA are optional (*648*).

Administration and care of patients

Planning and delivery of RT should be done by a team of qualified personnel at an experienced oncology centre. As a minimum, the team should comprise radiation oncologists, radiologists, oncology nurses, physicists and radiographers. During RT, patients should be carefully and regularly monitored by clinicians and nurses for any treatment-related toxicities. Supportive measures such as nutritional supplementation, skin care, antiemetics, pain control and, if applicable, treatment for chemotherapy-related marrow toxicities should be readily provided. Assessment of post-treatment response in the nasopharynx and neck should be made via clinical and endoscopic examination and/or imaging studies. MRI is often used to evaluate the response to RT or chemoradiotherapy, especially for stage T3 and T4 tumours, although distinguishing between post-irradiation changes and recurrent tumours may be difficult. Follow-up for patients includes periodic examination of the nasopharynx and neck, cranial nerve function and evaluation of systemic complaints to identify distant metastasis. For stage T3 and T4 tumours, MRI might be used on a 6- to 12-month basis to evaluate the nasopharynx and the base of the skull, at least for the first few years after treatment. Evaluation of thyroid function in patients with irradiation to the neck is recommended at 1, 2 and 5 years (*648*).

Overview of regimens

The following include basic information on administration and dosing of chemotherapy during concurrent chemoradiotherapy, and palliative chemotherapy; no details are given of ancillary medications pertaining to the management of adverse events.

Standard regimens for concurrent chemotherapy during RT for non-metastatic stage II–IV NPC

- **Low-dose cisplatin at weekly intervals, starting at day 1 of RT (6–8 cycles)**
  - cisplatin 40 mg/m² IV infusion[9] weekly
- **High-dose cisplatin at 3-weekly intervals during RT**
  - cisplatin 100 mg/m² IV infusion on days 1, 22 and 43

The Expert Committee noted that the EML currently includes carboplatin with a square box symbol as representative of the therapeutic class of platinum

[9] Infusion time of cisplatin depends on the volume of normal saline in which cisplatin has been diluted and on the hydration scheme, which may vary across institutions. Prolonged infusion may need inpatient administration.

chemotherapy agents. However, the Committee highlighted that, in the treatment of NPC, cisplatin is the recommended standard and it was therefore appropriate that cisplatin be specifically included in the EML for this indication.

Oxaliplatin, another platinum agent, has also been shown to improve outcomes when combined with RT; however, it has not been shown to be superior to cisplatin and is more expensive. An alternative regimen of oxaliplatin is an option for patients who have contraindications or who cannot tolerate cisplatin.

- **Oxaliplatin for patients who cannot tolerate cisplatin or have contraindications**
  - oxaliplatin 70 mg/m² IV infusion weekly during radiation for 6 weeks

The Committee considered that carboplatin (already listed) was an alternative platinum-based treatment option to cisplatin for NPC and there was no clear justification for oxaliplatin being added to the EML for this indication.

Importantly, the Committee noted that the addition of adjuvant chemotherapy after concurrent treatment has not been shown to improve overall survival and is not recommended for all patients but has been included in some guidelines in Europe and USA. In the absence of a demonstrated survival advantage, the Committee considered that inclusion of adjuvant chemotherapy treatment options on the EML (for use after standard chemoradiation) was not supported.

Standard regimens for palliative or neoadjuvant chemotherapy

- **Fluorouracil and cisplatin (or carboplatin), 3-weekly schedule (6 cycles if palliative, 2–3 cycles if neoadjuvant)**
  - cisplatin 80–100 mg/m² IV infusion[10] on day 1 (*or* carboplatin AUC 5 or 6 IV infusion on day 1)
  - 5-FU 1000 mg/m² per 24 hours IV infusion on days 1–4 or 1–5
- **Paclitaxel and carboplatin (or cisplatin), 3-weekly schedule (6 cycles if palliative, 2–3 cycles if neoadjuvant)**
  - carboplatin AUC 5 or 6 IV infusion on day 1 (*or* cisplatin 80–100 mg/m² IV infusion on day 1)
  - paclitaxel 135 mg/m² IV infusion on day 1

[10] Infusion time of cisplatin depends on the volume of normal saline in which cisplatin has been diluted and on the hydration scheme, which may vary across institutions. Prolonged infusion may need inpatient administration.

Several other agents have been tested in this setting and would be considered appropriate alternatives. The application proposed listing only of these regimens on the basis of their common use and widespread availability.

Review of benefits and harms

Benefits

At least eight randomized studies have confirmed the survival benefit of adding concurrent platinum-based chemotherapy to RT in patients with non-metastatic stage II–IVB NPC (*649–656*). Two meta-analyses have reported an 18% reduction in the risk of death and an absolute survival benefit of 4–6% at 5 years with the use of chemotherapy in addition to radiation (*657*, *658*). The largest effect in terms of overall survival– from approximately 65% to 85% – was found for concomitant chemotherapy, with a pooled HR for death of 0.48 (95% CI: 0.32–0.72), which corresponds to an absolute survival benefit of 20% after 3 years (*658*). Metastatic or recurrent NPC is highly chemosensitive, and first-line doublet chemotherapy has been shown to achieve response rates of 50–80% in multiple phase II trials, with a median time to progression of 5–11 months and median overall survival of 12–20 months (*659–666*).

Few prospective randomized trials have been conducted in this setting. The impact on survival of palliative chemotherapy in the second and subsequent lines of treatment of metastatic or recurrent NPC is unclear.

Harms and toxicity considerations

Common

In patients receiving concurrent cisplatin-containing regimens during RT, the addition of chemotherapy commonly results in increased nausea and vomiting, myelosuppression, anaemia, renal impairment and RT-related oropharyngeal mucositis (which may result in odynophagia and weight loss). Carboplatin has a similar adverse effect profile in the above regimens (*667*). These acute toxicities can usually be successfully managed and palliated with good supportive care (*650*, *652*, *653*, *655*).

The impact of concurrent cisplatin on the incidence of late RT-related toxicities is still being defined. Some institutional reports suggest that cisplatin may exacerbate the risk of hearing impairment following RT, but not the risk of late neurological and endocrine toxicities. Low-grade peripheral neuropathy is common in patients treated with oxaliplatin but is typically mild and reversible (*656*).

Serious

The use of chemotherapy increases the risk of myelosuppression and thus the risk of febrile neutropenia and infections; however, the risk of severe infection with the above regimens in this population is low (1%) (*650*, *652*, *653*, *655*).

Recommendations

On the basis of the evidence presented in the application, the Expert Committee recommended that cisplatin be added to the complementary list of the EML for the treatment of nasopharyngeal cancer.

The Committee also endorsed the listing of carboplatin, fluorouracil and paclitaxel (already included in the complementary list) for this indication.

In the absence of evidence demonstrating a survival advantage of oxaliplatin over other platinum-based chemotherapy options, and the availability of both cisplatin and carboplatin on the EML, the Committee did not recommend the addition of oxaliplatin to the EML for treatment of nasopharyngeal cancer.

Non-small cell lung cancer – EML

The application sought the addition of vinorelbine, cisplatin, gemcitabine, erlotinib and gefitinib to the core list of the Essential Medicines List and the endorsement of etoposide, carboplatin and paclitaxel (currently included on the complementary list) for the treatment of non-small cell lung cancer.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

In 2013, there were approximately 1.8 million incident lung cancer cases diagnosed worldwide and approximately 1.6 million deaths from the disease (*668*). Lung cancer had the second highest absolute incidence globally after breast cancer, and in 93 countries was the leading cause of death from malignant disease, accounting for one fifth of the total global burden of disability-adjusted life years from cancer. Men were more likely to develop lung cancer than women, with 1 in 18 men and 1 in 51 women being diagnosed between birth and age 79 years (*668*). Non-small cell lung cancer (NSCLC) is the most common form of the disease, accounting for 85–90% of all lung cancers (*669*).

Most patients with NSCLC present with advanced stage disease – stage IV in particular – and half of all patients treated initially for potentially curable early-stage disease will experience recurrences with metastatic disease (*670*). Patients with stage IV disease are never curable, and chemotherapy, targeted therapy and radiation can only extend survival and palliate symptoms. Although NSCLC is generally regarded as a disease of the elderly, a third of cases are diagnosed in patients under 65 years of age (*670*).

Platinum-based doublet chemotherapy as adjuvant therapy is the standard treatment for patients with resectable stage II or III disease. Neoadjuvant and/or concurrent platinum-based doublet chemotherapy with radiotherapy is standard treatment for patients with unresectable stage III disease. Platinum-based doublet chemotherapy is also the standard first-line treatment for patients with advanced (stage IV) disease.

Where molecular diagnostics and targeted therapies are available, patients with activating mutations of epidermal growth factor receptor (EGFR) may benefit from treatment with EGFR tyrosine kinase inhibitors (TKIs – erlotinib, gefitinib, afatinib), which have been shown to improve progression-free survival in patients with advanced disease, while being associated with greater tolerability than standard chemotherapy.

Public health relevance

According to GLOBOCAN, lung cancer has been the most common cancer globally for several decades; estimated worldwide incidence in 2012 was

1 824 701 (12.9% of all cancers), with an age-standardized rate (ASR) of 23.1 per 100 000 (*255*). Of the 1.8 million new cases in 2012, 58% occurred in less-developed regions. ASR incidence rates in 2012 were highest in central and eastern Europe (53.5 per 100 000) and in eastern Asia (50.4 per 100 000) and were 25% higher for men than for women (205 and 165 per 100 000 respectively). GLOBOCAN estimated the global mortality rate in 2012 to be 1 589 925 with an ASR of 19.7 per 100 000.

Requirements for diagnosis, treatment, and monitoring

Diagnostics

Histopathological diagnosis from surgical sample, core- or fine-needle biopsies or cytology cell blocks from pleural effusion is essential. Adequate tissue must be obtained to permit the needed testing outlined here to be performed.

Immunohistochemistry (IHC) helps to subtype NSCLC: squamous cells are generally TTF1-negative and p40- and p63-positive, while adenocarcinomas are generally TTF1-positive and p40- and p63-negative (*671*, *672*). Molecular testing is crucial for first-line treatment with molecular targeted therapy. This includes EGFR gene mutation analysis by Sanger sequencing or amplification refractory mutation system and anaplastic lymphoma kinase (ALK) gene rearrangement by break-apart fluorescent-in-situ hybridization or IHC (*673*). Laboratories should use a validated mutation platform and participate in an external quality assurance programme.

Testing

Contrast-enhanced computerized tomography (CT) scan of the chest and upper abdomen, blood counts and blood chemistries for renal and hepatic function are required. CT scan or magnetic resonance imaging of brain or bone should be offered to patients with clinical symptoms suggestive of brain or bone metastases.

Administration and care of patients

Intravenous infusion capacity and regular patient access to acute clinical care are essential. Medications can be delivered in outpatient facilities. Antiemetics should accompany administration of all chemotherapy and intravenous hydration is essential before cisplatin. Clinical staff should be competent in identifying and managing soft tissue extravasation reactions from vinca alkaloids, and severe allergic reactions during taxane or carboplatin administration.

CT scans are required to assess response to treatment. Access to laboratory facilities for monitoring adverse effects is also required. Clinicians should be proficient in recognizing and addressing the potential side-effects of chemotherapy, and broad-spectrum antibiotics and transfusion facilities must

be available to manage life-threatening events such as bone marrow suppression and neutropenic fever. Social well-being is inevitably affected by the diagnosis and treatment of NSCLC, and the financial burden of treatment may be particularly heavy for patients with metastatic NSCLC as many drugs are still on patent. Psychological and social support professionals are best integrated into multidisciplinary teams to care for patients with NSCLC.

Overview of regimens

The following includes basic information on administration and dosing for the proposed standard regimen options; no details are given of ancillary medications pertaining to the management of adverse events.

Standard regimens – by stage of disease

- **Adjuvant chemotherapy for stage II and III NSCLC (every 21 days, 4 cycles)**
  - vinorelbine 25–30 mg/m² IV infusion on days 1 and 8
  - cisplatin 75–100 mg/m² IV infusion on day 1

  or
  - etoposide 50 mg/m² IV infusion on days 1–5
  - cisplatin 50 mg/m² IV infusion on days 1 and 8

  or
  - gemcitabine 1250 mg/m² IV infusion on days 1 and 8
  - cisplatin 75 mg/m² IV infusion on day 1

  or
  - paclitaxel 200 mg/m² IV infusion on day 1
  - carboplatin AUC 6 IV infusion on day 1

- **Concurrent chemotherapy/radiotherapy regimen for stage III unresectable NSCLC**

  If performance status good, age < 70 and adequate renal function:
  - etoposide 50 mg/m² IV infusion on days 1–5 and 29–33
  - cisplatin 50 mg/m² IV infusion on days 1, 8, 29 and 36

  concurrent with thoracic RT

  or
  - paclitaxel 45–50 mg/m² IV infusion weekly
  - carboplatin AUC 2 IV infusion weekly

  concurrent with thoracic RT

followed by:

– paclitaxel 200 mg/m² IV infusion on day1
– carboplatin AUC 6 IV infusion on day 1

two cycles, starting 2–4 weeks after completion of radiation therapy

If age > 70, or fair performance status, or CrCl 50–60:

– cisplatin 40 mg/m² IV infusion on first day of each treatment week of thoracic RT

Standard regimens – first-line chemotherapy for metastatic NSCLC

The regimens detailed below are for patients with no detectable targeted mutation or in whom mutation analysis could not be done. They have similar outcomes in relation to NSCLC survival. Toxicities vary among regimens but are not greatly different overall. Regimen choice can be based on drug availability and cost. Platinum agents improve survival only in patients without prior platinum exposure in the first-line setting (*674*).

– paclitaxel 90 mg/m² IV infusion on days 1, 8 and 15
– carboplatin AUC 6 IV infusion on day 1

every 21 days for 4–6 cycles

or

– paclitaxel 200 mg/m² IV infusion on day 1
– carboplatin AUC 6 IV infusion on day 1

every 21 days for 4–6 cycles

or

– gemcitabine 1000 mg/m² IV infusion on days 1, 8 and 15
– cisplatin 75 mg/m² IV infusion on day 1

every 28 days for 4–6 cycles

or

– gemcitabine 1000 mg/m² IV infusion on days 1 and 8
– cisplatin 75 mg/m² IV infusion on day 1

every 21 days for 4–6 cycles

or

– gemcitabine 1000 mg/m² IV infusion on days 1 and 8
– carboplatin AUC 5 IV infusion on day 1

every 21 days for 4–6 cycles

Standard regimens – TKI for metastatic NSCLC with activating EGFR mutations

– erlotinib 150 mg/day orally

or

– gefitinib 250 mg/day orally

Review of benefits and harms

Benefits

Surgery and adjuvant chemotherapy are important contributors to cure for early-stage disease. Combined modality treatment preserves a chance of long-term survival for patients with unresectable stage III disease.

A significant improvement in overall survival has been confirmed by several systematic reviews of randomized controlled studies assessing modern cisplatin-based chemotherapies. A first meta-analysis showed an absolute 5-year survival improvement of 5.4% (hazard ratio (HR) 0.89; 95% CI: 0.82–0.96) after adjuvant chemotherapy (*675*). Heterogeneity of chemotherapy effect among trials was limited ($I^2 = 6\%$). The effect of cisplatin and vinorelbine was marginally better than that of other chemotherapy combinations: vinorelbine (HR 0.80; 95% CI: 0.70–0.91), etoposide or vinca alkaloid (HR 0.92; 95% CI: 0.80–1.07), or other (HR 0.97; 95% CI: 0.84–1.13); test for interaction, $P = 0.11$. With the exception of cisplatin plus vinorelbine, the effect of chemotherapy was independent of whether patients received two- or three-drug regimens. The benefit varied with stage (test for trend, $P = 0.04$; for stage IA, HR 1.40; 95% CI: 0.95–2.06; for stage IB, HR 0.93; 95% CI: 0.78–1.10; for stage II, HR 0.83; 95% CI: 0.73–0.95; and for stage III, HR 0.83; 95% CI: 0.72–0.94). A second meta-analysis showed an absolute improvement of 4% (95% CI: 3–6) at 5 years associated with adjuvant chemotherapy, with the main survival benefit being in stage II and III disease (*676*). After surgery, studies have shown that doublet chemotherapy produces a relevant extension of life for patients, with survival extending to up to 10–12 months.

A systematic review confirmed the benefit for survival of platinum-based regimens compared with non-platinum chemotherapy in advanced NSCLC (*677*). Platinum-based chemotherapy was associated with a reduction in the risk of death at 1 year (odds ratio (OR) 0.88; 95% CI: 0.78–0.99; $P = 0.044$) compared with non-platinum chemotherapy, but also with an increased risk of grade 3–4 gastrointestinal and haematological toxicity. Another systematic review investigated whether chemotherapy given in addition to supportive care could prolong survival in advanced NSCLC (*678*). Trials in the meta-analysis included patients who were unsuitable for surgery or radical radiation therapy who had received either chemotherapy and supportive care or supportive care

alone. Survival analyses were based on 2533 deaths and 2714 patients from 16 trials. Chemotherapy was associated with a highly statistically significant benefit for survival (HR 0.77; 95% CI: 0.71–0.83). This benefit translated to an absolute improvement of 9% at 12 months increasing survival from 20% to 29% or an absolute increase in median survival of 1.5 months (from 4.5 months to 6 months).

In an indirect comparison, the effects of preoperative and postoperative chemotherapy on survival rates were compared in patients with operable NSCLC (*679*). Both adjuvant and preoperative (neoadjuvant) chemotherapy had similar effects on overall survival. The relative HR of postoperative to preoperative administration on survival was 0.99 (95% CI: 0.81–1.21; $P = 0.91$), a statistically non-significant difference. In clinical practice, adjuvant chemotherapy has become the standard of care as it represents a more pragmatic and feasible approach (*680*). First-line platinum-based doublets commonly use docetaxel, etoposide, gemcitabine, paclitaxel and vinorelbine.

The majority of patients with stage IV NSCLC will inevitably progress after first-line or maintenance treatment. For elderly or frail patients, single-agent vinorelbine or low-dose weekly carboplatin and paclitaxel are treatment options, although doublet chemotherapy is generally preferred.

In the supportive setting, platinum-based chemotherapy does not adversely affect quality of life (*681*). Side-effects of chemotherapy (e.g. fatigue, reduced functioning) are likely to be balanced by the palliative effect on symptoms such as pain. When platinum-based regimens in association with gemcitabine or vinorelbine were compared with a regimen of gemcitabine plus vinorelbine, quality-of-life scores were similar in the two arms of the trial. More haematological toxicity, renal toxicity and ototoxicity were seen in the platinum arm, but there was more hepatic toxicity in the gemcitabine-based arm (*682*).

Where molecular diagnostics and targeted therapies are available, tumours could be subjected to molecular analysis, in particular EGFR gene mutation status and ALK gene rearrangement. Gefitinib and erlotinib have been shown to be effective in patients with mutations in the EGFR kinase region and were proposed for inclusion on the EML for these patients as first-line therapy. Fewer data were available to support use of afatinib, which was therefore not proposed for EML inclusion at this time.

In the 10–15% of NSCLC with EGFR-activating mutations (defined as in-frame deletions in exon 19 and L858R substitution in exon 21), EGFR-TKIs (erlotinib, gefitinib, afatinib) achieve tumour response rates of 70–80% and progression-free survival (PFS) of 10–14 months (*683–689*). Several systematic reviews of randomized controlled trials compared TKI monotherapy with platinum-based doublet chemotherapy in first-line treatment of advanced or metastatic NSCLC (*690–692*). Meta-analyses showed an improved efficacy of

TKIs on overall response rates and PFS. However, the advantages for surrogate outcomes did not translate into a difference for mortality. OS data were similar for TKIs and chemotherapy (1-year: OR 1.04; 95% CI: 0.79–1.36, $P = 0.79$; 2-year: OR 0.95; 95% CI 0.76–1.17, $P = 0.62$) (*692*). A second meta-analysis provided overlapping results, with similar benefit for OS among patients who first received TKI or chemotherapy (HR 0.98; 95% CI: 0.87–1.10, fixed-effect model) (*690*).

TKIs have a different toxicity profile from that of chemotherapy (*683–689*). Rash (relative risk (RR) 6.29; 95% CI: 4.05–9.77), diarrhoea (RR 3.51; 95% CI: 2.15–5.75), stomatitis (RR 3.57; 95% CI: 1.81–7.04), and interstitial lung disease (RR 6.07; 95% CI: 1.66–22.2) were significantly more frequent after TKIs. Fatigue (RR 0.38; 95% CI 0.32–0.45), nausea/vomiting (RR 0.19; 95% CI: 0.11–0.32), and haematological disorders, including thrombocytopenia (RR 0.18; 95 % CI: 0.09–0.35), anaemia (RR 0.22; 95% CI: 0.15–0.33), and grade 3–4 neutropenia (RR 0.06; 95% CI: 0.04–0.08) were significantly more frequent after chemotherapy (*690*). Indirect comparisons showed that EGFR-TKIs have similar efficacy but they might differ within class in terms of toxicities (*692*, *693*).

For patients with ALK gene rearrangements, first-line crizotinib has been associated with a tumour response rate of 71% and PFS of 11.9 months (*694*). Patients with driver oncogenes who failed to receive a targeted therapy previously may be treated with EGFR-TKIs or crizotinib as salvage therapy (*695*, *696*). When compared with chemotherapy, there are improvements in quality of life and PFS, but no significant improvements in OS among patients given crizotinib (*697*, *698*). Since there is, as yet, no clear evidence of an effect to extend OS, crizotinib was not proposed for inclusion in the EML at this time.

Harms and toxicity considerations

Because of the multitude of couplet options available for treatment of NSCLC, chemotherapeutic-specific harms and toxicities for this briefing are described below by drug or drug class rather than by regimen.

Platinum agents

Platinum agents, including cisplatin and carboplatin, cause myelosuppression with dose-limiting thrombocytopenia, and can also cause ototoxicity and asthenia. Nausea and vomiting occur in almost all patients treated with cisplatin and carboplatin and is often severe, necessitating the use of antiemetic medications. Renal toxicity caused by cisplatin can be significant and may result in electrolyte abnormalities. Intravenous hydration both before and after administration of cisplatin is necessary to reduce the incidence of renal toxicity (*380*). Notably, carboplatin causes less nephrotoxicity, ototoxicity, and nausea and vomiting in this patient population but more frequent severe thrombocytopenia (*699*).

Paclitaxel

Paclitaxel is associated with high incidences of neutropenia, which is frequently severe (grade 3–4) (*700*). Paclitaxel can cause hypersensitivity reactions in up to 30% of patients and premedication is required to reduce this risk. Most infusion reactions are mild and easily managed (*367*). Paclitaxel causes universal alopecia and many patients experience peripheral neuropathy; both of which are reversible.

Gemcitabine

Gemcitabine frequently causes myelosuppression with dose-limiting thrombocytopenia and leukopenia and associated risk of infection. Gemcitabine is also associated with increased hepatic transaminases, which may lead to more severe hepatotoxicity in up to 10% of patients. Many patients experience oedema and dyspnoea (*614*).

Vinorelbine

Vinorelbine often causes severe neutropenia and granulocytopenia, which increase patients' risk of infection. Like other vinca alkaloids, vinorelbine also frequently causes constipation. It is a strong vesicant and care must be taken to avoid extravasation and associated tissue damage (*613*).

Etoposide

The most frequent dose-limiting toxicity for etoposide is myelosuppression, primarily leukopenia, which can be grade 3–4 in >10% of patients. A small percentage (up to 2%) of patients receiving intravenous etoposide experience hypersensitivity reactions, which may include angioedema, bronchospasm and/or chest discomfort. Etoposide also causes reversible alopecia in up to 60% of patients (*469*). The use of etoposide has been associated with a small but increased risk of secondary cancers.

EGFR tyrosine kinase inhibitors

EGFR tyrosine kinase inhibitors are well tolerated by many patients. Agents have similar toxicity profiles, although the incidence of toxicity depends on the drug. Diarrhoea is common, occurring in more than 60% of patients treated with EGFR-TKIs. Rarely, more severe gastrointestinal toxicity, including perforation, can occur, particularly with erlotinib. All agents are associated with characteristic dermatological toxicity and rash, and they may also cause hepatic toxicity and increased hepatic transaminases. Although the incidence is small, hepatic failure and hepatorenal syndrome have been reported in patients treated with erlotinib (*701–703*).

Recommendations

On the basis of the evidence presented in the application, the Expert Committee endorsed etoposide, carboplatin and paclitaxel (already included on the complementary list) for use in the treatment of non-small cell lung cancer. The Committee also recommended the addition of vinorelbine, gemcitabine and cisplatin to the complementary list for this indication. The Committee noted that cisplatin is the preferred platinum agent for use in adjuvant treatment and as a radio-sensitizer.

The Committee noted that combination chemotherapy with the regimens described in the application has been associated with modest improvements in overall survival and improved quality of life during extended survival.

The Committee did not recommend addition of the TKIs gefitinib and erlotinib to the complementary list of the EML for the treatment of non-small cell lung cancer. The Committee acknowledged that, while individual patients with a drug-sensitive EGFR mutation may derive a substantial extension of life, the average increase in progression-free survival was modest (3–4 months). The Committee considered that substantial infrastructure would be required to establish routine and reliable molecular testing for EGFR mutations in NSCLC. The Committee considered it was neither practical nor cost–effective to establish molecular testing, and therefore the use of tyrosine kinase inhibitors as essential medicines for this disease could not be supported at this time. Afatinib and crizotinib were not proposed for inclusion by applicants or recommended by the Expert Committee.

Osteosarcoma – EMLc

The application sought the addition of doxorubicin, cisplatin, methotrexate, carboplatin and ifosfamide to the core list of Essential Medicines for Children for the treatment of osteosarcoma.

The Committee noted that doxorubicin and methotrexate are currently included on the complementary list of the EMLc for other indications.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Osteosarcoma is the most common primary malignant bone tumour in children and young adults and accounts for 3–5% of all paediatric malignancies. It is a very aggressive type of cancer, but most patients can be cured with a combination of chemotherapy and surgery. The standard regimen of chemotherapy is a combination of doxorubicin, cisplatin and methotrexate; in limited-resource settings, a combination of doxorubicin, carboplatin and ifosfamide may be considered. In addition, complete surgical resection of the primary bone tumour and all detectable metastatic lesions should be pursued. Radiation therapy does not have a role in the primary treatment of conventional osteosarcoma. The 5-year survival rate for children with localized disease is 60–80%; while for those with metastatic disease the 5-year survival rate is about 15% to 30% (*704*). In metastatic disease, survival is about 40% if the cancer has spread only to the lungs, or if all of the metastases and primary tumour can be surgically removed.

Public health relevance

While osteosarcoma is relatively rare, it is the eighth most common cancer in children and adolescents and the most common bone cancer (*705*). A 2009 study used data collected on five continents to determine the global incidence and distribution of osteosarcoma in children. Annual global incidence was estimated to be 3–5 cases per 1 million children, adolescents and young adults (0–24 years of age) (*706*). Incidence was relatively consistent throughout the world, with Italy, parts of Latin America, Sudan, and Uganda reporting slightly higher rates than other regions. Among those aged 0 to 24 years, osteosarcoma affects males at a rate of 3–5 per million and females at 2–4 per million (*706*). Peak incidence (about 8.5 cases per million per year) occurs in young men aged 15–19 years. The onset of osteosarcoma tends to occur at younger ages in females than in males. A possible risk factor is rapid bone growth, which suggests a link between adolescent growth spurts and disease onset (*705*).

Requirements for diagnosis, treatment, and monitoring

Diagnostics

Histological analysis of tumour tissue obtained by biopsy is required for diagnosis. Biopsy should be undertaken by an orthopaedic surgeon experienced in orthopaedic oncology, who will probably also perform the definitive surgery. Core needle biopsy by an interventional radiologist may be performed after discussion with the orthopaedic surgeon about the appropriate biopsy tract.

Testing

Plain radiographs of the primary site are the initial investigation of choice in a patient with symptoms suggestive of a bone tumour. Once osteosarcoma is suspected, contrast-enhanced magnetic resonance imaging of the entire length of the involved bone should be performed (*707*). There are no specific blood tests for osteosarcoma, but lactate dehydrogenase and alkaline phosphatase levels may serve as a surrogate to track tumour burden. Additional imaging studies should be carried out at diagnosis to assess the extent of the primary tumour and the presence of metastatic disease; computerized tomography scan of the chest and radionuclide bone scan are used to detect lung and bone metastases, respectively (*708*, *709*). Organ function measurements before the start of chemotherapy include complete blood counts, liver function tests, renal function tests, evaluation of hearing capacity and cardiac function.

Administration and care of patients

Chemotherapy should be administered in a cancer centre with capacity for intravenous chemotherapy infusion and monitoring. Cisplatin can cause severe nausea and vomiting and requires administration of prophylactic antiemetics. It is preferable to administer chemotherapy using a centrally placed intravenous catheter. Doxorubicin extravasation can lead to local tissue injury and necrosis. Methotrexate-containing regimens require frequent monitoring of methotrexate levels, intravenous hydration, urinary alkalinization and folinic acid rescue. Supportive care with administration of granulocyte colony-stimulating factor may be required to ensure timely therapy, especially towards the end of treatment.

Patients should be monitored for treatment response and adverse effects of therapy. Disease evaluation scans should be performed preoperatively and then approximately every 3 months. Patients should be monitored regularly for bone marrow suppression with blood counts, for hearing loss with audiological examination, for cardiac dysfunction with echocardiogram, and for liver and renal toxicity.

Overview of regimens

The following sections include basic information on administration and dosing for MAP (high-dose methotrexate (HDMTX), cisplatin, and doxorubicin) and OS99 (carboplatin, ifosfamide, and doxorubicin) chemotherapy regimens; no details are given of ancillary medications pertaining to the management of adverse events.

Standard regimens

- **MAP (6 cycles)**
  - doxorubicin (A) 37.5 mg/m² IV infusion on days 1 and 2 of weeks specified below (cumulative anthracycline dose 450 mg/m²)
  - cisplatin (P) 60 mg/m² IV infusion on days 1 and 2 of weeks specified below
  - methotrexate (M) 12 g/m² IV infusion given over 4 hours in weeks specified below

Week	1	4	5	6	9	10	**Surgery**	12	15	16	17	20	21	22	24	25	26	28	29
Chemo	A P	M	M	A P	M	M		A P	M	M	A P	M	M	A	M	M	A	M	M

- **OS99 (12 cycles)**
  - doxorubicin (D) 25 mg/m² IV infusion on days 1, 2 and 3 in one cycle before surgery and on days 1 and 2 in six cycles after surgery of weeks specified below (cumulative anthracycline dose: 375 mg/m²)
  - carboplatin (C) IV infusion on day 1 of weeks specified below (dose calculated using the formula: 8× [(0.93 × glomerular filtration rate in ml/min per m²) +15]
  - ifosfamide[11] (I) 2.65 g/m² IV infusion on days 1, 2 and 3 of weeks specified below

Week	0	3	6	9	**Surgery**	14	17	20	23	26	29	32	35
Chemo	C I	C I	C I	D		I D	C I	C D	I D	C I	C D	I D	C D

[11] Administration of ifosfamide requires the accompanying drug, mesna. The Committee noted that mesna is currently included on the EMLc as an adjuvant medicine.

In addition to the chemotherapy described above, patients who present with metastatic disease in the lungs should undergo surgical resection of all pulmonary nodules if possible. This procedure is usually performed after administration of neoadjuvant chemotherapy.

Review of benefits and harms

Benefits

Because osteosarcoma occurs in adolescents and young adults, curative regimens may result in many life-years gained. Before the use of chemotherapy, surgical resection resulted in only 20% survival (*710*). Even after complete surgical resection by amputation in localized disease, the majority of patients developed clinically detectable pulmonary lesions and died. This indicated that microscopic lung disease was present in most patients at diagnosis.

The value of chemotherapy was supported by the results of the Multi-Institutional Osteosarcoma Study, a randomized controlled trial of 36 patients with non-metastatic high-grade osteosarcoma of the extremity (*711*). This trial showed 17% event-free survival (EFS) in the surgery-only arm and 66% EFS in the adjuvant chemotherapy arm.

The MAP regimen of high-dose methotrexate, doxorubicin and cisplatin has become the standard of care for localized osteosarcoma (*712*). The ISG/OS-1 trial compared the efficacy and toxicity of two MAP-based chemotherapy regimens, with or without ifosfamide, in 246 patients with non-metastatic osteosarcoma of the extremity. The two treatment arms (A and B) received the same cumulative doses of MAP. Patients in treatment arm A received postoperative ifosfamide only if they had a poor histological response to chemotherapy. Patients in treatment arm B were given ifosfamide with MAP in the primary phase of chemotherapy. No statistically significant differences were observed between arms A and B in the 5-year rates of overall survival (OS) (73% and 74%, respectively) or EFS (64% and 55%, respectively). Patients in treatment arm B experienced a greater incidence of grade 4 haematological toxicity (leukopenia, thrombocytopenia, febrile neutropenia).

Intergroup Study 0133 was a prospective, randomized, phase III trial of 662 patients with newly diagnosed osteosarcoma without clinically detectable metastatic disease. The study compared four prospectively randomized treatments in a 2×2 factorial design: MAP chemotherapy and MAP plus ifosfamide, with or without addition of muramyl tripeptide (MTP), a synthetic lipophilic glycopeptide capable of activating monocytes and macrophages to a tumoricidal state (*713*). The primary end-points for analysis were EFS and OS. Patients in the MAP-only treatment arm had a 6-year EFS of 64% compared with 58% for patients in the MAP-plus-ifosfamide arm. Six-year OS rates were similar in the two groups (71% and 70%, respectively). The addition of MTP to

chemotherapy improved 6-year OS from 70% to 78% ($P = 0.03$). The hazard ratio for OS with the addition of MTP was 0.71 (95% CI: 0.52–0.96). The role of MTP has been disputed, as a possible interaction between MTP and ifosfamide is suspected, calling for prudent interpretation of the role of MTP (*714*). Immunotherapy with MTP might offer additional marginal benefit but the potential role of MTP in combination with chemotherapy remains to be confirmed. The application did not propose inclusion of MTP in the EMLc.

The OS99 regimen (doxorubicin, carboplatin and ifosfamide) has been proposed as an alternative to MAP to simplify the management of osteosarcoma in settings unable to provide the required monitoring for methotrexate and for patients unable to tolerate high-dose methotrexate (*715*). The results of the phase II OS99 trial of 72 patients found that this regimen was associated with survival outcomes comparable to those seen with regimens containing cisplatin or high-dose methotrexate, with 5-year EFS and OS of 66.7% and 78.9%, respectively (*715*).

In contrast to localized disease, the prognosis for metastatic, relapsed or recurrent osteosarcoma remains poor, with 5-year OS less than 30% (*704*). In addition to chemotherapy, complete surgical resection is critical for survival benefit. In one study, patients who underwent complete surgical resection had an overall survival of 65% compared with 15% for those who underwent incomplete resection (*716*). Survival is highly dependent on the amount of tumour necrosis following neoadjuvant chemotherapy, as determined by comprehensive histological analysis of the resected tumour.

Harms and toxicity considerations

Nausea, vomiting, myelosuppression, alopecia and mucositis are common to all chemotherapy regimens for osteosarcoma (*717*). Sepsis is the most serious acute complication that may lead to death. Cisplatin can cause ototoxicity and nephrotoxicity and may also lead to infertility. The cumulative doxorubicin dose is relatively high in most regimens and may result in cardiac dysfunction in up to 4% of patients (*718*). Inability to excrete high-dose methotrexate adequately may result in acute renal failure and severe mucositis (*719*). Ifosfamide administration may result in acute neurotoxicity, which may manifest as weakness, altered mental status and seizures (*720*). The cumulative incidence of second malignant neoplasm in osteosarcoma survivors at 25 years was 5.4% (*721*).

Recommendations

On the basis of the evidence presented in the application, the Expert Committee recommended the addition of doxorubicin, cisplatin (1 mg/mL, 50-mL and 100-mL vials), methotrexate, carboplatin and ifosfamide to the complementary list of the EMLc for the treatment of osteosarcoma. The Committee considered

that the results of the trials supported the use of the MAP regimen as standard therapy for osteosarcoma as it was associated with clinically relevant improvements in EFS and OS. Although OS99 chemotherapy has not been widely adopted, the Committee noted that this chemotherapy was associated with similar benefits to MAP in terms of EFS and OS, and it may be a treatment option in some settings.

The Committee also recommended that these medicines be included on the complementary list of Essential Medicines for adults, noting that the peak incidence of osteosarcoma is in the second decade of life and the EMLc is intended for use only for children up to the age of 12 years.

Given the requirement for treatment with high-dose methotrexate to be accompanied by calcium folinate (leucovorin/folinic acid) rescue, the Committee also recommended inclusion of calcium folinate on the complementary lists (both EMLc and EML) for this indication. Similarly, given the requirement for treatment with ifosfamide to be accompanied by mesna, the Committee recommended inclusion of mesna on the complementary lists (both EMLc and EML) for this indication.

Ovarian germ cell tumours – EML and EMLc

The application sought endorsement of the following medicines, currently included on the complementary list of the Model List of Essential Medicines for the treatment of ovarian germ cell tumours: bleomycin, etoposide, paclitaxel, ifosfamide and mesna. The application also sought the addition of cisplatin and granulocyte colony-stimulating factor (G-CSF, filgrastim) to the core list for use in this indication. As ovarian germ cell tumours (OGCTs) affect both adults and children, the application proposed inclusion of these medicines in the both the EML and EMLc.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Ovarian germ cell tumours (OGCTs) are derived from primordial germ cells of the ovary. They are highly malignant and rapidly growing tumours that affect both adults and children, with peak incidence occurring in adolescent girls and young women (*722*). Incidence varies geographically: OGCTs account for less than 5% of malignant ovarian tumours in developed countries, but up to 15% among Asian and black populations (*722*).

OGCTs are broadly classified into two types – dysgerminomas and non-dysgerminomas. Non-dysgerminomas are further divided into a number of subtypes: immature teratoma, embryonal cell carcinoma, yolk sac tumours, primary ovarian (non-gestational) choriocarcinomas, polyembryoma, and mixed germ cell tumours (*723*).

Surgery is the initial treatment, to establish the diagnosis and staging and to remove or optimally debulk the tumour. Fertility-sparing surgery is the standard procedure in young women wherever possible (*722*). For patients with stage IA dysgerminoma or stage IA, grade 1 immature teratoma, treatment is with surgery alone: rates of recurrence are low. Postoperative chemotherapy is used in most other cases.

Before the introduction of combination chemotherapy, survival from OGCTs was negligible (*723*). However, OGCTs have proved to be highly chemosensitive and, since 1990, the standard postoperative chemotherapy regimen has been bleomycin, etoposide and cisplatin (BEP) (*724*). Surgery plus BEP has been associated with survival rates of 95–100% at 5 years among patients with early-stage disease and 75–80% among those with advanced disease (*722*, *725*, *726*). A significant survival gain is thus achieved by adding the BEP regimen to surgery. Drugs used in the BEP regimen are off-patent and are also used in the treatment of testicular germ cell tumours, which are much common than OGCTs.

Public health relevance

OGCT is a rare disease in adult cancer overall but is the one of the common solid malignancies among women aged between 15 and 30 years. According to the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute, the 30-year, age-adjusted incidence rate per 100 000 woman–years is 0.338, decreasing by 29.4% for dysgerminomas and by 31.5% for mixed OGCTs (*723*). Incidence rates were higher for Asians, Pacific Islanders and Hispanics. Although global epidemiological data on OGCT burden are limited, the combined evidence from discrete studies warrants urgent action to expand access to chemotherapy drugs. In its GLOBOCAN analysis, the International Agency for Research on Cancer reports incidence of cancer only by site and not by histology, making it impossible to differentiate rates of OGCTs from those of other malignant ovarian tumours. Epidemiological data from various national databases support the conclusions that the burden of OGCTs is not confined to high-income settings.

Requirements for diagnosis, treatment, and monitoring

Diagnostics

Pathomorphological analysis of surgically resected ovarian tumour is required. Elevated tumour serum markers (alpha-fetoprotein, beta-human chorionic gonadotropin, lactate dehydrogenase) assist in making the correct diagnosis preoperatively.

Testing

The final stage is assigned after surgery, where the tumour burden in abdomen is assessed in accordance with FIGO (International Federation of Gynecology and Obstetrics) classification. Presurgical tests include tumour markers, chest X-ray, abdominal and pelvic ultrasound (or contrast-enhanced computerized tomography scan), and blood counts and chemistries to assess critical organ function, including renal and hepatic function.

Administration and care of patients

Patients should preferably be treated in centres that are experienced in the management of germ cell tumours. Typically, cytoreductive fertility-sparing surgery, which includes unilateral salpingo-oophorectomy, is the first step of the treatment. It is also critical to examine the peritoneal fluid (either ascitic fluid or peritoneal washings) to ascertain whether there is evidence of spread outside the ovary. Twenty-five percent of patients who would otherwise be classified as stage I have positive peritoneal cytology. Treatment decisions are based on the pathological stage, residual tumour and tumour histology. Further treatment

options include active observation for patients with stage I disease or three to four cycles of BEP for those with stage II–IV.

Intravenous cisplatin infusions require inpatient facilities, since prolonged intravenous hydration, forced diuresis and antiemetics are also necessary. Monitoring requires that clinicians have access to laboratory facilities, as well as the ability to recognize and address potential adverse events caused by the treatment itself, including bone marrow suppression, infection, and pulmonary, renal and gastrointestinal toxicity. Social and financial well-being can be impacted by the side-effects of treatment and should also be monitored and addressed.

Patients who have residual tumour after treatment with chemotherapy should undergo secondary surgery so that all residual tumour lesions are excised. Second-look surgery following complete response to primary surgery and chemotherapy is not routinely recommended (*727*, *728*). For low-resource settings, if a patient has had inadequate staging, it is not recommended that a second surgery be undertaken; rather, the patient should be given chemotherapy and assessed after treatment to resect residual disease.

Overview of regimens

The administration and dosing schedule for BEP is described below. Three cycles should be administered to patients with stage II–III disease and four cycles to patients with stage IV. Cycles should be repeated every 3 weeks. Treatment compliance and maintenance of treatment intensity is necessary.

Standard regimens – first line treatment

- **BEP – adult (21-day cycle; 3 or 4 cycles)**
  - bleomycin 30 U IV bolus on days 1, 8, 15
  - etoposide 100 mg/m² IV infusion on days 1–5
  - cisplatin 20 mg/m² IV infusion on days 1–5
- **BEP – prepubertal children (21-day cycle; 3 or 4 cycles)**
  - bleomycin 15 U/m² (max. 30 U) IV bolus on day 1
  - etoposide 100 mg/m² IV infusion on days 1–5
  - cisplatin[12] 20 mg/m² IV infusion on days 1–5

[12] An accepted substitution for cisplatin among prepubertal children is carboplatin at a dose of AUC 7.9, which has less renal toxicity.

Standard regimens – salvage therapy (previously treated patients)

- **VeIP (21-day cycle; 4 cycles)**
  - vinblastine 0.11 mg/kg IV infusion on days 1 and 2
  - ifosfamide 1.2 g/m² IV infusion on days 1–5
  - cisplatin 20 mg/m² IV infusion on days 1–5
- **TIP (21-day cycle; 4 cycles)**

  (Premedications pertaining to the administration of paclitaxel are not shown.)
  - paclitaxel 250 mg/m² IV infusion over 24 hours on day 1
  - ifosfamide[13] 1.5 g/m² IV infusion on days 2–5
  - cisplatin 25 mg/m² IV infusion on days 2–5

G-CSF (5 μg/kg) may be administered by subcutaneous injection daily from days 7 to 18, or until recovery of absolute neutrophil count to greater than 1000/mm³ (whichever occurs first). It should be discontinued 24 hours before starting the next chemotherapy treatment.

Review of benefits and harms

Benefits

The rarity of ovarian germ cell tumours has meant there are no randomized controlled trials (RCTs) of treatments. Experience from RCTs for the more common testicular germ cell tumours has been extrapolated to the OGCT setting and has provided an evidence base for treatment decisions (*729*).

Cisplatin-based chemotherapy for OGTC has been associated with survival rates ranging from 87% to 96%. A retrospective Australian study sought to evaluate cisplatin-based treatment of OGCT with regard to survival and toxicity (*730*). The authors concluded that cisplatin-based chemotherapy for OGCT is highly effective, with 5-year overall survival of 87% based on data obtained from 58 patients. A prospective trial by the Gynecologic Oncology Group established postoperative chemotherapy with three cycles of BEP as the standard treatment for OGCTs (*731*). This study reported 96% disease-free survival at a median follow-up of 38.6 months. In another prospective study of 48 patients with stage I–IV OGCTs, patients were administered a modified 3-day BEP regimen of either three or four cycles depending on disease staging. In this study, disease-free survival at five years was also 96% (*732*).

[13] Administration of ifosfamide requires the accompanying drug, mesna.

Given that patients diagnosed with stage II–III OGCT who do not receive treatment cannot survive, the survival benefit obtained with BEP chemotherapy is highly relevant.

Despite the efficacy of BEP regimen, around 15% of patients relapse. Second-line salvage treatment with cisplatin, ifosfamide and either vinblastine (VeIP) or paclitaxel (TIP) has achieved cure in up to 65% of patients who relapse following first-line treatment (*733–735*).

Harms and toxicity considerations

Common

Patients receiving BEP will suffer both alopecia and myelosuppression – particularly neutropenia, which increases the risk of infection. However, the incidence of serious infections in these patients is low (*732*).

Renal toxicity with cisplatin is common. Close monitoring of routine laboratory tests and aggressive intravenous hydration are necessary to avoid significant decline in renal function. With prophylactic hydration, reductions in glomerular filtration rate occur in 20–30% of patients treated with cisplatin (*736*).

Administration of paclitaxel is associated with hypersensitivity reactions, and prophylactic pretreatment with dexamethasone and H1- and H2-receptor antagonists is recommended (*700*).

Serious

The toxicities associated with BEP can be significant, including risks for acute and later-onset pulmonary toxicity associated with bleomycin and a minimal but increased risk of treatment-related myeloid neoplasms associated with etoposide (*737*).

Bleomycin at the doses used in the regimens above is essentially devoid of any clinically significant pulmonary toxicity (*601*, *732*). However, the risk of toxicity is dose-dependent, increasing with cumulative doses above 400 units, and patients should be closely monitored for respiratory lag or rales, which can be a sign of early bleomycin-induced pulmonary disease. In the absence of pulmonary function tests, any rales (especially in lung bases) that do not clear with coughing are an indication to stop bleomycin therapy.

Recommendations

The Expert Committee noted the available evidence for high cure rates associated with the proposed chemotherapy regimens for ovarian germ cell tumours and recommended the addition of cisplatin to the complementary list of the Model List of Essential Medicines and the Model List of Essential Medicines for Children and the endorsement of bleomycin, etoposide, ifosfamide, paclitaxel

and vinblastine on both lists for treatment of OGCT. Additionally, given the requirement for treatment with ifosfamide to be accompanied by mesna, the Committee recommended inclusion of mesna on the complementary lists of the EML and EMLc for this indication.

The inclusion of G-CSF on the EML and EMLc was considered by the Expert Committee in a separate application.

Paediatric cancers: Burkitt lymphoma, acute lymphocytic leukaemia (ALL), Wilms tumour – EMLc

The Union for International Cancer Control task team on essential medicines requested the Expert Committee to reconsider the cancer drugs listed in the current Model List of Essential Medicines for Children (EMLc).

In 2007, when the first WHO EMLc was published, the list of cancer medicines was modelled directly on those that had been included for adults. In 2011 an application was submitted to divide the EMLc by cancer type instead of by individual drug. The three diseases included were: acute lymphoblastic leukaemia (ALL), Wilms tumour and Burkitt lymphoma (*738*). The applicants requested inclusion on the EMLc of several medicines that were not incorporated. Thus, in this current application, the Expert Committee was requested to reconsider the following two specific items: medicines for Wilms tumour and medicines for ALL and Burkitt lymphoma.

Medicines for Wilms tumour

In 2011, applicants called for the standard regimen for Wilms tumour to be adopted. This regimen included the essential drugs dactinomycin, doxorubicin and vincristine, as well as several others. When the subsequent edition of the EMLc was published, the medicines listed under Wilms tumour were listed as dactinomycin, *daunorubicin* and vincristine. Daunorubicin is not therapeutic in Wilms tumour patients and is not part of treatment protocols. This was not corrected when the next List was published in 2013, and daunorubicin remained. Doxorubicin is listed in the EMLc for both ALL and Burkitt lymphoma; it would not be a new addition. The application requested a change to the original 2011 recommendation, with daunorubicin being replaced by doxorubicin.

The Expert Committee considered that the inclusion of daunorubicin instead of doxorubicin on the EMLc in 2011 was probably a clerical error which should therefore be corrected. The Committee agreed that daunorubicin is not therapeutic for treatment of Wilms tumour and should not be included on the EMLc for this indication. For the treatment of Wilms tumour, the Committee recommended that the medicines included on the EMLc should be dactinomycin, doxorubicin and vincristine.

Medicines for ALL and Burkitt lymphoma

In 2011, applicants also called for etoposide to be included in the regimens for ALL and Burkitt lymphoma. Given that the clinical context of treatment remains the same since the 2011 recommendation, the application requested inclusion of etoposide be reconsidered as well. It was noted that etoposide is included already in the Essential Medicine List for adults and is approved for use in children.

Acute lymphocytic leukaemia

In 2011, the Committee considered, and agreed to adopt, a stepwise approach to essential medicine requirements, allowing increasing treatment requirements as experience of management of patients with increasing risk factors is progressively acquired. A five-step approach was recommended:

Step 1: A common protocol for all patients

Step 2: Additional drugs for high-risk patients

Step 3: Dose intensification and need for alternative forms of medicine in steps 1 and 2

Step 4: Medicines requiring intensive monitoring and supportive treatment to ensure safe use

Step 5: The full range of treatment options, including transplant where appropriate (*738*).

The 2011 Committee considered that medicines listed in steps 1 and 2 should be on the complementary list of the EMLc. These medicines included: prednisolone, methylprednisolone, dexamethasone, vincristine, asparaginase, methotrexate, mercaptopurine (step 1); and doxorubicin, daunorubicin, cyclophosphamide, cytosine arabinoside (cytarabine), hydrocortisone, methotrexate at doses not requiring "rescue" and tioguanine (step 2). These medicines are currently included on the EMLc for treatment of ALL. Etoposide was classified as a step 5 medicine and was not included.

The current Committee noted that, since that review, therapy for children with ALL has continued to advance, and management of these children has become increasingly standardized as paediatric oncologists around the world have become more familiar with successful regimens. Moreover, the toxicities of treatment and necessary supportive care have become familiar to oncologists. Etoposide has been a component medicine in regimens for children with ALL with higher risk features and has contributed to the improving outcome for such children. The incorporation of this medicine has not resulted in a substantial change in the overall toxicity of the regimens.

The Committee agreed that children with ALL with higher risk features should now be offered the more intensive regimens that have been shown to improve outcome. Such regimens include etoposide in addition to the medicines listed above. The Committee recognized that etoposide was an appropriate medicine for treatment of children with high-risk ALL and should now be classified as a step 2 medicine and included in the EMLc for treatment of ALL.

Burkitt lymphoma

In 2011, the Committee noted that the three core medicines for treatment of Burkitt lymphoma were cyclophosphamide, methotrexate and vincristine. Addition of prednisone, escalation of doses of methotrexate, and dose intensity had beneficial effects. Intensive protocols aimed at B-cell non-Hodgkin lymphoma and B-cell ALL, including etoposide, doxorubicin and cytarabine, had led to 90% event-free survival in developed countries, and these protocols have been adapted to low-income countries. The 2011 Committee accepted that treatment typically includes three phases: induction (using cyclophosphamide, prednisone and vincristine); intensive chemotherapy after induction (using the above with doxorubicin, and methotrexate with leucovorin rescue); and consolidation (using cytarabine and methotrexate, and cytarabine with etoposide). The 2011 Committee concluded that all the above-mentioned medicines should be included in the complementary list of the EMLc.

The current Committee noted that medicines currently included on the EMLc for Burkitt lymphoma are cyclophosphamide, cytarabine, doxorubicin, prednisolone and vincristine. In view of the conclusions reached by the 2011 Committee, the present Committee could see no obvious explanation for methotrexate (and calcium folinate (as rescue)) and etoposide not being included. The Committee recommended that the following medicines should be included on the EMLc for the treatment of Burkitt lymphoma: cyclophosphamide, cytarabine, doxorubicin, prednisolone, vincristine, methotrexate, calcium folinate and etoposide.

Retinoblastoma – EMLc

The application sought the addition of cisplatin, carboplatin and etoposide to the core list of Essential Medicines for Children for the treatment of retinoblastoma. The application also sought endorsement for the use of vincristine (already on the complementary list of the EMLc for other indications) for retinoblastoma.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Retinoblastoma is the most frequent neoplasm of the eye in childhood and represents 3% of all childhood malignancies. It is a cancer of the very young: two thirds of cases are diagnosed before 2 years of age and 95% before 5 years (*739*). For these reasons, therapeutic approaches need to consider not only cure of the disease but also the need to preserve vision with minimal long-term side-effects. The average age-adjusted incidence rate of retinoblastoma in Europe and the United States is 2–5 per one million children. Incidence of retinoblastoma is not evenly distributed around the world and appears to be higher in Africa, India, and among children of Native American descent in the North American continent (*740*). Whether these geographical variations are due to ethnic or socioeconomic factors is unclear but the fact that, even in industrialized countries, an increased incidence of retinoblastoma is associated with poverty and low levels of maternal education suggests a role for the environment (*741*, *742*).

Retinoblastoma presents in two distinct clinical forms:

- bilateral (both eyes) or multifocal (one eye with multiple distinctly separate tumour foci), heritable form (25% of all cases), characterized by the presence of germline mutations of the *RB1* gene and predisposition for developing second cancers later in life; and
- unifocal (affecting one retinal cell only and unilateral disease) form (75% of all cases), 90% of which are non-hereditary.

The most common presenting sign of retinoblastoma is leukocoria, and some patients may also present with strabismus. As the disease advances, patients present with buphthalmos, orbital exophthalmos and metastatic disease. Early diagnosis, while the disease is still intraocular, is therefore key, and cancer control initiatives aimed at early recognition of signs of retinoblastoma have the potential for enormous impact, both improving cure rates and minimizing the need for intensive treatments.

The treatment of retinoblastoma is multidisciplinary, aims to save life and preserve vision, and needs to be adapted to laterality and to the extent of disease (intra and extraocular). Intraocular disease is highly curable: more

than 90% of patients survive. Early intraocular stages are candidates for ocular preservation; treatment includes systemic neoadjuvant chemotherapy for chemoreduction, coupled with aggressive focal therapies such as thermotherapy, brachytherapy, cryotherapy and external-beam radiation therapy. Advanced intraocular disease requires enucleation; adjuvant chemotherapy and radiation therapy may be indicated in a subset of patients with high risk pathology. Outcome is much worse in patients with extraocular disease. If the disease is limited to the orbit, a combination of chemotherapy, surgery and radiation therapy may be effective and cure 50–70% of patients. The presence of extraorbital (metastatic) disease carries a poor prognosis; less than 20% of patients are cured with standard treatments. However, if metastases do not include the central nervous system, the use of consolidation treatment with high-dose chemotherapy and autologous haematopoietic stem cell rescue may cure 50–70% of patients. Patients with bilateral disease and a germline mutation are at high-risk for second malignancies; this risk increases with the use of radiation therapy.

Public health relevance

Epidemiology summary

The estimated incidence of retinoblastoma is 1 in 16 000 – 18 000 births annually, with between 7000 and 8000 new cases per year worldwide (*743*). In the United States, the mean age-adjusted incidence is 11.8 per million children younger than 5 years of age (*744*). While survival rates in the United States are nearly 100%, they are much lower in developing nations, ranging from 80–89% in more developed Latin American countries to as low as 20–46% in certain African countries. More than 90% of children with retinoblastoma live in low- and middle-income countries (LMICs), but those countries have 90% of the cases presenting with metastatic disease and almost all the cases that abandon therapy (*745*). As a result of lower survival rates, there are an estimated 3000–4000 deaths annually due to retinoblastoma (*746*). The discrepancies in survival rates emphasize the potential for reducing retinoblastoma-related deaths through timely diagnosis and proper treatment.

Additional details regarding burden of disease

Importance of early detection

Successful management of retinoblastoma depends on the ability to detect the disease while it is still intraocular. Disease stage correlates with delay in diagnosis; growth and invasion occur as a sequence of events, and extraretinal extension occurs only once the tumour has reached large intraocular dimensions. Although retinoblastoma is very curable when diagnosed early and treated appropriately, the prognosis is dismal when the basic elements of

diagnosis and treatment are lacking. In high-income countries, retinoblastoma typically presents intraocularly, while 60–90% of cases in LMICs present with extraocular disease. Lack of education, limited access to health care, and complex and deficient socioeconomic environments are associated with delayed diagnosis or under-diagnosis in LMICs. However, the magnitude of the problem is difficult to ascertain given the paucity of population-based cancer registries. Even in high-income countries, children with retinoblastoma are not always diagnosed with early-stage intraocular disease; by the time leukocoria is obvious, the tumour is usually filling more than 50% of the eye globe, making ocular salvage a major challenge. Most eyes with unilateral disease are enucleated, and children with bilateral retinoblastoma undergo aggressive treatments. The tremendous impact that modern ocular-preservation treatments have on these young children and their families should not be underestimated (*747*).

Importance of public health initiatives in retinoblastoma

Educational and public awareness campaigns have been shown to increase referrals for retinoblastoma, reduce rates of advanced disease, and improve outcomes in LMICs (*748*, *749*). The level of awareness of the first-contact health provider in identifying the problem and making the appropriate referrals is critical. Lack of knowledge among first-contact physicians has been shown to be a significant barrier to early diagnosis and to result in high incidence of metastatic disease, thus highlighting the importance of targeting primary health-care providers (*750*). Since retinoblastoma is a cancer of infants and young children, initiatives aimed at early recognition during standard health supervision and immunization visits should facilitate diagnosis, reduce the disease and treatment burden, and increase survival (*751*). Published results from several countries reveal that coordinated efforts in primary and secondary care settings and development of centres of excellence for conservative management of retinoblastoma were associated with improvements in 5-year survival rates, number of patients presenting with extraocular disease, and median age at diagnosis (*752–754*).

Requirements for diagnosis, treatment, and monitoring

Diagnostics

Diagnosis of intraocular retinoblastoma does not require pathological confirmation; an examination under anaesthesia with a maximally dilated pupil and scleral indentation is required to inspect the entire retina. Highly detailed documentation of the number, location and size of tumours, the presence of retinal detachment and subretinal fluid and of vitreous and subretinal seeds is essential. Evaluation of the enucleated eye includes basic histology since

retinoblastoma has a very distinct histology and no specific markers are necessary. Evaluation of disease extension into the anterior chamber, choroid, sclera and optic nerve is required for proper treatment considerations.

Loco-regional dissemination occurs by direct extension through the sclera into the orbital contents and pre-auricular lymph nodes, and extraorbital disease manifests as intracranial dissemination and haematogenous metastases, usually to bones, bone marrow and liver.

Testing

Additional imaging studies that aid in the diagnosis and staging include two-dimensional ocular ultrasound, computerized tomography and magnetic resonance imaging. These imaging studies are particularly important for evaluating extraocular extension and differentiating retinoblastoma from other causes of leukocoria. For patients with evidence of extraocular disease or with high-risk pathology in the enucleated eye, evaluation for the presence of metastatic disease also needs to be considered, and additional staging procedures, including bone scintigraphy, bone marrow aspirates and biopsies, and lumbar puncture, must be performed (*755*).

Administration and care of patients

Treatment decisions (eye salvage versus enucleation) are usually made on best clinical judgement by an experienced ophthalmologist.

Administration of chemotherapy requires intravenous infusion capacity and regular patient access to clinical care. For patients with intraocular disease, chemotherapy is used as either neoadjuvant or chemoreductive therapy for ocular salvage and, in the adjuvant setting, after enucleation for patients with advanced disease who are at high risk for recurrence. The VCE regimen (vincristine, carboplatin, etoposide) is used in both settings. Chemotherapy can usually be given in the outpatient setting and toxicity is moderate; patients require standard hydration and antiemetics. Infusion of vincristine requires close monitoring to prevent extravasation. Myelosuppression is mild to moderate; transfusional support is not always required and, while growth factor support is recommended, it is not always necessary. In high-income countries, ocular salvage treatment for patients with early intraocular disease may include direct infusion of chemotherapy (usually melphalan) into the ophthalmic artery of the affected eye, which requires sophisticated interventional radiology. The toxicity of this approach is quite low.

Treatment for patients with advanced (extraocular) disease is more intensive. Cisplatin-based regimens are often used during the induction phase. Administration of chemotherapy is usually in the inpatient setting; aggressive

hydration and antiemetic therapy are needed, and renal function and electrolyte balance need to be monitored closely. Toxicity is high; most patients require transfusional and growth factor support. The less toxic VCE regimen described above can be used in LMICs for patients whose disease is limited to the orbit. For patients with extraocular disease, consolidation with high-dose chemotherapy and autologous haematopoietic stem-cell rescue is recommended, but this approach is available only in high-income countries.

Radiation therapy is indicated in patients with bilateral disease in the setting of an ocular salvage plan and in all patients with extraocular disease.

Long-term follow-up for survivors of retinoblastoma requires close coordination with primary care, the school system and supporting social infrastructure. Visual impairment and difficult integration into school and society are constants in retinoblastoma survivors, and survivorship programmes must coordinate initiatives with programmes aimed at visually disabled individuals. More importantly, survivors of bilateral or hereditary disease have a significantly increased risk of developing second malignancies. The cumulative incidence of a second cancer is in excess of 30–40%, and this risk is particularly high in patients who receive radiation therapy (*756*). Almost every neoplasm has been described in survivors of retinoblastoma; the most common second tumour is osteosarcoma, both inside and outside the radiation field, and soft tissue sarcomas and melanomas are the second most common.

Overview of regimens

Essential regimen

Indicated for intraocular disease, either for ocular salvage or after enucleation for patients with high-risk pathology; also effective in patients with extraocular disease limited to the orbit.

- **VCE (6 cycles)**
  - vincristine[14] IV infusion (push) on day 1 — < 36 months: 0.05 mg/kg; > 36 months: 1.5 mg/m²
  - carboplatin IV infusion (1 hour) on day 1 — < 36 months: 18.6 mg/kg; > 36 months: 560 mg/m²
  - etoposide IV infusion (1 hour) on days 1 and 2 — < 36 months: 5 mg/kg; > 36 months: 150 mg/m²

Ancillary medications pertaining to the management of side-effects have not been included.

[14] Maximum dose = 2 mg.

Review of benefits and harms

Survival benefits

The aims of treatment are to ensure survival, preserve the eye and salvage useful vision. Historically, enucleation has been the standard treatment for patients with early-stage unilateral intraocular disease. However, approximately 20–30% of patients treated by enucleation may have high-risk pathology and require adjuvant chemotherapy and external beam radiation therapy. The latter is associated with the risk of developing radiation-induced secondary tumours and other long-term complications, including cataracts, dry eye and facial growth asymmetry. This has led to an increasing trend towards the use of focal conservative treatments and chemotherapy, where possible.

Some studies have shown that the outcomes for patients with unilateral disease that has been enucleated are positive, with good functional results (e.g. large majority of children with normal vision in at least one eye) and minimal long-term effects (e.g. large majority normal in growth and health, average mental and motor development scores in normal range) (*757*).

Retrospective and prospective controlled studies have investigated the efficacy of post-enucleation adjunctive chemotherapy using VCE in preventing metastasis in patients with high-risk retinoblastoma (*758*, *759*). In one study involving 80 patients, post-enucleation adjuvant VCE was administered to 25 patients with high-risk retinoblastoma, while another 21 patients received the older regimen of vincristine, doxorubicin and cyclophosphamide (*758*). Median follow-up was almost 5 years, after which the rates of metastasis were 4% and 24% in the adjuvant therapy and no adjuvant therapy treatment groups, respectively. The authors concluded that adjuvant therapy was responsible for significantly reducing the risk of metastases in patients with retinoblastoma with high-risk characteristics. In a second study of 52 eyes (in 51 patients), treatment with VCE chemotherapy resulted in a 0% incidence (95% CI 0%: 14%) of metastasis after a median follow-up of 5 years (*759*). No deaths were recorded. The authors concluded that VCE was effective as post-enucleation chemotherapy in high-risk retinoblastoma patients in terms of preventing systemic metastases, and was thus likely to improve survival.

A systematic review exploring the findings of studies comparing chemotherapy with no chemotherapy, or differences between chemotherapy regimens, was unable to draw meaningful conclusions because of the small number of patients in the studies, the lack of information about the treatment received by the comparison group, and the lack of consideration of potential confounding factors (*760*). The most commonly used chemotherapeutic drugs are vincristine, etoposide and carboplatin, with or without the addition of ciclosporin. The number of cycles varies from two to more than eight in different

treatment centres, although this is related to the stage of disease (*761*), with longer courses typically required to treat systemic retinoblastoma.

The treatment in tertiary care centres of patients with bilateral retinoblastoma, in whom ocular salvage is the aim, incorporates initial chemotherapy, intended to achieve maximum chemoreduction of the intraocular tumour burden early in the treatment, followed by aggressive focal therapies. This approach has resulted in an increase in eye salvage rates and in a decrease (and delay) in the use of radiation therapy. For patients with advanced intraocular tumours, ocular salvage rates can exceed 60–70%, with survival rates in excess of 90% (*762*). Intra-arterial chemotherapy delivery can result in better ocular salvage rates, although this approach is limited to advanced tertiary care centres (*763–766*). Patients presenting with orbital disease benefit from more intensive systemic therapy and orbital radiotherapy; using this approach 50–80% of patients can be cured (*767*). Up to 50% of patients with metastatic retinoblastoma without central nervous system disease can be cured using high-dose, marrow-ablative chemotherapy and autologous haematopoietic stem-cell rescue (*768*). Intracranial dissemination of retinoblastoma carries a poor prognosis; the role of therapeutic intensification with high-dose, marrow ablative chemotherapy and autologous haematopoietic stem cell rescue has been explored but remains unclear (*769*).

Harms and toxicity considerations

Vincristine commonly causes neurotoxicity – including sensory and motor neuropathies – which is typically dose-related. Neurotoxicity is usually reversible, although recovery may be gradual and possibly incomplete. Vincristine also causes constipation which can be severe; patients should receive prophylaxis (*274*).

The most frequent dose-limiting toxicity for etoposide is myelosuppression, primarily leukopenia, which can be grade 3–4 in >10% of patients. A small percentage (up to 2%) of patients receiving intravenous etoposide experience hypersensitivity reactions, which may include angioedema, bronchospasm and/or chest discomfort (*367*). Etoposide also causes reversible alopecia in up to 60% of patients (*469*). The use of etoposide has been associated with a small but increased risk of second cancers.

Platinum-based agents, including cisplatin and carboplatin, cause myelosuppression with dose-limiting thrombocytopenia and can also cause ototoxicity and asthenia. Nausea and vomiting occur in almost all patients treated with cisplatin and carboplatin and are often severe, necessitating the use of antiemetic medications. Renal toxicity caused by cisplatin can be significant and may result in electrolyte abnormalities. Intravenous hydration both before and after administration of cisplatin is necessary to reduce the incidence of renal toxicity (*380*).

Cyclophosphamide can cause bladder toxicity, and patients require additional hydration (> 2 L/m² daily) and frequent voiding in order to reduce the risk of haemorrhagic cystitis. It also commonly causes alopecia, mucositis and stomatitis, and may result in infertility (*770*).

Paediatric patients treated for retinoblastoma have a significant risk of developing secondary malignancies; the risk may be as high as 35% and is markedly increased in patients receiving radiation, particularly at a very young age (*771*).

Overall, only a limited number of studies reported data on adverse events, and a small proportion of patients were monitored to assess the impact of treatment on children's general development, including cosmetic complications and visual acuity. Data on adverse events and emotional and psychological development have apparently been only rarely gathered, which limits the quality of evidence.

Recommendations

On the basis of the evidence presented in the application, the Expert Committee recommended addition of vincristine, carboplatin, cisplatin and etoposide to the Model List of Essential Medicines for Children for the treatment of retinoblastoma. The Committee noted that vincristine is currently listed on the EMLc for use in the treatment of other cancers.

Rhabdomyosarcoma – EMLc

The application sought the addition of ifosfamide to the core list of Essential Medicines for Children for the treatment of rhabdomyosarcoma. The application also sought endorsement for use of vincristine, dactinomycin and cyclophosphamide, already on the complementary list of the EMLc for other indications, for rhabdomyosarcoma.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Rhabdomyosarcoma (RMS) is an aggressive and highly malignant soft tissue sarcoma that typically affects children and adolescents and can develop in virtually any part of the body where mesenchymal tissue is present. The two largest histological subgroups are embryonal (ERMS) and alveolar (ARMS). Historically, up to the 1960s, less than 15% of children survived (*772*). Survival rates for RMS have increased dramatically over recent decades. For RMS and ERMS in 1976–1980, the 5-year survival was about 53% and 61%, respectively. Between 1996 and 2000 the 5-year survival reached 62% and 73%, respectively. Improvements for ARMS were more limited, being 40% and 48% at the end of the 1980s and 1990s, respectively (*773*). In the 1970s, large cooperative national and international study groups started to adopt a systematic multidisciplinary approach including multidrug chemotherapy coordinated with surgery and radiotherapy. This led to a progressive increase of survival, now often above 70% (*774*), and to the identification of a number of prognostic factors (e.g. tumour histotype, tumour size and site, resectability, presence of nodal or distant metastases, patient age) that can be used to tailor the treatment (*775*).

More recently, clinical protocols have been linked to pathology and biological studies that have added important insight to the nature of RMS and may give new therapeutic opportunities in the near future. In particular, new treatment strategies are needed for those categories at major risk of treatment failure, e.g. patients with alveolar RMS or metastatic disease. RMS is a chemosensitive tumour and various drugs have proved to be effective. However, despite several drugs in addition to the standard chemotherapy having been investigated in randomized clinical trials over the years, the VAC (vincristine, dactinomycin, cyclophosphamide) and IVA (ifosfamide, vincristine, dactinomycin) regimens are still the gold standard in North America and Europe, respectively (*776*). New chemotherapeutic strategies are intensification with irinotecan-based therapy or with the "dose-compression" (in North American Children's Oncology Group (COG) protocols) (*777*) and the maintenance "metronomic" therapy with low-dose chemotherapy (for example with vinorelbine and low-dose cyclophosphamide) added at

the end of conventional treatments (in the European pediatric Soft Tissue Sarcoma Study Group (EpSSG) studies) (*778*). Various novel target agents are under investigation, e.g. mammalian target of rapamycin (mTOR), (insulin-like growth factor 1 receptor (IGF1R) and vascular endothelial growth factor (VEGF) inhibitors. The application proposed inclusion on the EMLc only of regimens that are currently considered to be standard care.

Public health relevance

RMS is the soft tissue sarcoma (STS) found most commonly in children and adolescents under 20 years of age. About 7% of all malignancies are STSs, and rhabdomyosarcoma (RMS) accounts for about 40% of paediatric STSs worldwide (*779*). While global epidemiological data are limited, there are country-specific studies that examine the incidence and prevalence of RMS. For instance, data from the Surveillance, Epidemiology, and End Results (SEER) Program were used to determine incidence of RMS in children in the USA from 1975 to 2005. The study estimated incidence to be 4.5 cases per million children/adolescents per year with more than 50% of cases occurring in children under 10 years of age (*773*). About 350 new cases of RMS occur each year in the United States.

Requirements for diagnosis, treatment, and monitoring

Diagnostics

Generally speaking, most tumours are ERMS and tend to develop in the head and neck area or in the genital and urinary tracts. Pathological assessment is necessary to identify the histological nature of the tumour. The initial biopsy is intended to define the histological diagnosis but also to provide enough material for immunochemistry, cytogenetics, biological studies and eventual central pathology review or tissue banking for patients who could be included in multicentre trials. Biopsy is recommended as the initial surgical procedure in all patients and when primary excision with adequate margins seems possible. Initial biopsy must be carefully planned by experienced surgeons, taking into account the possible subsequent definitive surgery.

Testing

An adequate patient stratification is needed for risk-adapted therapy. Treatment intensity is stratified in order to improve cure rates in patients with less favourable disease by using more intensive therapy, and to avoid over-treatment and limit side-effects – without jeopardizing results – in cases with more favourable features (*776*).

A definitive diagnosis involves several pretreatment assessments:

- Ultrasonogram is often the first instrumental assessment

- Computerized tomography (CT) scan or magnetic resonance imaging (MRI) of the primary site is essential for the local extension assessment before any treatment. (MRI can be considered superior in defining soft tissue extension)
- Distant assessments include:
  - chest CT scan
  - technetium bone scan
  - abdominal ultrasound
  - bone marrow aspiration plus trephine biopsy
  - particular evaluations of special sites if required, e.g. cerebrospinal fluid cytology in parameningeal RMS, to assess meningeal dissemination; regional lymph node biopsy in extremity RMS; retroperitoneal lymph node sampling in paratesticular RMS in boys older than 10 years.

Administration and care of patients

Administration requires intravenous infusion capacity and regular patient access to expert clinical care. For example, full blood count, renal and liver function tests should be evaluated periodically. Careful monitoring is required for patients less than 3 years old and particularly for infants less than 12 months old (e.g. careful dosing of chemotherapeutic agents to avoid hepatotoxicity (e.g. hepatic veno-occlusive disease)).

The "cost" of survival in term of late side-effects must be addressed and should guide the definition of treatment strategies, according to patients' risk stratification, in order to minimize functional and cosmetic damage without limiting potential benefit.

Late complications may be related to chemotherapy: infertility can be a consequence of cyclophosphamide, and long-term renal damage may be caused by ifosfamide-based regimens (*467*, *468*). Moreover, the continuing use of high doses of alkylating agents contributes, together with radiotherapy, to the significantly increased risk of second malignancies in long-term survivors (*780*). Radiotherapy carries a high risk of causing severe late sequelae, particularly when delivered to young children. For example, survivors who have been treated for parameningeal RMS are at high risk of important sequelae such as facial growth retardation (bone and soft tissue hypoplasia, facial asymmetry), dental abnormalities, neuroendocrine dysfunctions (growth hormone deficiency, hypothyroidism), visual problems and hearing loss and delayed intellectual development (*781*). Long-term follow-up is necessary according to the treatment received: periodic evaluation of renal, cardiac, and endocrine functions are recommended, and particular attention should be given to any signs and symptoms that suggest the development of second malignant neoplasms.

Overview of regimens

The following sections include basic information on administration and dosing for IVA (ifosfamide, vincristine and dactinomycin) and VAC (vincristine, dactinomycin and cyclophosphamide,) regimens; no details are given of ancillary medications pertaining to the management of adverse events.

Standard regimens (of equivalent efficacy)

- **IVA (9 cycles)**
  - ifosfamide[15] 3 g/m² IV infusion for two days
  - vincristine 1.5 mg/m² (max. 2 mg) IV infusion for one day
  - dactinomycin 1.5 mg/m² (max. 2 mg) IV infusion for one day
- **VAC (9–15 cycles)**
  - vincristine 1.5 mg/m² (max. 2 mg) IV infusion for one day
  - dactinomycin 1.5 mg/m² (max. 2 mg) IV infusion for one day
  - cyclophosphamide 1200 mg/m² IV infusion for one day

Review of benefits and harms

Survival benefits

RMS is always characterized as a high-grade malignancy, with local invasiveness and a marked propensity to metastasize, to the point that all RMS patients should be assumed to have micrometastatic disease at diagnosis. All patients with RMS should therefore be treated with chemotherapy, even in the case of small tumours completely resected after diagnosis. The disease is generally characterized by a good response to chemotherapy (more than 80% of newly-diagnosed cases respond to chemotherapy) and chemotherapy is thus considered the keystone of treatment for RMS (*782*, *783*).

Since the 1970s, the cure rate for RMS has improved dramatically from 25–30% using local treatments with or without single-agent chemotherapy to approximately 70%. This improvement is largely due to the development of treatment approaches that involve cooperative multi-institutional trials, using multidisciplinary treatment (surgery, radiotherapy and multi-agent chemotherapy) and risk-adapted to take account of known prognostic factors and enable appropriate stratification of treatment intensity (*782*). However, survival is strongly dependent on the type of RMS and risk group. The prognosis depends on how much of the tumour can be removed surgically.

[15] Administration of ifosfamide requires the accompanying drug mesna. The Committee noted that mesna is currently included on the EMLc as an adjuvant medicine.

The IVA and VAC regimens are considered the standard treatments in North America and Europe respectively, and can be considered essentially the same in terms of efficacy. The VAC regimen was launched by the Intergroup Rhabdomyosarcoma Study Group in the 1970s and achieved a 5-year overall survival of approximately 55% across all risk groups – a result welcomed as a large success (*784*, *785*). Overall percentages of patients surviving varied from 20% in the high-risk group to 93% in the low-risk group. In Europe the standard regimen differs in the choice of the alkylating agent: ifosfamide, vincristine and dactinomycin. In the Intergroup Rhabdomyosarcoma Study-IV (IRS-IV), 883 patients with non-metastatic rhabdomyosarcoma following surgery were randomized by primary tumour site, group and stage of disease to one of three chemotherapy regimens: VAC, IVA, or vincristine, ifosfamide and etoposide (VIE). Patients with group 3 tumours were also randomized to receive radiotherapy (conventional or hyperfractionated) (*786*). The overall 3-year failure-free survival (FFS) rate was 77%, and the survival rate was 86%. In the three chemotherapy groups, FFS rates were 75%, 77% and 77% for VAC, IVA and VIE, respectively. No significant difference was noted between the two radiotherapy arms, leading the authors to conclude that the three chemotherapy regimens with surgery, and with or without radiotherapy, were equally effective for patients with local or regional rhabdomyosarcoma.

Overall, survival of RMS patients with localized disease is around 70% but this is strictly correlated to the risk group. The prognosis for high-risk patients (e.g. patients with alveolar RMS, patients with metastases) is still unsatisfactory and effective therapies must be found (*782*). For this reason various alternatives to the VAC and IVA regimens have been investigated over the years by various cooperative groups. The role and effectiveness of cisplatin, etoposide, doxorubicin, melphalan, topotecan and irinotecan in various combinations have been explored, but trials have failed to demonstrate substantial improvements in survival over the established VAC or IVA regimens, or demonstrated only limited progress in other outcomes (*787–792*).

Harms and toxicity considerations

Patients treated with ifosfamide have a high risk of bladder toxicity and of haemorrhagic cystitis due to the accumulation of active metabolites in urine. Patients need to be suprahydrated (at least 2 L/day) and need to void frequently and/or receive mesna prophylaxis to reduce the incidence of haemorrhagic cystitis (*467*). Ifosfamide also causes alopecia and myelosuppression in most patients.

Cyclophosphamide can also cause bladder toxicity; patients require additional hydration and frequent voiding in order to reduce the risk of haemorrhagic cystitis. It also commonly causes alopecia, mucositis and stomatitis and may result in infertility (*468*).

Vincristine commonly causes neurotoxicity, including sensory and motor neuropathies, which is typically dose-related. Neurotoxicity is usually reversible, although recovery may be gradual and possibly incomplete. Vincristine also causes constipation, which can be severe; patients should receive appropriate prophylaxis (*274*).

Dactinomycin is associated with high emetic potential; patients should receive antiemetics as prophylaxis. It is very corrosive to soft tissue and can lead to tissue damage if extravasation occurs. Dactinomycin causes alopecia in most patients (*793*).

Recommendations

The Expert Committee noted that the use of multidrug chemotherapy using VAC and IVA, in conjunction with local control measures for the primary tumour, has resulted in survival rates of around 70% in multidisciplinary care settings and across different risks of relapse.

On the basis of the evidence presented, the Committee recommended addition of vincristine, ifosfamide, dactinomycin and cyclophosphamide to the Model List of Essential Medicines for Children for the treatment of rhabdomyosarcoma. The Committee noted that vincristine, dactinomycin and cyclophosphamide are currently listed on the EMLc for use in the treatment of other cancers.

Administration of ifosfamide requires the accompanying drug mesna. The Committee noted that mesna is currently included on the EMLc as an adjuvant medicine but considered that its use should be specifically endorsed for treatment of rhabdomyosarcoma alongside ifosfamide.

As rhabdomyosarcoma also affects older children and adolescents, the Committee considered it appropriate to also include vincristine, ifosfamide, dactinomycin, cyclophosphamide and mesna on the Model List for adults, specifically for the treatment of rhabdomyosarcoma.

Testicular germ cell tumours – EML and EMLc

The application sought endorsement of the following medicines, currently included on the complementary list of the Model List of Essential Medicines, for the treatment of testicular germ cell tumours: bleomycin, etoposide, ifosfamide and mesna. The application also sought the addition of cisplatin and granulocyte colony-stimulating factor (G-CSF, filgrastim) to the core list for use in this indication.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Testicular germ cell tumours account for approximately 1% of all newly diagnosed male cancers worldwide, and in 2012 there were estimated to be more than 10 000 deaths from this disease (*255*). Testicular cancer is most commonly seen in young men but can also be seen in paediatric patients; the benefits of therapy are similar in the two age groups.

Testicular germ cell tumours are divided into two groups, seminomas and non-seminomas, with non-seminomas being further subdivided into four distinct histologies (yolk sac tumour, choriocarcinoma, embryonal cell carcinoma, and teratoma) (*794*). Approximately 95% of germ cell tumours arise in the testes, although extragonadal primary tumours of the retroperitoneum, mediastinum and pineal gland do occur (*795*). While most extragonadal tumours are more challenging to treat, germ cell tumours generally have an excellent overall prognosis, with 5-year survival rates in excess of 95% in developed countries. Cure rates for clinical stage I tumours approach 100%, and even patients who present with distant metastatic disease have impressive rates of long-term overall survival when treated with appropriate chemotherapy (*796*).

Management options for stage I patients include aggressive surveillance or radiation for seminoma, and surveillance, retroperitoneal lymph node dissection (RPLND) or short-course chemotherapy for non-seminoma. In addition to radical inguinal orchidectomy, the backbone of standard therapy includes cisplatin-based combination chemotherapy, most often bleomycin, etoposide and cisplatin (BEP). The duration of treatment is based on stratification of advanced-disease patients into three risk groups – good risk, intermediate risk and poor risk – based on pathology, degree of tumour marker elevation (alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (β-hCG) and lactate dehydrogenase (LDH)) and imaging. In good-risk disease, either three cycles of BEP or four cycles of a combination of etoposide and cisplatin (EP) can be given with similar efficacy (*797–803*). In poor-risk disease, patients should receive four cycles of BEP or, for those with baseline lung disease, the alternative regimen of etoposide, ifosfamide and cisplatin (VIP) which has shown similar efficacy but with increased haematological toxicity (*804*, *805*).

Salvage surgery also plays a major role in the treatment of these patients, and surgical resection should be considered in the setting of radiographically persistent disease with normal tumour markers as this may represent teratoma, which is not chemosensitive, or residual viable cancer. This surgery is not recommended outside specialized centres of excellence, not typically seen in most low- and middle-income countries (LMICs). In patients with advanced disease, the combination of the above therapies gives approximate cure rates of over 90% for good risk, 75% for intermediate risk and 50% for poor risk status (*806*).

Public health relevance

Epidemiological information concerning germ cell tumours of the testes is limited. However, more than 90% of testicular cancers develop in germ cells, so epidemiological data for testicular cancer is a close approximation. For 2012, GLOBOCAN estimated the worldwide incidence of testicular cancer to be 55 266 (age-standardized rate (ASR) 1.5 per 100 000) (*255*); incidence in more developed regions was 32 740 (ASR 5.2 per 100 000) and in less developed regions 22 526 (ASR 0.7 per 100 000). In LMICs, the incidence of testicular cancer is far less, with a cumulative lifetime risk similar to that of Hodgkin lymphoma, melanoma and multiple myeloma (*807*).

GLOBOCAN estimated global mortality rate due to testicular cancer in 2012 to be 10 351 (ASR 0.3 per 100 000). Mortality rates in more developed regions (2209; ASR 0.4 per 100 000) and less developed regions (8142; ASR 0.3 per 100 000) were comparable. In developed countries testicular cancer is the most commonly diagnosed malignancy in men aged 15–40 years (*808*). Given that the disease is highly curable, improved outcomes are important both medically and economically because of the number of productive life-years gained with treatment.

Requirements for diagnosis, treatment, and monitoring

Diagnostics

Initial evaluation of a suspicious testicular mass should include a complete history and physical examination, tumour markers including AFP, β-hCG and LDH, blood chemistries, a chest X-ray and testicular ultrasound. Transcrotal illumination may differentiate solid masses from hydroceles but cannot be used to rule out cancer because 20% of patients with testicular cancer have associated hydroceles. If a hypo-echoic testicular mass is found on ultrasound, radical inguinal orchidectomy is recommended since approximately 95% of these lesions are malignant. Scrotal biopsy is not advised – most masses are malignant and biopsy can result in seeding of the biopsy tract with malignant cells (*806*). Pathology will distinguish between a seminoma and a non-seminoma and, among non-seminomas, will determine histological subtype (i.e. yolk sac

tumour, choriocarcinoma, embryonal cell carcinoma or teratoma). Tumour markers aid in diagnosis (e.g. elevated AFP is consistent with a non-seminoma or a mixed seminoma/non-seminoma) and are used to determine prognosis and direct decisions on postoperative treatment.

Staging and risk categories

Staging of testicular cancer involves degree of spread within the scrotum and surrounding tissues, absence/presence and extent of retroperitoneal involvement, pulmonary metastases, other visceral metastases, and levels of biomarkers including β-hCG, AFP and LDH.

Testing

Postoperative evaluation of patients with testicular cancer should include contrast-enhanced abdominal/pelvic computerized tomography (CT) and repeat tumour markers (AFP and β-hCG). A chest CT should be obtained if an abnormality on the original chest X-ray or abdominal/pelvic CT is reported. Other pretreatment laboratory tests, including complete blood count and tests of renal and hepatic function, should also be ordered. Where available, some clinicians obtain baseline pulmonary function tests, including diffusion capacity testing, before initiation of bleomycin. Imaging of the brain is recommended only in the setting of neurological signs or symptoms.

Administration and care of patients

The medical management of testicular cancer is based on pathology (seminoma versus non-seminoma), disease stage and the status of the tumour as defined by tumour markers, and sites of disease. Postoperative chemotherapy is administered to men at risk for disease recurrence, with longer-course treatment for those with higher-risk disease. Administration of chemotherapy requires intravenous infusion capacity, and regular and ready patient access to clinical care. Chemotherapy is typically given in an outpatient facility, although inpatient admission is sometimes required to control the side-effects of chemotherapy or for close monitoring of seriously ill patients with advanced disease. Intravenous hydration and close laboratory monitoring are requirements with cisplatin administration in order to prevent nephrotoxicity. Careful monitoring by history and physical examination for bleomycin toxicity (e.g. new pulmonary symptoms, basilar rales or pulmonary restriction) is essential, with early discontinuation if signs, symptoms or altered pulmonary function develop (*809*). Prophylactic antiemetics are essential, since cisplatin is highly emetogenic.

Monitoring requires that clinicians have access to laboratory facilities, as well as the ability to recognize and address potential adverse events caused by the treatment itself, including nephrotoxicity, bone marrow suppression,

infection, gastrointestinal toxicity and pulmonary toxicity. Serum markers should be obtained with each course of chemotherapy to monitor for appropriate treatment response. The half-life of β-hCG is 1.5 days and that of AFP 5 days; prolonged half-lives of these markers during chemotherapy predict increased risk of recurrence and adverse prognosis.

Overview of regimens

Standard regimens for stage II and III seminoma or non-seminoma – good risk patients

- **BEP (adult) – 21-day cycle, 3 cycles**
  - bleomycin 30 units IV bolus on days 1, 8 and 15
  - etoposide 100 mg/m² per day IV infused over 30 minutes on days 1–5
  - cisplatin 20 mg/m² per day IV infused over 15–30 minutes on days 1–5
- **BEP (prepubertal children) – 21-day cycle, 3 cycles**
  - bleomycin 15 units/m² IV bolus on day 1 (maximum dose 30 units)
  - etoposide 100 mg/m² per day IV infused over 30 minutes on days 1–5
  - cisplatin[16] 20 mg/m² per day IV infused over 15–30 minutes on days 1–5

Alternative regimen

- **EP (adult) – 21-day cycle, 4 cycles**
  - etoposide 100 mg/m² per day IV infused over 30 minutes on days 1–5
  - cisplatin 20 mg/m² per day IV infused over 15–30 minutes on days 1–5

Standard regimens for stage IIIB or IV, intermediate-risk seminoma or intermediate- or poor risk nonseminoma

- **BEP (adult) – 21-day cycle, 4 cycles**
  - bleomycin 30 units IV bolus on days 1, 8 and 15

[16] For BEP in prepubertal children, an accepted substitution for cisplatin is carboplatin with a dose of AUC 7.9. This has less renal toxicity.

  - etoposide 100 mg/m² per day IV infused over 30 minutes on days 1–5
  - cisplatin 20 mg/m² per day IV infused over 15–30 minutes on days 1–5

- **BEP (prepubertal children) – 21-day cycle, 4 cycles**
  - bleomycin 15 units/m² IV bolus on day 1; (maximum dose 30 units)
  - etoposide 100 mg/m² per day IV infused over 30 minutes on days 1–5
  - cisplatin 20 mg/m² per day IV infused over 15–30 minutes on days 1–5

Alternative regimens for patients unable to tolerate bleomycin

- **VIP (adult) – 21-day cycle, 4 cycles**
  - etoposide (VP-16) 75 mg/m² per day IV on days 1–5
  - ifosfamide[17] 1.2 g/m² per day IV on days 1–5
  - cisplatin 20 mg/m² per day IV on days 1–5

VIP has similar efficacy to BEP but is associated with greater haematological toxicity. BEP is therefore considered the standard of care for most patients, except those with pre-existing lung disease.

Standard regimen – salvage regimen (previously treated patients)

- **VeIP (adult) – 21 day cycle, 4 cycles**
  - vinblastine 0.11 mg/kg per day IV on days 1–2
  - ifosfamide 1.2 g/m² per day IV on days 1–5
  - cisplatin 20 mg/m² per day IV on days 1–5

Review of benefits and harms

Benefits

Both testicular and extragonadal germ cell tumours have the potential to be very aggressive. Without treatment, patients who develop these malignancies cannot survive, and both surgical resection of primary lesions and chemotherapy for more advanced disease are therefore extremely important. The most important improvement in the treatment of this disease was the discovery of cisplatin

[17] Administration of ifosfamide requires the accompanying drug, mesna.

in the 1970s, and the observation of responses in patients with testicular tumours (*796*). Since that time, various regimens and treatment schedules incorporating this drug have been used with significant improvements in response rates and overall survival. In combination with orchidectomy, these treatments produce an overall survival rate that approaches 100% for clinical stage I disease. Stage II disease has a cure rate of > 95%, and even patients with advanced disease have overall survival rates that far exceed those in almost any other type of cancer. For patients with stage III disease, the prognosis is good, albeit dependent on stratification to good-, intermediate- and poor-risk categories (*806*).

The efficacy of BEP and VIP chemotherapy regimens for treatment of testicular cancer has been demonstrated in numerous phase III randomized trials. For patients with low-risk stage III disease, treatment with three cycles of BEP or four cycles of cisplatin plus etoposide is associated with favourable outcomes, with cure rates and overall survival often in excess of 90% (*797*, *798*, *800*, *802*). Patients with intermediate-risk stage III disease have achieved progression-free survival of 60–80% with four cycles of BEP or VIP and overall survival of 70–90% (*804*, *805*, *810*). In high-risk stage III patients, durable responses are of the order of 60%, with overall survival rates mostly above 50% two years after the start of treatment (*804*, *811–814*) and the majority of late relapses occurring after more than five years (*815*). The role of chemotherapy in this disease is thus of paramount importance.

BEP and VIP regimens were compared in an analysis of an intergroup trial of 283 patients with advanced germ cell tumours (*805*). After a median follow-up of 7.3 years, rates of overall and progression-free survival were comparable for the two regimens; however, greater toxicity – primarily haematological – was observed in the VIP arm.

In relapsed disease, standard-dose therapy with cisplatin, combined with two drugs not received by the patient in the first-line regimen, is indicated. Depending on the composition of first-line therapy, salvage treatment with vinblastine, ifosfamide and cisplatin (VeIP) or VIP has shown efficacy and these regimens are commonly used (*734*, *735*, *806*).

Harms and toxicity considerations

Common

Common toxicities associated with treatment include myelosuppression, coronary artery disease, hypogonadism and decreased spermatogenesis, occasionally leading to infertility. Men treated with cisplatin commonly experience peripheral neuropathy, tinnitus and some degree of hearing loss (*736*). With regard to risks during surgery, common issues would include wound infection and intra-operative surgical complications.

The most important toxicities to consider with standard chemotherapy regimens for germ cell tumours are marrow suppression, neutropenic fever, cisplatin-induced nephrotoxicity and bleomycin-induced pulmonary toxicity. With cisplatin, close monitoring of routine laboratory tests and aggressive intravenous hydration before and after chemotherapy are necessary to avoid significant decline in renal function. With prophylactic hydration, reductions in glomerular filtration rate occurs in 20–30% of patients on cisplatin (*736*).

Serious

It has been shown that 9 weeks (3 cycles) of bleomycin is essentially devoid of any clinically significant pulmonary toxicity (*798*, *799*, *816*, *817*). However, the risk of toxicity is dose-dependent (increasing with cumulative doses above 450 units) (*736*), and patients should be closely monitored for cough, dyspnoea, fever, lung restriction, hypoxia or rales, which can be signs and symptoms of early bleomycin-induced pulmonary disease. In the absence of pulmonary function tests, any rales (especially in lung bases) that do not clear with coughing are an indication to stop bleomycin therapy. Risk factors for bleomycin lung toxicity are underlying lung disease, age over 50 years, renal dysfunction and smoking, and consideration of alternative therapies is often indicated.

There is a small but significant increase in the risk for secondary solid cancers that are typically diagnosed years after completion of treatment. Testicular cancer survivors, particularly those who received cumulative etoposide doses of more than 2000 mg/m² contained in the VIP regimen, are also at risk for myelodysplastic syndrome or acute leukaemia (*816–820*).

One adverse event that is more specific to patients who undergo RPLND is retrograde ejaculation, which can be reduced if the procedure is performed with a nerve-sparing surgical approach (*796*). Sperm banking is indicated before chemotherapy, radiation therapy for seminoma and RPLND.

Recommendations

The Expert Committee noted the available evidence demonstrating high cure rates associated with the proposed chemotherapy regimens for testicular germ cell tumours and recommended the addition of cisplatin to the complementary list of the Model List of Essential Medicines and the Model List of Essential Medicines for Children. The Committee also recommended that bleomycin, etoposide, ifosfamide and vinblastine be included on both Model Lists for this indication. Additionally, given the requirement for treatment with ifosfamide to be accompanied by mesna, the Committee recommended inclusion of mesna on the complementary lists of the EML and EMLc for this indication.

Inclusion of G-CSF on the EML was considered by the Expert Committee in a separate application.

Section 9: Antiparkinsonism medicines

Dopamine agonists (review) – EML

During the 19th meeting of the WHO Expert Committee in 2013, the Committee called for a detailed application for the addition of a dopamine agonist to the EML (*11*). Subsequently, an application reviewing the available evidence on oral dopamine agonists (bromocriptine, cabergoline, dihydroergocryptine mesylate, pramipexole, ropinirole) for the treatment of Parkinson disease was submitted by Dr Francesco Nonino, Drug Evaluation Unit and WHO Collaborating Centre in Evidence-Based Research Synthesis and Guideline Development, Emilia Romagna Health and Social Care Agency, Bologna, Italy.

Expert reviews of the application were prepared by two members of the Expert Committee. No public comments were received in relation to the application.

Parkinson disease (PD) is one of the commonest progressive neurodegenerative diseases in elderly people. The prevalence of PD varies from 30 to 180 per 100 000 population and increases with age in low-, middle- and high-income countries (*821–824*). The disease affects both males and females and is diagnosed in about 1.6% of people over the age of 65 years. The onset of PD is gradual and the disease evolves slowly: mean survival is more than 10 years. Diagnosis is primarily clinical and depends on the presence of a specific set of symptoms and signs, as well as on the response to drug therapy. The most common clinical manifestations are tremor at rest, rigidity, slowness of movement (bradykinesia) and poverty of movement (hypokinesia). Gait disturbances, postural instability and falls may develop.

The Expert Committee acknowledged that:

- Current pharmacological treatment is centred upon dopamine replacement to alleviate symptoms.
- So far, no medicine has proved to be disease-modifying, stopping or reversing the neurodegenerative process that leads to PD. Motor symptoms therefore continue to progress and increasing doses of medication are required, resulting in short-term adverse effects and in medium- to long-term motor complications.
- Most clinicians adopt the therapeutic strategy of delaying the start of pharmacological treatment until symptoms interfere with daily life.
- The available pharmacological therapies for early-stage PD include levodopa, dopamine receptor agonists (DAs) and monoamine oxidase B inhibitors. Anticholinergics, beta-blockers and amantadine may be used in selected patients but are not generally recommended as drugs of first choice (*825*).

- Starting drug treatment in the early stage of PD with either DAs or levodopa monotherapy has been widely debated, since both approaches offer benefits and disadvantages. Postponing the introduction of levodopa gives the advantage of "shifting onwards" the occurrence of levodopa-related motor fluctuations and may give better control of motor symptoms for a longer period. Starting with levodopa may achieve a better tolerability and quality of life in the longer term.
- Patients with advanced-stage PD require levodopa, and motor fluctuations are then inevitable.

The mainstay of PD treatment is levodopa, the amino acid precursor of dopamine, combined with a peripheral dopa decarboxylase inhibitor; this has been the standard symptomatic therapy for PD for more than 40 years. The current EML lists levodopa + carbidopa as 100 mg + 10 mg, 100 mg + 25 mg, and 250 mg + 25 mg. The main limitations of levodopa are its decreasing efficacy over time and the fluctuating responses to treatment. Use of DAs may offer some advantages in terms of lower occurrence of dyskinesia and motor fluctuations during the first 4-5 years of treatment. However their use is limited by a higher incidence of disabling non-motor adverse reactions.

The older DAs – bromocriptine, pergolide, lisuride and dihydroergocryptine mesylate – are ergot derivatives, while ropinirole and pramipexole are non-ergot derivatives. Lisuride and pergolide are not considered in this application, since the former is no longer available and the latter has been withdrawn for safety reasons.

Most trials and systematic reviews investigated the benefit of use of DAs, distinguishing early-stage and advanced-stage PD, as stand-alone treatment or as adjunct to levodopa (*826–831*). When compared with placebo, DAs produced a significant improvement in symptom control in both early- and advanced-stage PD; however, when DAs were combined with levodopa and compared with levodopa and placebo, there was usually no difference observed between treatment arms at any time and with any scoring system (*827*, *828*). Non-ergot long-acting DAs (e.g. extended-release pramipexole, prolonged-release ropinirole and transdermal rotigotine) consistently showed a significant benefit over placebo; comparison with levodopa, however, showed no significant differences for any outcome (*830*, *831*). A network meta-analysis of non-ergot DAs found that improvements with pramipexole and ropinirole were slightly less than with levodopa (*829*). The PD MED trial, a large, independent, pragmatic trial, compared early initiation with levodopa or initiation with a DA (i.e. ropinirole or pramipexole) in individuals with newly diagnosed PD (*832*). During 7 years of follow up, at no point was there any significant difference in quality of life,

measured using the 39-item Parkinson Disease Questionnaire (PDQ-39) quality of life scale, between the levodopa arm and the DA arm., Average scores were consistently better among patients treated with levodopa, as were the average scores for the activities of daily living subscales. Improvements in quality-adjusted life-years were greater in the early-levodopa arm despite a higher proportion of patients suffering levodopa-related dyskinesias.

Evidence concerning which class of add-on treatment is the more efficacious in advanced PD is lacking and there are uncertainties about differences in efficacy between DAs and other classes of drugs (e.g. catechol O-methyltransferase inhibitors (COMTI) and monoamine oxidase type B inhibitors (MAOBI)).

With regard to safety, the risk of developing dyskinesia, motor fluctuations or dystonia among patients with early PD treated with DAs is lower than that among patients treated with levodopa. However, all DAs (ergot and non-ergot) may cause neurological and psychiatric adverse events related to their dopaminergic action. Confusion, impulse control disorders (pathological gambling, hypersexual behaviour, compulsive shopping), daytime sleepiness and hallucinations have been associated with their use, while ergot-derived DAs can, more rarely, induce retroperitoneal, pleural and pericardial fibrosis and cardiac valvulopathy. Cardiac valvular fibrosis and retroperitoneal fibrosis can have severe clinical consequences, and led to withdrawal from the market of lisuride and pergolide. Cabergoline has also been withdrawn in some developed countries. Because of these risks, the clinical use of ergot DAs has been declining. The risk of the above-mentioned non-motor complications is increased among patients taking DAs compared with those given placebo or levodopa alone (*827*, *828*, *833*). Treatment tolerability, assessed by discontinuation rates, was better in patients given early levodopa than in patients initiated with DAs, mainly because of side-effects associated with the use of DAs (*832*). These findings are reported in systematic reviews that considered DAs as a class as well as in those that investigated individual agents or long-acting non-ergot DAs, regardless of the stage of the disease. Systematic reviews of observational studies consistently report that the use of ergot DAs increases the risk of valvular regurgitation, with the effect being dose-dependent (*834–836*).

Non-ergot DAs are more expensive than ergot DAs. All DAs are more expensive than levodopa. In high-income countries the price of DAs varies considerably. Only bromocriptine mesylate 30 x 2.5 mg tab-cap is included in the International Drug Price Indicator Guide. The unit price of bromocriptine ranges from US$ 0.04 in Sudan to US$ 0.30 in South Africa, with a median price of US$ 0.16. In India the annual cost of DAs (mean +/– standard deviation) ranges from US$ 109.4 (+/– US$ 111.9) for the earliest stages of the disease to US$ 128.1 (+/– US$ 144) for advanced stages (*837*).

The Expert Committee noted that several international guidelines deal with the use of DAs in the treatment of PD. Most of them (NICE 2011; SIGN 2010; EFNS 2011) have produced distinct recommendations for use of DAs in early-stage PD and, as an adjunct to levodopa, in advanced-stage PD (*825*, *838*, *839*).

In early-stage PD, DAs are among the drugs that may be recommended as monotherapy and as a symptomatic treatment, particularly in younger patients. Ergot derivatives are not recommended as first-choice drugs, however, because of the monitoring required in relation to the risk of fibrosis.

In advanced-stage PD, DAs are considered as a therapeutic option for the management of motor complications in patients being treated with levodopa. Decisions regarding the timing of introduction and the type of drug should be made on an individual basis. Non-ergot DAs are the preferred choice.

The Committee noted that the availability of antiparkinsonism medicines in primary care is variable, ranging from 12.5% in Africa to 79.1% in Europe (*840*).

The Expert Committee concluded that the most effective treatment for PD is levodopa. Dopamine agonists – like other available treatments for PD – do not modify the course of the disease, and their action is symptomatic.

The Expert Committee decided that there was insufficient evidence to show that dopamine agonists offered any clinically relevant efficacy or safety advantages over the existing medicines included in the EML. The Committee therefore recommended that the proposed dopamine agonist medicines should not be added to the EML.

Section 10: Medicines affecting the blood

10.1: Antianaemia medicines

Folic acid (new formulation) – EML

An application was submitted by Ms Hala Boukerdenna, Dr Juan Pablo Pena-Rosas, Dr Lisa Rogers and Dr Maria Nieves Garcia-Casal, on behalf of the WHO Department of Nutrition for Health and Development, for the inclusion on the Model List of a new formulation of folic acid (400 μg tablet) for periconceptional supplementation in women of childbearing age as a public health intervention for prevention of neural tube defects (NTDs).

The application requested listing in Section 27, Vitamins and minerals, although existing listings for folic acid are in Section 10.1, Antianaemia medicines.

Reviews of the application were prepared by two members of the Expert Committee. Comments on the application were received from Dr Myriam Henkens, International Medical Coordinator, Médecins Sans Frontières.

Folic acid is the synthetic form of folate (water-soluble vitamin B9), which is used in dietary supplements and added to foods. The bioavailability of folic acid from supplements and folic acid-fortified foods appears to be substantially higher than folate bioavailability from consumption of natural folate-rich foods such as beef liver, leafy green vegetables, oranges and legumes (*841*).

The most prevalent types of NTDs are anencephaly, encephalocele and spina bifida. Congenital anomalies (also referred as birth defects) affect an estimated 1 in 33 infants and result in approximately 3.2 million birth defect-related disabilities every year. The NTD burden was recently assessed in 18 countries in the six WHO regions. The overall burden calculated using the median was 1.67/1000 live births for total NTD burden, 1.13/1000 for spina bifida, 0.25/1000 for anencephaly and 0.15/1000 for encephalocele (*842*). It was also estimated that, in low- and middle-income countries, about 190 000 babies are born each year with an NTD.

Studies have shown that the occurrence of NTDs can be significantly reduced by increasing the consumption of folic acid by women during the periconceptional period. This has led WHO to recommend that a woman who has not previously had a fetus diagnosed as affected by an NTD or given birth to a baby with an NTD should consume 400 μg of folic acid daily, from the time she begins trying to conceive until 12 weeks of gestation (*843*).

The Expert Committee noted that the 18th EML currently includes folic acid tablets in 1 mg and 5 mg strengths, and folic acid (400 μg) in combination with iron (60 mg elemental iron) (*11*). The application asserted the importance for women who have difficulties in taking or who choose not to take iron supplements, or for whom iron is not recommended for other reasons, to have the option of consuming folic acid alone in the recommended dose for the prevention of first occurrence of NTDs.

The application described a Cochrane systematic review of five trials involving 6,105 women that assessed the effects of periconceptual folic acid supplementation to reduce NTDs. Two of the included trials involved 299 women who received either folic acid (360 µg or 4 mg) or no treatment/placebo. Overall, there was a statistically significant reduction in risk of recurrence of NTDs (RR 0.32, 95% CI: 0.08–1.34) in patients receiving folic acid supplementation (*844*). Supplementation was started before pregnancy and continued throughout the first trimester. The women in both trials had a history of previous pregnancy affected by NTD. In the trial that involved the 360 µg folic acid dose, the difference between groups was not statistically significant. The Expert Committee noted that for women with a history of NTD-affected pregnancy, the WHO-recommended dose of folic acid supplementation for prevention of recurrent NTD is 5 mg daily.

Studies have demonstrated an inverse relationship between the risks of NTDs and maternal red blood cell (RBC) folate. Dose-related median increases in RBC folate concentrations have been measured in a double-blind, randomized, controlled trial of several folic acid doses (100, 200 or 400 µg), with results as follows: 100 µg folic acid/day: 67 µg/L (95% CI: 43–120); 200 µg folic acid/day: 130 µg/L (95% CI: 108–184); and 400 µg folic acid/day: 200 µg/L (95% CI: 125–312) (*845*). A 1995 study (*846*) showed that women with RBC folate values below 150 µg/L had an NTD risk of 6.6 per 1000 births. When RBC folate exceeded 400 µg/L, the risk was only 0.8 per 1000 births, and the overall population risk was 1.9 per 1000 births.

A cohort study conducted in China evaluated the prevalence of NTDs in fetuses and in infants born to women taking 400 µg folic acid ($n = 130\,142$) or receiving no treatment ($n = 117\,689$) at any time before or during pregnancy. Supplementation with 400 µg folic acid daily led to a 79% reduction in the risk of a fetus or infant having an NTD (*847*).

Following consideration of the available evidence, the Expert Committee recommended inclusion of 400-µg folic acid tablets on the core list of the EML for periconceptional use in women of childbearing age for the prevention of the first occurrence of NTDs. The Committee noted that this recommendation was consistent with recommendations in WHO's *Standards for maternal and neonatal care*. The Committee recommended listing in Section 10.1.

The Expert Committee acknowledged that periconceptional daily supplementation with folic acid in women of childbearing age was an effective and clinically important public health intervention.

The Committee noted that 5 mg daily remains the recommended dose of folic acid supplementation for prevention of recurrent NTDs in women who have previously had an NTD-affected pregnancy, and that this higher strength is currently included on the EML.

Ferrous salt + folic acid (new formulation) – EML

An application was submitted by Ms Hala Boukerdenna, Dr Juan Pablo Pena-Rosas and Dr Maria Nieves Garcia-Casal, on behalf of the WHO Department of Nutrition for Health and Development, for the inclusion on the Model List of a new formulation of iron (60 mg elemental iron) plus folic acid (2.8 mg) for use in menstruating women and adolescent girls as a public health intervention in areas where anaemia is 20% or higher and no interventions are in place to control anaemia.

Reviews of the application were prepared by two members of the Expert Committee. No public comments were received in relation to this application.

Doses of 60 mg elemental iron and 2.8 mg folic acid taken once a week are recommended in the 2011 WHO guideline *Intermittent iron and folic acid supplementation in menstruating women* (*848*) (strong recommendation) to improve haemoglobin concentrations and iron status and reduce the risk of anaemia in menstruating women living in settings where anaemia is highly prevalent. It is recommended that supplements be taken for three months, followed by no supplementation for three months, after which supplementation should be restarted.

The Expert Committee noted that the 18th EML currently includes a ferrous salt plus folic acid formulation (iron equivalent to 60 mg plus 400 µg folic acid) as a nutritional supplement for use during pregnancy (*11*). This application proposed the addition of a different strength preparation (iron equivalent to 60 mg plus 2.8 mg folic acid) for prevention of anaemia in menstruating women, consistent with recommendations in the WHO guidelines.

This application was a resubmission of an application from 2013 and provided additional data on the efficacy of weekly folic acid regimen in improving red blood cell (RBC) folate concentration and preventing neural tube defects (NTDs). In 2013, the Expert Committee recognized the programmatic needs for appropriate supplementation in pregnancy but, after careful consideration, decided not to include the proposed combination in the EML because the data did not show the intermittent regimen to be at least equivalent to the listed fixed-dose combination (ferrous salt + folic acid tablet, equivalent to 60 mg iron + 400 µg folic acid), taken once daily (*11*). While daily supplementation with iron and folic acid for a period of 3 months has been the standard approach for the prevention and treatment of iron-deficiency anaemia among women of reproductive age, its success in public health programmes has been limited; this is in part due to low coverage rates, insufficient tablet distribution and low adherence because of side-effects (e.g. constipation, dark stools, metallic taste) (*848*). The current application argued that intermittent regimens may increase acceptability and adherence, while improvements in iron and folate status before pregnancy may also help to prevent NTDs.

A Cochrane systematic review (*849*) undertaken as part of the 2011 guideline development compared intermittent iron supplementation (alone or with folic acid or other micronutrients) with no supplementation, and daily with intermittent administration schedules. Compared with no supplements or placebo, women taking intermittent iron supplements (alone or in combination with folic acid or other micronutrients) had higher haemoglobin (mean difference 4.58 g/L; 95% CI: 2.56–6.59; 13 studies) and ferritin concentrations (mean difference 8.32 µg/L; 95% CI: 4.97–11.66; six studies) and were less likely to develop anaemia (average risk ratio (RR) 0.73; 95% CI 0.56–0.95; 10 studies). Compared with daily iron supplements, women receiving intermittent supplements were more likely to be anaemic (RR 1.26; 95% CI: 1.04–1.51; six studies), have lower ferritin concentrations (mean difference –11.32 µg/L; 95% CI: –22.61 to –0.02; three studies), with no difference in haemoglobin (mean difference –0.15 g/L; 95%: CI –2.20 to 1.91; eight studies).

With regard to safety, the Cochrane review found no evidence to suggest a significant difference in adverse effects between once-weekly intermittent iron supplementation and daily iron supplementation (RR 0.36; 95% CI 0.10–1.31).

The Committee noted the conclusion of the Cochrane review that "intermittent iron supplementation in menstruating women is a feasible intervention in settings where daily supplementation is likely to be unsuccessful or not possible". Intermittent supplementation was found to be less effective than daily supplementation with regard to prevention and control of anaemia.

Two clinical trials that were included in the application examined the prevention of NTDs and showed that weekly folic acid supplementation (2.8 mg or 4 mg) was not equivalent to daily supplementation with 0.4 mg (*850*, *851*). Compared with daily supplementation, 12 weeks of weekly supplementation resulted in a lower plasma folate concentration (mean difference –12.5; 95% CI: 1.04-1.51) and a lower RBC folate concentration (mean difference –136.04; 95% CI: 185.24–6.83). Both studies showed that the rise in RBC folate was linear and did not plateau during the studies; after 12 weeks of weekly supplementation with 2.8 mg folic acid, RBC folate concentration had reached 900 nmol/L (95% CI: 828– 978), which approaches 906 nmol/L – defined as the threshold for optimal RBC folate concentration to prevent NTDs.

In all the studies listed above, compliance among menstruating women and adolescent girls was also taken into account in identifying the most effective regimen in terms of public health intervention.

The Committee noted that the proposed fixed-dose combination formulation is not widely commercially available. Concern about this lack of commercial availability was also expressed by the Expert Committee in 2013 (*11*).

Following consideration of the available evidence, the Expert Committee did not recommend addition of the new fixed-dose combination formulation of ferrous salt plus folic acid (60 mg + 2.8 mg) to the Model List. The Committee

considered that the evidence presented for efficacy of intermittent supplementation was insufficient to support such a recommendation. The overall quality of evidence for outcomes of iron supplementation, intermittent or daily, with or without folic acid, ranged from low to moderate. The Committee considered that, although claimed as an advantage of an intermittent supplementation regimen, adherence has yet to be adequately reported.

The Committee also noted that commercial availability of the proposed fixed-dose combination product was limited to one country.

10.2: Medicines affecting coagulation

Desmopressin (addition) – EML

An application was submitted on behalf of the World Federation of Hemophilia for the addition of desmopressin injection and nasal spray to the Model List of Essential Medicines for the treatment of select patients with type I von Willebrand disease, haemophilia A and other rare bleeding disorders.

Reviews of the application were prepared by two members of the Expert Committee. Numerous public comments were received in support of the application, and are available on the WHO website.

Haemophilia A is a hereditary X-linked disorder characterised by quantitative or qualitative deficiency of coagulation factor VIII (*852*). Haemophilia A is the most common type of haemophilia and mainly affects boys and men. It is a rare condition, affecting approximately 1 in 10 000 males (*853*). In addition, around 10% of female carriers of haemophilia are also at risk of bleeding.

Von Willebrand disease (VWD) is the most common hereditary bleeding disorder, with an estimated prevalence of 0.6–1.3% and affecting men and women with equal frequency (*854*). It is caused by deficiency or dysfunction of von Willebrand factor (a coagulation factor) and is classified into three major types, which are specifically treated: partial quantitative deficiency (type 1); qualitative deficiency (type 2, with four variants – 2A, 2B, 2M and 2N); and total deficiency (type 3) (*855*). Acquired VWD comprises defects in von Willebrand factor concentration, structure or function arising from medical disorders or treatments.

Desmopressin (or DDAVP) is an antidiuretic hormone analogue and a specific vasopressin V2 receptor agonist. It increases renal tubular reabsorption of water and is used as first-line treatment in pituitary diabetes insipidus. Desmopressin also increases factor VIII and von Willebrand factor (VWF) coagulation activity and is therefore used to control bleeding in certain types of bleeding disease including haemophilia A and type 1 VWD.

In support of addition of desmopressin to the EML, the application included guidelines of the World Federation of Hemophilia (*856*) the European

Society of Anaesthesiology (*855*), the British Committee for Standards in Haematology (*857*) and the National Heart, Lung and Blood Institute (*854*). The application also included reviews of the available studies in relation to the efficacy and safety of desmopressin (*858–860*). The Expert Committee noted that clinical experience with desmopressin is based largely on anecdotal reports and small case series, but that the number of prospective and retrospective reports is growing *(858*).

The World Federation of Hemophilia guidelines note that desmopressin may be the treatment of choice for patients with mild or moderate haemophilia A, when factor VIII can be raised to an appropriate therapeutic level, as it avoids the expense and potential hazards of using a clotting factor concentrate (*856*). The guidelines also note that desmopressin is particularly useful in the treatment or prevention of bleeding in carriers of haemophilia. Desmopressin does not affect factor IX levels and is of no value in haemophilia B.

According to the United Kingdom Haemophilia Centre Doctors' Organisation guidelines, desmopressin is often effective in type 1 VWD where increasing VWF levels by a factor of 2–5 is sufficient for haemostasis (*861*). In types 2A and 2M VWD, desmopressin increases the levels of the abnormal VWF and has a variable clinical effect. The guidelines emphasize that the use of desmopressin in type 2B VWD is controversial: it has been said to be contraindicated as the release of the abnormal VWF may induce platelet aggregation and thrombocytopenia. However, it has been argued that the thrombocytopenia may be an in vitro artefact and that desmopressin is safe and may be clinically effective in type 2B disease. According to clinical studies, desmopressin has no therapeutic use in type 3 VWD.

Given the significant differences between individuals in response to desmopressin, each patient's response should be tested before therapeutic use of the drug. An individual patient's responses are usually consistent, so that patients can be labelled as responsive or not. Compared with IV administration, responses to intranasally administered desmopressin are more variable and therefore less predictable. Desmopressin may also be useful in controlling bleeding and reducing the prolongation of bleeding time associated with disorders of haemostasis, including some congenital platelet disorders. In some settings, it is used as home medication for patients with inherited bleeding disorders (*860*).

With regard to safety, desmopressin is not licensed for use in pregnancy, but there is evidence that it can be safely used during delivery and in the postpartum period in an uncomplicated pregnancy. However, its use should be avoided in pre-eclampsia and eclampsia because of the already high levels of VWF. The major advantages of desmopressin over plasma products are the much lower cost and the absence of any risk of transmission of viral infections (*861*).

The most common side-effects of desmopressin are tachycardia, flushing and headache, which are generally mild (*860*). As desmopressin is a potent

antidiuretic agent, it can cause hyponatraemia and even seizures in patients receiving generous amounts of hypotonic intravenous or oral fluids, necessitating fluid restriction during desmopressin treatment. The antidiuretic effect of desmopressin is much greater when it is administered intravenously than when it is given intranasally or subcutaneously.

The Expert Committee considered that the available evidence supports the efficacy and safety of desmopressin for prevention and treatment of bleeding in selected patients with haemophilia A, VWD and other congenital bleeding disorders. For selected patients, desmopressin offers a safer and more affordable alternative to plasma products and fresh blood components. The Committee noted that use of desmopressin has led to a substantial reduction in the use of blood products for the prevention and treatment of bleeding episodes and is recommended in national and international guidelines. The Committee also noted that the use of desmopressin requires access to specialist and laboratory services.

While noting that the evidence of efficacy and safety in most clinical settings is largely empirical, the Expert Committee acknowledged that desmopressin is an important medicine in the haemostatic armamentarium for patients with bleeding disorders, particularly in view of the ease of administration (notably the intranasal formulation), low cost and the potential for avoidance of blood derivatives. The Expert Committee therefore recommended the inclusion of desmopressin in the complementary list of the EML and EMLc.

Low-molecular-weight heparin (addition) – EML

An application was submitted by the Scientific and Standardization Committee on Control of Anticoagulation (led by Dr Walter Ageno, University of Insubria, Varese, Italy), on behalf of the International Society on Thrombosis and Haemostasis (ISTH), Carrboro, NC, USA, for the inclusion of low-molecular-weight heparins (LMWHs) on the Model List of Essential Medicines for three indications:

- prophylaxis of venous thromboembolism (VTE) in hospitalized patients;
- treatment of VTE; and
- treatment of acute coronary syndromes.

Reviews of the application were prepared by two members of the Expert Committee. Comments on the application were received from Dr Myriam Henkens, International Medical Coordinator, Médecins Sans Frontières. The Committee noted that heparin sodium (unfractionated heparin (UFH)) has been on the EML since 1977 and that LMWHs had not previously been evaluated for inclusion on the EML.

Venous thromboembolism is a frequent disease and a major health problem: the annual incidence rate was estimated to vary from 57 to 133 per 100 000 persons in different continents (*862–864*). It is associated with long-term clinical sequelae, including chronic thromboembolic pulmonary hypertension and post-thrombotic syndrome – a cluster of symptoms (pain, cramps, heaviness, paraesthesia, pruritus) and signs (pretibial oedema, skin induration and hyperpigmentation, venous ectasia) that can have a significant impact on quality of life. Case-fatality rates after a first VTE event have been estimated to be 5% (95% CI: 1–9%) after an idiopathic event, 7% (95% CI: 2–13%) after a VTE provoked by trauma, surgery or immobilization, and 25% (95% CI: 15–36%) in patients with cancer (*865*). The incidence of first-time VTE rises exponentially with age (*866*). Ethnicity is another major determinant, with higher incidence of VTE and pulmonary embolism in white persons and African-Americans than in Asians and Pacific Islanders (*867*, *868*). A large cross-sectional survey of hospital inpatients in 32 countries found 51.8% of patients to be at risk for VTE (*869*). Surgical procedures, in particular major orthopaedic surgery and cancer surgery, are commonly complicated by VTE (*870*).

Low-dose UFH has been the standard treatment of VTE for several years. It has a rapid onset of action but requires frequent laboratory monitoring, dose titration and multiple injections per day. In contrast, LMWHs can be administered once or twice daily in fixed, weight-adjusted doses, limiting the need for laboratory monitoring to attain the recommended dose in selected patients (e.g. renal failure, young children, obese patients, pregnant women).

Prophylaxis of venous thromboembolism in surgical patients

Several randomized controlled trials have tested LMWHs against various comparators in different surgical populations. Evidence is usually stratified according to orthopaedic and non-orthopaedic surgery since the risk of VTE differs between the two populations, with orthopaedic patients being at greater risk. As the evidence has accumulated across both settings and the confidence in benefit has increased, LMWHs have become the standard prophylaxis (*871*). In general and specialized surgery (e.g. gastrointestinal, gynaecological, laparoscopic, thoracic, urological, orthopaedic (including total hip or knee arthroplasty and hip fracture surgery), LMWHs are clearly more effective than no prophylaxis for reducing the risk of symptomatic VTE and pulmonary embolism (relative risk reduction approximately 80%). They are at least as effective as UFH for prevention and treatment of VTE (*872–874*). When used for perioperative thromboprophylaxis in cancer patients undergoing surgery, LMWHs and UFH show only limited differences for preventing mortality, pulmonary embolism, deep vein thrombosis or bleeding outcomes (*875*). For initial anticoagulation, LMWHs are often preferred to other interventions such as mechanical prophylaxis, vitamin K antagonists and aspirin (*873*, *876*).

With regard to safety, LMWHs have been associated with haemorrhagic and non-haemorrhagic complications. Meta-analyses of trials comparing LMWHs with no prophylaxis in hip fracture surgery, hip and knee replacement surgery, and general surgery have shown that LMWHs approximately double the risk of major bleeding and wound haematoma (from a baseline level of 1%) (*872*, *874*). The expected risk of major bleeding with LMWHs has been shown to be very close to that with UFH. In a network meta-analysis, LMWH and UFH were indirectly compared using no prophylaxis and other interventions as the reference comparator: LMWH did not significantly increase bleeding, while UFH did (*873*, *874*).

Several factors influence the incidence of heparin-induced thrombocytopenia (HIT), a potentially severe complication, including the type and preparation of heparin (UFH or LMWH) and the heparin-exposed patient population, with postoperative patients presenting a higher risk. A Cochrane systematic review compared the incidence of HIT after exposure to UFH or LMWH following any surgical intervention: LMWHs were associated with a reduction in the risk of HIT compared with UFH (*877*).

The costs of prophylactic doses of LMWHs ranged from US$ 2.25 to US$ 18.5 per dose, depending on dose and type of heparin. Biosimilar LMWHs can be found at lower prices. Studies assessing the cost–effectiveness of VTE prophylaxis in hospitalized patients have been carried out in Australia, Europe and North America. The use of pharmacological prophylaxis in hospital settings has been associated with substantial cost savings (*878–882*).

Treatment of venous thromboembolism

A Cochrane systematic review compared LMWH with UFH for the initial treatment of VTE (*883*). Fixed-dose LMWH was found to be more effective than adjusted-dose UFH in reducing the risk of recurrent VTE during both initial treatment and follow-up. Moreover, overall mortality was significantly reduced. Compared with UFH, LMWH is associated with 15 fewer recurrent VTE events and 10 fewer deaths from any cause per 1000 patients (*884*).

Major bleeding during the initial phase of treatment was significantly reduced with LMWH compared with UFH, with an incidence of 1.1% versus 1.9% (*883*). The advantage of LMWH can be summarized as five fewer major bleeding episodes per 1000 patients (*884*). In patients with active cancer and pregnant women, LMWHs are preferred to other agents (UFH, warfarin) because they have a more favourable safety profile.

The American College of Chest Physicians (ACCP) recommends initial treatment of acute VTE with parenteral anticoagulation (LMWH, fondaparinux, UFH) and recommends LMWHs over intravenous or subcutaneous UFH (*884*).

The greater efficacy and favourable safety profile of LMWHs, together with their greater ease of use, mean patients with acute VTE of the leg, whose

home circumstances are adequate, can be treated at home with LMWHs rather than in hospitals (*885*). For these reasons, LMWHs are likely to be preferred by patients.

Treatment of acute coronary syndromes

Acute coronary syndrome (ACS) refers to a spectrum of clinical presentations related to acute myocardial ischaemia caused by atherosclerotic coronary disease; it includes ST-elevation myocardial infarction (STEMI), non ST-elevation myocardial infarction (NSTEMI), and unstable angina (UA). It is the most common cause of death worldwide: ischaemic heart disease accounted for 7.4 million deaths worldwide in 2012 (*886*). The proportion of deaths is higher in high-income countries but it is rapidly increasing in lower-middle-income countries. The percentage of ACS or MI cases with ST-segment elevation varies in different registries and depends on the age of patients considered and the surveillance systems, varying from 30% to 50% (*887*). In recent years there has been a progressive increase in the proportions of patients who present with UA compared with acute MI and with NSTEMI compared with STEMI. In industrialized countries the annual incidence of UA is around six cases per 10 000 people (*888*).

UFH has been in use as therapy for patients with NSTEMI or UA for more than two decades, and as an adjunctive therapy to fibrinolysis or percutaneous coronary intervention in STEMI.

Non-ST elevation ACS

Based on evidence for UFH and LWMHs, anticoagulant therapy is superior to no anticoagulant therapy in patients with non-ST elevation ACS (*889*, *890*). Enoxaparin had a significantly lower rate of the combined end-point of death, MI, and angina compared with UFH in patients with UA or NSTEMI who were treated with a conservative medical approach (*891–893*). Other LMWHs appear to have equivalent efficacy to UFH, but possible differences with enoxaparin cannot be excluded. In patients who underwent percutaneous coronary revascularization or coronary artery bypass graft surgery, evidence favouring enoxaparin is less straightforward: enoxaparin and UFH have similar efficacy (*894*) but enoxaparin might be associated with a significant increase in major bleeding (*895*). Nevertheless, enoxaparin is easier to administer than UFH and does not require laboratory monitoring.

ST-elevation ACS

A systematic review compared the efficacy and safety of LMWH with UFH across the spectrum of ACS (*896*). LMWH was found to be associated with a statistically significant lower risk of death or MI at 30 days. Across the entire ACS spectrum, LWMH (enoxaparin) reduced the risk of death or MI from 13.5% to

12.5%, with a better efficacy profile in patients with STEMI. Another systematic review compared LMWH (enoxaparin) with UFH in the context of primary percutaneous coronary intervention in STEMI; LMWH was associated with significant reductions in death (1.66% absolute risk reduction) and MI (*894*).

In patients with STEMI, NSTEMI or UA, differences in major bleeding were slightly more frequent in patients treated with UFH compared with those treated with LWMH (*894*). Notably, during percutaneous coronary interventions, the evidence is inconsistent: major bleeding might be more frequent with UFH or LWMHs depending on route of administration (i.e. intravenous or subcutaneous enoxaparin) and other variables (*894*, *895*).

In patients with ACS, LMWH (enoxaparin) is a cost–effective strategy, both improving important clinical outcomes and saving money relative to therapy with standard UFH (*897*). However, drug acquisition costs per day for LMWH can be higher than the costs for UFH. The adoption of LMWH necessitates demonstration of economic attractiveness over UFH, taking into account other associated costs occurring throughout the continuum of care (e.g. advantages related to there being no need for laboratory monitoring and to safety of administration in outpatient settings).

The European Society of Cardiology guidelines on the management of NSTEMI or UA recommend the use of anticoagulant therapy for all patients in addition to antiplatelet therapy (*898*). In the management of STEMI, guidelines recommend anticoagulation in patients treated with thrombolytics until revascularization (if performed) or for the duration of hospital stay up to 8 days. LMWH is preferred to UFH (*899*).

In patients with severe renal insufficiency, repeated doses of LMWH may lead to accumulation and increased risk of bleeding, as LMWH is primarily renally cleared. Dose adjustment may be required. Older and obese patients may also require dose-adjustments of LMWH. LMWH is safe for use during pregnancy and pregnant patients can be given the same dose as non-pregnant patients. In the event of significant increase in maternal weight, however, dose adjustments may be required (*900*).

LMWH offers several pharmacological advantages over UFH, including better absorption after subcutaneous administration, less protein binding and a more predictable dose–effect relationship. LMWHs are similar products but are not identical and they can differ chemically and pharmacokinetically (*901*). A wide spectrum of in vitro and in vivo coagulation tests detected some measurable pharmacodynamic differences between currently available LMWH preparations when administered using equivalent anti-activated factor Xa doses. Evidence from a small number of studies that directly compared different LMWHs in VTE has shown no clinically meaningful differences.

Overall, the Expert Committee considered that the available evidence showed that LMWHs are safe and effective in the prophylaxis and treatment of

VTE, and in the treatment of acute coronary syndromes. Being administered subcutaneously, they are also easier to use than IV unfractionated heparin. No routine monitoring is required, which adds to their convenience.

The Committee agreed that LMWHs meet the criteria for inclusion as an essential medicine in health systems and therefore recommended addition of the pharmacological class of LMWHs to the core list of the Model List of Essential Medicines. The Committee considered that, as there is more evidence for its effectiveness and safety, enoxaparin should be listed with a square box symbol as representative of the class. The Committee recommended a note limiting alternatives to nadroparin and dalteparin, since the available evidence supports their use in the three indications for which listing was sought. The Committee considered cost and noted the availability of cheaper, biosimilar generic alternatives.

Novel oral anticoagulants (NOACs – dabigatran, rivaroxaban, apixaban) (addition) – EML

An application was submitted by Drs Ignacio Neumann and Holger Schünemann, Department of Clinical Epidemiology and Biostatistics and WHO Collaborating Centre for Evidence-Informed Policy, McMaster University, Hamilton, ON, Canada, for the inclusion of dabigatran, rivaroxaban and apixaban as a therapeutic group on the EML for the treatment of non-valvular atrial fibrillation.

Expert reviews of the application were prepared by two members of the Expert Committee. No public comments on the application were received.

Non-valvular atrial fibrillation (NVAF) is the most common sustained cardiac arrhythmia. In developed countries its prevalence has been estimated as 6.6 per 1000 in men and 3.9 per 1000 in women; in developing countries, prevalence is 5.7 per 1000 in men and 3.7 per 1000 in women (*902*). The global burden of disease has increased in the past 20 years. In 1990, the estimated age-adjusted disability-adjusted life years resulting from atrial fibrillation were 54.3 for men and 38.6 for women (per 100 000 individuals). In 2010, these numbers increased to 64.5 for men and 45.9 for women (*902*).

Without antithrombotic treatment, the risk of stroke in patients with NVAF is around 5% per year, but it can be higher than 10% if other risk factors are present. The use of oral anticoagulation can reduce the relative risk of stroke by 66% in individuals with AF (*903*). The mainstay of anticoagulation treatment for AF is warfarin, a vitamin K antagonist (VKA). Warfarin requires frequent laboratory monitoring and dose adjustment to achieve and maintain appropriate levels of anticoagulation, as measured by the international normalized ratio (INR). It is also subject to numerous drug–drug interactions, and its effect can be modified by dietary intake of vitamin K. New-generation novel oral anticoagulants (NOACs), however, are not subject to the same stringent monitoring requirements or to specific dietary restrictions.

The application conducted a meta-analysis of the RE-LY (dabigatran), ROCKET-AF (rivaroxaban), ARISTOTLE and ARISTOTLE-J (apixaban), and PETRO (dabigatran) trials (*904–908*), using the Mantel–Haenszel method, random effect model, and GRADE methodology to assess confidence in the estimates of effects, and presented a summary of findings table. The application concluded that the use of NOACs instead of VKAs can reduce the risk of death by 12%, corresponding to 5 fewer deaths per 1000 patients (7 to 2 fewer per 1000) and the risk of stroke by 24% (corresponding to 2–9 fewer strokes per 1000 patients, depending upon CHADS2 score) (high-quality evidence). Further, the application found that there was moderate-quality evidence that the use of NOACs probably reduces the risk of major bleeding (by 1–3 people per 1000) compared with VKAs.

In consideration of the application's findings, the Expert Committee noted that the patients included in the trials were on average less than 75 years of age, with good renal function and no history of gastrointestinal bleeding. The Committee was concerned that the trial population was not fully representative of the population who would receive treatment with NOACs outside clinical trials, in everyday clinical practice. The Committee agreed that, in practice, patients are likely to be older, have comorbidities such as chronic kidney diseases, and be at higher risk of gastrointestinal and major bleeding. Furthermore, patients aged over 80 years (a large proportion of the target population, at least in developed countries), with body weight below 60 kg, and/or serum creatinine level ≥ 1.5 mg/dL would often require down-titration of NOAC doses (*909*). The Committee therefore considered it was appropriate to downgrade the overall quality of evidence to moderate quality because of indirectness for both mortality and stroke outcomes. The summary of findings, as revised by the Expert Committee, is presented in Table 9.

The Expert Committee also noted that the magnitude of the relative effect size (relative risk reduction 12%) contrasted with the magnitude of the absolute effect size (absolute risk reduction 0.5%). The confidence intervals around the absolute effects for the overall estimate on death included limited differences between the medicines that were judged to be unlikely to be clinically relevant. For all-cause mortality, the lower bound of the 95% confidence interval (2 fewer deaths per 1000 patients) excluded a relevant treatment benefit, and even the upper bound included a treatment benefit of less than 1%, which the Committee concluded was of marginal clinical relevance.

Table 9

Should novel oral anticoagulants (NOACs) rather than vitamin K antagonists (VKA) be used in patients with non-valvular atrial fibrillation? Summary of findings

Note: CI = confidence interval; RR = risk ratio; $CHADS_2$ = Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes, previous Stroke.

Patient or population: patients with non-valvular atrial fibrillation
Intervention: novel oral anticoagulants (NOAC)
Comparison: vitamin K antagonists (VKA)
Settings: outpatients
No. of participants (studies): 44 827 (5 studies) (all outcomes)
Follow-up: 3 to 30 months (all outcomes)

Outcomes No. of participants (studies)	Relative effects (95% CI)	Expected absolute effects			Quality of evidence (GRADE)	What happens
		With VKA	With NOAC	Difference (95% CI)		
All-cause mortality	RR 0.88 (0.82–0.95)	38 deaths per 1000 patients at 1 year[a]	33 deaths per 1000 patients at 1 year	5 fewer deaths (from 7 to 2 fewer per 1000 patients)	⊕⊕⊕⊖ **Moderate**[b, c] due to indirectness	NOACs reduce mortality
Stroke	RR 0.76 (0.66–0.88)	*$CHADS_2$ score 1* 8 strokes per 1000 patients at 1 year[a]	6 strokes per 1000 patients at 1 year	2 fewer strokes (from 3 to 1 fewer per 1000 patients)	⊕⊕⊕⊖ **Moderate**[b] due to indirectness	NOACs reduce risk of stroke

Table 9 *continued*

Outcomes No. of participants (studies)	Relative effects (95% CI)	Expected absolute effects			Quality of evidence (GRADE)	What happens
		With VKA	With NOAC	Difference (95% CI)		
		$CHADS_2$ score 2				
		17 strokes per 1000 patients at 1 year[a]	13 strokes per 1000 patients at 1 year	4 fewer strokes (from 6 to 2 fewer per 1000 patients)		
		$CHADS_2$ score 3–6				
		36 strokes per 1000 patients at 1 year[a]	27 strokes per 1000 patients at 1 year	9 fewer strokes (from 12 to 4 fewer per 1000 patients)		
Systemic embolism	RR 0.59 (0.27–1.29)	2 embolisms per 1000 patients at 1 year[a]	1 embolism per 1000 patients at 1 year	1 fewer embolism (from 1 fewer to 1 more per 1000 patients)	⨁⨁⨁⊖ **Moderate**[d, e] due to inconsistency	NOACs probably do not change the risk of systemic embolism

Table 9 *continued*

Outcomes No. of participants (studies)	Relative effects (95% CI)	Expected absolute effects			Quality of evidence (GRADE)	What happens
		With VKA	With NOAC	Difference (95% CI)		
Major bleeding	RR 0.87 (0.71–1.08)	13 bleeds per 1000 patients at 1 year[a]	11 bleeds per 1000 patients at 1 year	2 fewer bleeds (from 4 fewer to 1 more per 1000 patients)	⨁⨁⨁⊖ **Moderate**[b, d, e] due to inconsistency	NOACs probably reduce the risk of major bleeding

[a] To estimate the absolute effects, base-line risks used were those reported by Antithrombotic therapy and prevention of thrombosis, ninth edition (Glenview, IL: American College of Chest Physician; 2012).

[b] Patients included in the trials were on average younger than 75 years, with good renal function and no history of gastrointestinal bleeding. In everyday practice, patients treated with NOACs are older, with comorbidities including renal impairment, and at higher risk of gastrointestinal bleeding, and the Expert Committee therefore considered it appropriate to downgrade the overall quality of evidence for indirectness (applicability).

[c] Focusing on the 95% CI around the absolute effects, the Expert Committee considered that the lower bound of the 95% CI for all-cause mortality did not represent a substantial treatment effect (2 fewer deaths per 1000 patients), and the upper bound represented a treatment effect approaching clinical relevance (7 fewer deaths per 1000 patients). The Committee therefore considered that the absolute effects, though statistically significant, do not necessarily represent a prominent public health effect (absolute risk difference was 0.5%).

[d] Although the 95% confidence interval around the relative effect is wide, the 95% confidence interval around the absolute effect is precise and the quality of evidence was not downgraded for imprecision. The imprecision is also a result of the inconsistency.

[e] Substantial unexplained inconsistency in the point estimates and high I^2 in the meta-analysis were observed.

A 2013 Cochrane systematic review assessed the effectiveness and safety of factor Xa inhibitors (including apixaban and rivaroxaban) versus VKAs for the prevention of embolic events in patients in AF. This review included the ROCKET-AF, ARISTOTLE and ARISTOTLE-J trials presented in the application and others assessing alternative factor Xa agents. Most data (> 80%) came from the studies with apixaban and rivaroxaban (*910*). Factor Xa inhibitors significantly reduced the number of strokes, systemic embolic events and major bleeding events compared with warfarin. Evidence to determine which factor Xa inhibitor is safer and more effective for long-term anticoagulant treatment of patients with AF is elusive, as head-to-head studies of the different factor Xa inhibitors have not yet been performed. The review highlighted the high numbers needed to treat (NNTs), which indicate that factor Xa inhibitors are only marginally more effective in the prevention of strokes and systemic embolic events than treatment with dose-adjusted warfarin, with follow-up periods of more than one year (e.g. NNT 304 per year for apixaban and NNT 369 per year for rivaroxaban).

Another meta-analysis also investigated whether the benefit of NOACs was dependent on how well warfarin was managed during the trial, as assessed by the time in therapeutic range (*911*). The trials had varying success in management of warfarin: the median time in therapeutic range was considered good (58–68%) for most patients. In this meta-analysis, a threshold of 66% for time in therapeutic range was used. It was shown that, while the reduction in stroke or systemic embolism compared with warfarin was not dependent on how well warfarin is managed, the benefit from NOACs in terms of fewer major bleeds applies only to patients whose time in therapeutic range with warfarin is sub-optimal. A review by the Canadian Agency for Drugs and Technologies in Health (*912*) concluded that, for patients achieving at least 66% time in therapeutic range, NOACs were not associated with a reduction in stroke or systemic embolism compared with warfarin, and only apixaban was associated with a reduction in the risk of major bleeding compared with warfarin. For patients with time in therapeutic range below 66%, compared with warfarin only dabigatran 150 mg reduced the risk of stroke or systemic embolism, while dabigatran (110 mg and 150 mg) and apixaban reduced the risk of major bleeding.

NOACs undergo renal excretion (to varying extents): dose reduction may be necessary in patients with renal impairment. Data on participants with severe renal failure (creatinine clearance < 30 mL/min), who have a high risk of both thromboembolic events and bleedings, are scarce because these patients were excluded from participation in most of the above-mentioned trials. As treatment for NVAF is invariably long-term and renal impairment is known to develop and/or deteriorate over time, patients prescribed NOACs should have their renal function monitored periodically so that any dose adjustments

necessary to ensure safe and appropriate use of the medicine can be made. The high rate of renal elimination of dabigatran and rivaroxaban is not an ideal feature in patients with AF, many of whom are old and are likely to have some degree of renal insufficiency.

Limited data were presented on the comparative safety of NOACs and VKAs. The application stated that no long-term safety data are available, and no detailed report is available on adverse events from the ARISTOTLE trial of apixaban. The adverse events reported in the RE-LY and ROCKET-AF trials were presented, along with safety results from a post-marketing study of 134 000 Medicare patients aged 65 years or more conducted in the United States (*913*). In this post-marketing study, an increase in the rate of gastrointestinal bleeding of 7.7 per 1000 patient-years was observed for dabigatran compared with warfarin (adjusted hazard ratio 1.28 (95% CI: 1.14–1.44). A meta-analysis of randomized controlled trials of dabigatran that reported on myocardial infarction or acute coronary syndrome as secondary outcomes found that the risk of myocardial infarction or acute coronary syndrome is increased with dabigatran compared with various control treatments, which included adjusted-dose warfarin, enoxaparin, or placebo. Although the relative risk increase was 33%, the absolute risk increase was very small, at 0.27% (*914*).

All anticoagulants are associated with an increased risk of bleeding. Bleeding complications, haemorrhage, or overdose associated with VKAs can be managed with administration of vitamin K, frozen plasma or coagulation factor concentrates. Unlike bleeds related to warfarin, which can be reversed using vitamin K, there are currently no specific antidotes available for reversing bleeds or reversing the anticoagulant effects of NOACs in case of emergency.

In patients with NVAF, the net effect of anticoagulation treatment varies with the baseline risks of stroke and bleeding. $CHADS_2$ and CHA_2DS_2VASc are commonly used and validated risk stratification measures. $CHADS_2$ gives a single point to each of heart failure, hypertension, age over 75 years and diabetes mellitus, and two points to prior stroke or transient ischaemic attack (TIA) (*915*). CHA_2DS_2VASc combines the same factors as $CHADS_2$ with three additional risk factors – age over 65 years, female sex and presence of vascular disease (*916*). For both $CHADS_2$ and CHA_2DS_2VASc, the higher the score, the higher the risk of stroke. NOACs are indicated for use in patients with NVAF and at least one risk factor for stroke or systemic embolism (*917*). The mean $CHADS_2$ score of the randomized participants was high, suggesting that people who are at "very low" risk of stroke are probably not included. Caution is thus needed when drawing any conclusions on the effectiveness and safety of NOACs compared with warfarin in people at low risk.

With regard to cost, the daily treatment cost of NOAC treatment is between two and four times more expensive than VKAs plus INR monitoring (*5*). However, NOACs do not require the same laboratory monitoring as VKAs.

A systematic review of 16 economic evaluations of NOACs found that all of them concluded NOACs to be cost–effective compared with warfarin or aspirin, despite substantial heterogeneity in the numerical estimates of incremental costs and benefits across the evaluations (*5*).

Currently, there is no approved WHO guideline for treatment of NVAF. The United Kingdom National Institute for Health and Clinical Excellence (NICE) recommends offering anticoagulation (with apixaban, dabigatran, rivaroxaban or a VKA) to people with a CHA_2DS_2VASc score of 2 or above, and considering anticoagulation (with apixaban, dabigatran, rivaroxaban or a VKA) for men with a CHA_2DS_2VASc score of 1 (*917*). The NICE guidelines do not differentiate between NOACs and VKAs, but recommend that options for anticoagulation be discussed with patients and treatment choice be based on their clinical features and personal preferences. In contrast, in the ninth edition of *Antithrombotic therapy and prevention of thrombosis*, the American College of Chest Physicians recommends oral anticoagulation for patients with intermediate risk ($CHADS_2$ score of 1) and high risk ($CHADS_2$ score of 2 or more) of stroke. Oral anticoagulation with 150 mg dabigatran twice daily, rather than dose-adjusted VKA therapy, is "suggested" for patients with intermediate stroke risk and "recommended" for patients with high stroke risk (*903*).

The Expert Committee acknowledged that NOACs could represent a valid therapeutic option for patients who have genuine difficulty in attending for INR monitoring or in settings where laboratory monitoring is lacking. However, the alleged convenience of NOACs because of there being no requirement for monitoring has been questioned. Dose adjustments based on plasma concentrations of dabigatran might further improve its efficacy and safety profile, particularly reducing the risk of major bleeds compared with well-controlled warfarin. Data on dose adjustments have not been published or provided to regulators and might be associated with individual patient characteristics, such as age or kidney function, or concomitant interventions such as certain medications (*918*).

Although evidence indicates a favourable, overall clinical benefit of the NOACs over warfarin, the Expert Committee considered that the absolute magnitude of such benefit is limited, is inconsistent across trials and may be influenced by a number of factors, such as the quality of oral anticoagulation (e.g. time in therapeutic range).

Additionally, the Committee considered that, in order for countries to maximize use of available resources, further research is necessary to explore the unmet need in terms of anticoagulation in people unable to be stabilized with warfarin and in clinical settings where access to warfarin monitoring is not readily available, particularly in low- and middle-income countries. The Committee considered that comparative trials of NOACs would help to define

their place in therapy and their appropriate use in particular subgroups (e.g. those who cannot be adequately managed on VKAs, elderly patients, those with impaired renal function).

The Committee also expressed some concern regarding safety of the NOACs, noting that while warfarin-related bleeds can be reversed using vitamin K, there are currently no specific antidotes that will reverse the anticoagulant effects of NOACs in case of emergency.

Finally, the Committee acknowledged that the large difference in costs between NOACs and warfarin was disproportional to the observed incremental benefit.

The Expert Committee therefore did not recommend inclusion of the novel oral anticoagulants (dabigatran, rivaroxaban and apixaban) in the Model List of Essential Medicines.

Section 11: Blood products of human origin and plasma substitutes

11.2.3: Plasma proteins (new section)

Plasma-derived C1 esterase inhibitor (addition) – EML and EMLc

An application was submitted by CSL Behring, Marburg, Germany, for the inclusion of human plasma-derived C1-esterase inhibitor (C1-INH) as a complementary medicine on the EML and EMLc for the acute treatment of recurrent episodes of subcutaneous and submucosal oedema in patients with types I and II hereditary angioedema (HAE).

Reviews of the application were prepared by two members of the Expert Committee. No public comments were received in relation to the application.

Hereditary angioedema is a rare autosomal dominant genetic disorder, with estimated prevalence of approximately 1 in 50 000 persons; lower prevalence is reported in Asian populations (*919*, *920*). Historically HAE was described as resulting from either deficiency (type I) or dysfunction (type II) of the plasma protein C1-inhibitor (C1-INH) (*921*). Plasma-derived C1-INH acts as replacement therapy in types I and II HAE. A third familial form of oedema has been identified in which patients have normal C1-INH levels and activity (type III HAE) (*922*).

HAE is characterized by recurrent episodes of well-demarcated angioedema without urticaria, most often affecting the skin or the mucosal tissues of the upper respiratory and gastrointestinal tracts (*923*). In the absence of treatment, swelling generally resolves spontaneously in two to four days (924); however, laryngeal oedema (approximately 1% of all HAE attacks) may occur in up to 50% of patients and is potentially life-threatening (*923*, *925*). Gastrointestinal attacks range from mild to severe, usually resolving without serious complications. Cutaneous attacks do not have serious complications; however, repeated episodes significantly disrupt patients' lives (*926*).

Plasma-derived C1-INH is one of several medications available for acute treatment of episodes of angioedema in HAE. Others include icatibant, ecallantide and human plasma (either solvent/detergent-treated plasma or fresh frozen plasma, FFP). The application noted that, in regions where there is no access to plasma-derived C1-INH (or other newer treatments), the only treatment option for acute attacks in HAE patients is FFP. The Expert Committee noted that FFP is currently included on the EML and EMLc (*11*). However, clinical efficacy data for FFP in HAE are limited, and plasma contains substrates that could theoretically exacerbate symptoms (*919*, *927*). Oral androgens have been used as long-term prophylaxis to reduce the frequency and/or severity of attacks, but their side-effects (virilization, weight gain, menstrual irregularities) limit their use and they do not prevent life-threatening upper airway oedema with any certainty (*922*).

The World Allergy Organization guidelines make a strong recommendation for treating HAE attacks in the general population with C1-INH, ecallantide or icatibant; for children, and for pregnant or lactating patients, the guidelines recommend plasma-derived C1-INH as the preferred, "on-demand" treatment for attacks (*922*).

Treatment guidelines for hereditary angioedema are based on treatment initiated at the onset of acute attacks. Patients with laryngeal angioedema require immediate airway assessment because of the risk of fatal asphyxiation. Intubation may be needed in those with respiratory distress or stridor as even effective therapies take 30 minutes to begin working. The Committee noted that plasma-derived C1-INH can be self-administered, or given by a carer or nurse, through a peripheral intravenous line at the first sign of symptoms.

The Expert Committee noted that the available evidence generally supported use of plasma-derived C1-INH as a safe and effective treatment for acute attacks of HAE. However, the clinical trials identified in the application were designed to investigate efficacy in a relatively limited situation, namely treatment for established attacks (*928–931*) Most trials measured time to relief of symptoms as the primary end-point. The Committee considered that these intermediate outcomes may not directly reflect "real life" where symptoms are treated early or at prodromal stages. No head-to-head trials comparing plasma-derived C1-INH with alternative treatments were presented.

Plasma-derived C1-INH has wide regulatory approval in high-income countries, but registration in low- and middle-income countries is not as widespread. The application estimated treatment costs for a single acute attack ranging from US$ 1320–1980 in South America to US$ 3130–4695 in North America.

The Expert Committee acknowledged the distressing effects of HAE on individual patients and their families but considered that the public health relevance of its treatment with C1-INH was unclear. In the absence of compelling evidence of a clinically relevant improvement in important treatment outcomes such as morbidity and mortality, the Expert Committee decided not to recommend the addition of plasma-derived C1-esterase inhibitor to the EML or EMLc.

Section 12: Cardiovascular medicines

12.3: Antihypertensive medicines

12.4: Medicines used in heart failure

Atenolol (review) – EML

In 2011, the Expert Committee changed the nominated beta-blocker in the WHO Model List from atenolol to bisoprolol, partly because use of atenolol was not appropriate in heart failure. The change was implemented for four listings of beta-blockers in the Model List (Section 12.1 Antianginal medicines, Section 12.2 Antiarrhythmic medicines, Section 12.3 Antihypertensive medicines, and Section 12.4 Medicines used in heart failure). The square box listing includes a note that metoprolol and carvedilol are alternatives to bisoprolol (*738*).

This has caused some confusion at the country level where atenolol is widely available and used in practice: WHO has been asked whether countries should stop using atenolol.

A review was commissioned from Professor Anthony Smith, University of Newcastle, Callaghan, NSW, Australia, of the role of atenolol in the management of hypertension and heart failure. The review canvassed the key trials and meta-analyses published since 2000.

Expert reviews of the commissioned review were prepared by two members of the Expert Committee. Comments were received from Dr Myriam Henkens, International Medical Coordinator, Médecins Sans Frontières.

The 2002 LIFE study, which included 9 222 participants, reignited the debate over the role of atenolol in hypertension, reporting a greater incidence of stroke with this beta-blocker compared with losartan (5% losartan versus 7% atenolol; HR 0.75; 95% CI: 0.63–0.89), which contributed to the composite end-point and overall cardiovascular mortality (*932*). The trial allowed add-on therapy with hydrochlorothiazide and then other antihypertensive agents, however addition of angiotensin-converting-enzyme inhibitors (ACEI), angiotensin II receptor antagonists (AIIRA) and/or beta-blockers was not permitted. A pre-specified subgroup analysis of 1195 patients with diabetes and hypertension from the LIFE trial produced similar findings, with greater stroke incidence in the atenolol group (9% losartan versus 11% atenolol; HR 0.79; 95% CI: 0.55–1.14 (adjusted for degree of left-ventricular hypertrophy and Framingham risk score at randomisation)) (*933*).

The 2003 INVEST multicentre study of hypertension in 22 576 patients with confirmed coronary artery disease found similar blood pressure control and clinical outcomes, including nonfatal stroke, in patients treated with either verapamil or atenolol (with add-on trandolapril and/or hydrochlorothiazide) (*934*). The authors concluded that the two treatments were equi-effective.

The 2005 ASCOT-BPLA trial of 19 257 patients (aged 49–75 years) with hypertension and at least three other cardiovascular risk factors was stopped

ahead of time as the mortality rate in the atenolol group (with add-on thiazide diuretic and potassium (as required)) was higher than in the amlodipine group (with add-on perindopril) (*935*). However, a subsequent multivariate analysis of the data concluded that there were no statistically significant differences between the treatment groups (*936*).

A 2005 meta-analysis including both LIFE and ASCOT studies concluded that the "effect of beta-blockers is less than optimum with a raised risk of stroke" (RR 1.16; 95% CI: 1.04–1.30, favouring medicine other than atenolol), with no statistically significant differences in all-cause total mortality and myocardial infarction (*937*). A 2007 Canadian database study observed similar two-year rates of myocardial infarction, unstable angina, stroke or death in cohorts receiving atenolol, ACEI, thiazide diuretics or calcium blockers (total population 19 249 people, average age 60.6 years) (*938*). Eligible patients were first-time users of antihypertensive treatment as monotherapy. The authors concluded that atenolol was not associated with a significant burden of cardiovascular morbidity or mortality in uncomplicated hypertension.

Long-term follow-up of the United Kingdom Prospective Diabetes Study showed no detrimental effects in those initially randomized to beta-blockers; in particular, there was no excess in stroke (*939*).

A 2006 meta-analysis of 21 hypertension trials showed similar efficacy in reduction of cardiovascular events in younger patients treated with beta-blockers compared with other agents but more composite end-points (death, stroke, myocardial infarction) in patients over 60 years of age (RR 1.12; 95% CI 1.02–1.24) (*940*). An additional analysis by Khan et al. (*10*) excluded three studies also excluded by Lindholm et al. (*937*), generating an excess composite risk in patients over 60 years, driven largely by an excess risk of stroke (RR 1.18; 95% CI 1.07–1.30).

A 2009 meta-analysis included 46 trials designed to determine the efficacy of different classes of blood-pressure-lowering drugs in preventing coronary heart disease (CHD) and stroke and to identify which patients should receive treatment. In the trials assessing blood pressure reduction, beta-blockers had the additional effect of preventing recurrent CHD events in patients with a history of CHD (*941*). This effect was limited to a "few years" after a myocardial event. All classes of blood-pressure-lowering drugs had a similar effect in reducing CHD events and stroke for a given reduction in blood pressure.

A 2009 reappraisal of European guidelines by the European Society of Hypertension Task Force noted that reduction in blood pressure is the prime factor in reducing cardiovascular morbidity and mortality and recommended all classes of medicines as first-line therapy (*942*).

In its 2011 guidance on the initial treatment of primary hypertension, the National Institute for Health and Care Excellence (NICE) recommends an

ACEI or an AIIRA as first-line therapy in those aged less than 55 years, with a note to consider beta-blockers in younger patients (*943*).

The European Society of Hypertension/European Society of Cardiology 2013 guidelines for the management of arterial hypertension describe compelling (e.g. asthma, grade 2 or 3 atrioventricular block) and possible (e.g. metabolic syndrome, glucose intolerance, athletes/physically active patients, chronic obstructive pulmonary disease) contraindications to beta-blockers as well as the preferred conditions for treatment with beta-blockers (hypertension with previous myocardial infarction, angina pectoris, heart failure, atrial fibrillation). The guidelines also suggest "all-purpose ranking of drugs for general antihypertensive usage is not evidence-based" (*944*).

The US Joint National Committee 2014 guideline for the management of high blood pressure in adults concluded "the panel did not recommend beta-blockers for the initial treatment of hypertension because in one study (LIFE trial) use of beta-blockers resulted in higher rate of the primary composite outcome of cardiovascular death, myocardial infarction or stroke compared to use of an AIIRA, a finding that was driven largely by an increase in stroke" (*945*).

The 2014 recommendations of the Canadian Hypertension Education Program are for initial treatment with a single thiazide/thiazide-like diuretic, a beta-blocker (in patients aged less than 60 years), or an ACEI. Beta-blockers are not recommended as first-line treatment for uncomplicated hypertension in patients aged 60 years or more (*946*).

The Expert Committee agreed with evidence reviewed in the application, that atenolol should be considered as an appropriate first-line treatment option in hypertension associated with coronary heart disease, especially for treatment initiated after a myocardial infarction and in patients with angina and supraventricular arrhythmias. It is both reasonable and concordant with the evidence to recommend atenolol as a first-line treatment in younger hypertensive patients, perhaps with a cut-off at 60 years, in line with the Canadian and NICE recommendations. However, atenolol is not recommended as first-line treatment for uncomplicated hypertension in patients over the age of 60 years.

The Committee acknowledged that atenolol retains a place as add-on, second- or third-line treatment if blood pressure control is not achieved with other antihypertensive agents.

The retention of bisoprolol, carvedilol and metoprolol for the management of chronic cardiac failure is in line with the available evidence. While atenolol has been used in heart failure, the major outcome studies (not included in the commissioned review) have been conducted with these three compounds.

Atenolol is a beta 1-receptor blocker with a prolonged half-life that allows once daily dosing, which can assist with patient compliance/adherence.

It is not significantly metabolized and is therefore not a target for interactions through metabolic pathways. It is lost from the body by renal excretion and must be used with caution in renal impairment.

The Committee noted that atenolol is considerably cheaper than bisoprolol, carvedilol and metoprolol.

Based on the evidence presented, therefore, the Expert Committee recommended that atenolol be included as an additional alternative beta-blocker to metoprolol and carvedilol in the note associated with the listing of bisoprolol in Section 12.3, Antihypertensive medicines, of the Model List. The Committee also recommended that the note state that atenolol should not be used as first-line agent for uncomplicated hypertension in patients aged over 60 years.

The Expert Committee did not recommend any changes be made to the current listing of bisoprolol in Section 12.4, Medicines used in heart failure, of the Model List.

12.5: Antithrombotic medicines

Clopidogrel (addition) – EML

An application was submitted by Drs Amisha Patel, Mahesh Vidula and Mark Huffman, Northwestern University Feinberg School of Medicine, Chicago, IL, USA, Dr Sandeep Kishore, Yale University School of Medicine, New Haven, CT, USA, and Dr Rajesh Vedanthan, Icahn School of Medicine at Mount Sinai, New York, USA, for the inclusion of the thienopyridine class of medicines on the Model List, with clopidogrel as representative of the class for the treatment of acute coronary syndrome and post-percutaneous coronary intervention.

Reviews of the application were prepared by two members of the Expert Committee. Public comments in support of the application were received from Professor Valentin Fuster, past President of the American Heart Association and the World Heart Federation, Professor Bongani Mayosi, head of the Medicine Department at the University of Cape Town, South Africa, Dr D Prabhakaran, Executive Director of the Centre for Chronic Disease Control, New Delhi, India, and Professor Salim Yusuf, Population Health Research Institute, McMaster University, Hamilton, Canada.

Ischaemic heart disease is the largest single cause of mortality and loss of disability-adjusted life years (DALYs) worldwide, accounting for roughly 7.3 million deaths and 129 million DALYs each year (*947–949*). Acute coronary syndrome (ACS) is a frequent acute manifestation of ischaemic heart disease and includes ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA). Treatment of patients with ACS in low- and middle-income countries (LMICs) is highly variable and often suboptimal (*950*). In well-resourced settings, a combination of medical therapy, reperfusion and better overall intensive care has

led to dramatic reductions in case-fatality rates for ACS (*951–954*). Treatment outcomes in LMICs are worse and there is evidence of poor adherence to secondary prevention therapies. Antiplatelet medicines, including aspirin and clopidogrel, have been shown to have an independent mortality benefit in patients with ACS (*955–958*).

The reperfusion strategy of choice in patients with STEMI is percutaneous coronary intervention (PCI) (*956*, *959*); these procedures have become increasingly common with the growing availability of cardiac catheterization laboratories, including in LMICs (*960*).

A 2012 systematic review (*961*) reported a significant reduction in death associated with clopidogrel pretreatment compared with no pretreatment in a pre-specified subgroup of patients with STEMI (absolute risk 1.3% versus 2.5%; odds ratio (OR) 0.50; 95%: CI 0.26–0.96; number needed to treat (NNT) 79). Clopidogrel pretreatment was also associated with a reduction in major coronary events (composite outcome of death, MI and urgent target vessel revascularization; absolute risk 3.6% vs 6.4%; OR 0.54; 95% CI: 0.36–0.81; NNT 36). Among patients undergoing PCI, compared with no treatment, pretreatment with clopidogrel was associated with 23% lower odds of major coronary events (composite of death, MI and urgent target vessel revascularization) (9.8% vs 12.3%; OR 0.77: 95% CI: 0.66–0.89; NNT 40). Clopidogrel pretreatment was associated with an increased risk of bleeding compared with no treatment.

The Percutaneous Coronary Intervention – Clopidogrel as Adjunctive Reperfusion Therapy (PCI-CLARITY) trial in patients with STEMI undergoing fibrinolysis concluded that clopidogrel pretreatment significantly reduced the incidence of death or ischaemic complications both before and after PCI, with no significant increased risk of major or minor bleeding (*957*).

A 2011 Cochrane review (*962*) reported that, compared with aspirin alone, clopidogrel plus aspirin was associated with a small reduction in the risk of cardiovascular events (death, MI, UA, heart failure and ischaemic stroke) in patients with acute NSTEMI (absolute risk 10.1% vs 11.5%; OR 0.87; 95% CI: 0.81–0.94; NNT 71). Compared with aspirin alone, the risk of major bleeding was higher in the clopidogrel plus aspirin group (OR 1.34; 95% CI: 1.14–1.57; number needed to harm (NNH) 167). The review concluded that, in patients with acute non-ST coronary syndromes, combination treatment with clopidogrel and aspirin should be considered as the evidence suggests that the benefits of treatment outweigh the harms: for every 1000 patients treated, 13 cardiovascular events would be prevented while six major bleeds would be caused.

The CURE trial randomized patients presenting with UA/NSTEMI to receive clopidogrel (loading dose followed by maintenance dose) or placebo in addition to aspirin for 3–12 months. Compared with patients treated with aspirin alone, patients treated with a clopidogrel and aspirin combination had

a 20% reduction in the primary outcome of death from cardiovascular causes, nonfatal MI (absolute risk 9.3% vs 11.4%; OR 0.80: 95% CI: 0.72– 0.90; NNT 48) (*958*). The PCI-CURE trial evaluated a subset of patients from the CURE trial proceeding to PCI. In PCI-CURE, patients treated with both clopidogrel and aspirin had a significantly lower rate of the primary end-point (target vessel revascularization, death from cardiovascular etiologies, or nonfatal MI) at 30 days compared with those treated with aspirin alone (*963*).

A 2008 systematic review and meta-analysis of eight trials including CLARITY, CURE and PCI-CURE concluded that, compared with aspirin monotherapy, combination treatment with clopidogrel and aspirin for patients with ACS or those undergoing PCI is associated with a reduction in the risk of major coronary events and fatal or nonfatal MI. However, dual antiplatelet therapy was not shown to be associated with a reduced risk of all-cause mortality but did increase the risk of major bleeding when administered for more than one year. On balance, the authors concluded that the benefits of dual therapy outweigh the harms for patients with ACS and those undergoing PCI but not for other patient subgroups (*964*).

Overall, the applicants concluded that GRADE assessment found the evidence to be of high quality (RCTs with a low risk of bias and consistent findings) and this provided the basis for a strong recommendation for use of clopidogrel in patients with ACS and to reduce major coronary events in patients undergoing PCI. The evidence to support a claim of reduced mortality with clopidogrel in patients undergoing PCI was rated as being of moderate quality because of imprecision in the assessment of this outcome. The Expert Committee noted that no GRADE tables were included in the application to illustrate these conclusions.

The CAPRIE study (clopidogrel versus aspirin in patients at risk of ischaemic events) found similar rates of validated nonfatal primary intracranial haemorrhage and haemorrhagic death in aspirin-treated patients compared with clopidogrel-treated patients (0.5% vs 0.4%) but higher rates of gastrointestinal haemorrhage in aspirin-treated patients (2.7% vs 2.0%), leading to more hospitalizations for gastrointestinal bleeding in the aspirin-treated group. Clopidogrel was associated with fewer gastrointestinal events such as nausea, indigestion and vomiting than aspirin (15% vs 17.6%). There were more rashes (6% vs 5%) and severe rashes (0.3% vs 0.1%) in the clopidogrel-treated patients. Rates of neutropenia (0.1% vs 0.2%) and thrombocytopenia (0.3% vs 0.3%) were broadly similar for the two groups (*965*).

The 2008 meta-analysis by Bowry et al. concluded that there was a substantially increased risk of major bleeding with clopidogrel plus aspirin compared with aspirin alone when the combination was continued beyond the immediate post-acute care period or beyond six months after drug-eluting stent

implantation. The increase in risk was 1.35–3.37 across the trials included in the analysis (*964*).

Because of the increased risk of gastrointestinal bleeding associated with antiplatelet therapy, US consensus recommendations suggest concomitant use of proton-pump inhibitors in patients with a history of gastrointestinal bleeding or risk factors for bleeding who require antiplatelet therapy (*966*).

The Committee noted that, according to the 2013 International Drug Price Indicator, clopidogrel 75 mg has a median international cost of US$ 0.0526/tablet (range US$ 0.0238–1.1078) (*967*).

Based on the evidence presented, the Expert Committee recommended the addition of clopidogrel to the core list of the EML. The Committee did not agree with the request to list clopidogrel with a square box symbol as representative of the pharmacological class of thienopyridine agents, since no data were presented on other agents in the class.

The Committee accepted that dual anti-platelet therapy with clopidogrel in combination with aspirin is effective treatment in reducing the risk of major cardiovascular events and is superior to aspirin monotherapy for patients with acute coronary syndromes or those undergoing PCI. The Committee considered that, in these patient populations, the benefits of dual therapy outweigh the potential harms.

12.7: Fixed-dose combinations of cardiovascular medicines

Aspirin + statin + antihypertensive "polypill" (addition) – EML

An application was submitted by Dr Mark D. Huffman, Northwestern University Feinberg School of Medicine, Chicago, IL, USA, Dr Pablo Perel, London School of Hygiene and Tropical Medicine, London, England, Dr José Maria Castellano, Fundación Centro Nacional de Investigaciones Cardiovasculares Carlos III, Madrid, Spain, Dr Valentin Fuster, Mount Sinai School of Medicine, New York, NY, USA, Dr Anthony Rodgers and Dr Ruth Webster from The George Institute, Sydney, Australia, Dr Sidney C. Smith Jr, University of North Carolina, Chapel Hill, NC, USA and Professor Salim Yusuf, Population Health Research Institute, McMaster University, Hamilton, Canada, for the inclusion on the EML of fixed-dose combination (FDC) therapy or "polypill" for secondary prevention of cardiovascular disease (ischaemic heart disease and thrombotic stroke).

Reviews of the application were prepared by two members of the Expert Committee. Numerous public comments were received in support of the application and are available on the WHO website.

The application noted a number of different fixed-dose combinations (FDCs) including:

- aspirin 100 mg + simvastatin 40 mg + ramipril 2.5, 5 or 10 mg as a fixed-dose combination – available as "Trinomia"

- aspirin 100 mg + atorvastatin 20 mg + ramipril 2.5, 5 or 10 mg as a fixed-dose combination – available as "Trinomia"
- aspirin 100 mg + simvastatin 20 mg + atenolol 50 mg + hydrochlorothiazide 12.5 mg + ramipril 5 mg – available as "Polycap"
- aspirin 75 mg + simvastatin 40 mg + atenolol 50 mg + lisinopril 10 mg – available as "Red Heart Pill 1"
- aspirin 75 mg + simvastatin 40 mg + hydrochlorothiazide 12.5 mg + lisinopril 10 mg – available as "Red Heart Pill 2".

The application requested inclusion of one or more of the combination products and proposed listing as a therapeutic group with a square box symbol, allowing use of different combinations and formulations. The Committee expressed concerns over the practicality of listing a single polypill formulation, as the representative of a heterogeneous group, given the large number of different combinations and doses available.

The Expert Committee considered a similar application in 2013 (*11*). At that time, the Committee noted the need for access to effective and appropriate secondary prophylaxis for cardiovascular diseases. However, it was not clear to the 2013 Expert Committee which of these combinations was being proposed for inclusion in the EML; moreover, while there is wide acceptance of the strong rationale of using evidence-based interventions 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 in comparison to individual medicines. The 2013 Committee noted there was no trial using any of the FDCs powered to show a difference in morbidity and mortality. In addition, the Committee noted there were serious gaps in the data on the proposed FDC formulations, with only one of three identified dosage forms undergoing a bioavailability study comparing the individual components with the FDC.

The current application presented data from a 2014 Cochrane review that included nine randomized controlled trials (RCTs) of FDC therapy, containing at least one lipid-lowering medicine and one blood-pressure-lowering medicine for primary and secondary prevention of cardiovascular disease (*968*). The studies included in the systematic review differed in the composition of the FDCs, the patient populations and the comparison treatment. Three trials compared FDC therapy with usual care; the other six trials compared combination therapy with either active control (e.g. therapeutic lifestyle changes) or placebo. Only one of the included trials, UMPIRE 2013, compared FDC therapy, either (a) aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, atenolol 50 mg or (b) aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, hydrochlorothiazide 12.5 mg, with multiple individual medications (*969*).

Moreover, the reviewers found that five out of the nine trials had a high risk of bias in areas including selection, performance, detection and attrition (*968*). The reviewers' conclusions did not favour FDC therapy, as effectiveness in terms of all-cause mortality or cardiovascular events was uncertain.

The Committee noted that the main argument of the current application for inclusion of FDCs in the EML was the potential to improve secondary prevention by improving treatment adherence. In the UMPIRE 2013 trial, adherence was defined as taking aspirin, a statin, and two or more blood-pressure-lowering medicines at least four days per week. At 15 months, adherence was 86% in the intervention group compared with 65% in the comparator group (relative risk (RR) of being adherent, 1.33; 95% CI: 1.26–1.41) (*969*). Notably, participants randomized to the intervention arm received FDC therapy free of charge whereas participants randomized to usual care were responsible for their own drug costs, which may have led to increased adherence in the FDC arm (*968*).

The FOCUS study measured adherence in secondary prevention using a self-reported questionnaire. Patients were randomized to either a polypill (containing aspirin 100 mg, simvastatin 40 mg, and ramipril 2.5, 5 or 10 mg) or the three medicines given separately (usual care). In the intention-to-treat population, after nine months, 41% in the usual care group and 50.8% in the FDC group were reported to be taking the medication adequately (*970*). However, the study did not identify differences in mean systolic blood pressure, mean low-density lipoprotein (LDL) cholesterol levels, serious adverse events or death between the FDC group and the usual care arm (*970*). An FDC feasibility trial in Sri Lanka detected no statistically significant differences between FDC (75 mg aspirin, 20 mg simvastatin, 10 mg lisinopril and 12.5 mg hydrochlorothiazide) and standard care (not defined) in terms of reductions in systolic blood pressure, total cholesterol or 10-year risk of cardiovascular disease: more patients in the standard care group completed the study (93% compared with 86% of the FDC group) (*971*).

A 2012 meta-analysis of RCTs reviewed the evidence for efficacy of FDCs compared with placebo and current care on surrogate outcomes: the FDCs significantly reduced blood pressure and cholesterol. However, the observed reduction in systolic and diastolic blood pressure and in total and LDL cholesterol were often less than would have been expected from the component medications based on trials of these agents taken as single medications (*972*). These results are consistent with the Cochrane review, which also draws attention to a high degree of statistical heterogeneity in comparisons of blood pressure and lipids ($I^2 \geq 70\%$) that could not be explained, meaning that these results should be viewed with caution (*968*). Data on all-cause mortality and cardiovascular events are limited: mortality and cardiovascular event rates were

low in both groups (1.2% in the intervention group compared with 1.0% in the comparator group, and 4.0% rate in the intervention group compared with 2.9% in the comparator group) (*968*).

Data from the TIPS-1 and TIPS-2 studies of Polycap were presented, comparing full-dose treatment (2 x Polycaps plus 30 mEq/L potassium supplement) with half-dose treatment (1 x Polycap) (*973*). Higher-dose treatment was associated with statistically significantly larger reductions in total and LDL cholesterol and in systolic and diastolic blood pressure, with similar tolerability of the two doses (6.9% vs 7.8% discontinuations).

With regard to safety, FDC therapy is associated with modest increases in adverse events compared with placebo, single-drug active component, or usual care (multiple drug therapy) (30% versus 24%; RR 1.19; 95% CI: 1.09–1.30) (*968*). This may be associated with improved adherence to a multidrug regimen. Higher rates of discontinuation were reported in participants randomized to FDC in trials than in participants given an active control or placebo (14% versus 11.5%; RR 1.26; 95% CI 1.02–1.55) (*968*). These results are consistent with the meta-analysis by Elley et al. (*972*) and present limited heterogeneity across studies compared with other outcomes. The UMPIRE 2013 trial showed a higher rate of cardiovascular events in the FDC group (5.0%) than in the usual care group (3.5%), but this was not statistically different (*969*). The UMPIRE 2013 trial also reported on health-related quality-of-life measures using the EQ-5D instrument. Mean (standard error) summary index scores were similar in the intervention and comparator groups (0.82 (0.01) versus 0.81 (0.1), $P = 0.43$) (*969*).

The Committee noted that, although some preliminary evidence suggested improved adherence with FDC formulations, these improvements were limited and unlikely to be associated with relevant differences in clinical outcomes. The Committee was also concerned about the higher rates of adverse events and discontinuations reported in patients randomized to FDC therapy in the trials.

In addition, the Committee expressed concern about the difficulty that would be associated with dose titration or cessation of individual ingredients within the FDC formulations, as is a common occurrence with medicines used for prevention and treatment of cardiovascular disease.

The Expert Committee acknowledged the potential advantages of FDCs for improving adherence and for providing an affordable product for secondary prevention of cardiovascular diseases. On the basis of the evidence presented in the application for various FDCs, however, the Committee did not recommend addition of any of the preparations to the EML.

Section 14: Diagnostic agents

14.2: Radiocontrast media

Gadopentate dimeglumine (addition) – EML

Gadoterate meglumine (addition) – EML and EMLc

The Expert Committee considered two applications requesting inclusion of gadolinium-based contrast agents (Gd-CAs) on the EML and EMLc.

One application was submitted by Dr Daniel Patiño, University of Antioquia, Medellin, Colombia, and Dr Holger Schünemann, McMaster University, Hamilton, ON, Canada, for inclusion of gadopentate dimeglumine with a square box symbol (as representative of the therapeutic class of Gd-CAs) on the complementary list of the EML for use in the detection of lymph node metastases. The other application, submitted by Guerbet Group, Villepinte, France, requested inclusion of gadoterate meglumine on the EML and EMLc for use as a contrast agent in magnetic resonance imaging (MRI).

Expert reviews of each application were prepared by two members of the Expert Committee. No public comments were received in relation to the applications.

MRI is a non-invasive medical imagining technique used to assist in the diagnosis and treatment of disease. Contrast agents are used in around 40% of MRI examinations to increase the contrast between normal tissue and pathological structures, to speed up image acquisitions and to provide additional functional information on the tissues and organs under evaluation. MRI procedures are performed for a wide range of diseases including central nervous system diseases, cardiovascular diseases and cancer.

Gd-CAs are intravenous agents used for contrast enhancement with MRI. They have been shown to improve the diagnostic efficacy of MRI, providing better visualization of primary tumours and tumour vascularity. Studies have shown that, compared with unenhanced images, Gd-CAs help to improve detection and delineation of lesions, which can alter diagnosis in up to 40% of patients (*974*). Contrast-enhanced MRI may provide information on whether a lesion is suspicious for metastases as the administration of an IV contrast agent can reveal surrounding blood vessels and demonstrate additional morphological characteristics of tumour tissue, potentially resulting in a more accurate diagnosis (*975*, *976*).

A number of Gd-CAs are available and may be differentiated on the basis of their stability and physiochemical properties; however, they cannot be differentiated on the basis of efficacy (*977*). A limited number of studies have compared various Gd-CAs without showing clinically significant differences in diagnostic efficacy (*974*). The Expert Committee therefore decided to consider the two applications collectively as the therapeutic class

Gd-CAs, including gadopentate dimeglumine, gadodiamide, gadoversetamide, gadobenate dimeglumine, gadoteridol, gadoteric acid (gadoterate meglumine) and gadobutrol.

The Committee noted with concern the association between Gd-CAs and nephrogenic systemic fibrosis (NSF), a serious and potentially fatal fibrosing disease involving primarily the skin and subcutaneous tissues. Patients at risk of developing NSF are those with renal impairment, those in the perioperative transplantation period, infants and neonates, and pregnant and breastfeeding women (*977–980*) Individual Gd-CAs are classified as either high-, medium- or low-risk according to reported associations with NSF in vulnerable patients.

While noting that, compared with unenhanced imaging, Gd-CA-enhanced MRI has been reported to improve diagnostic efficacy, the Expert Committee considered that the applications did not provide adequate evidence linking this improved efficacy with improvements in patient management and clinical benefits for the indications described in the applications. With this in mind, the Committee considered whether Gd CAs meet the definition of an essential medicine. On the basis of the evidence presented in the applications, the Committee concluded that the public health need for Gd-CAs for enhanced MRI in various diagnostic indications could not be adequately determined and safety was a concern. Consequently, Gd-CAs were found not to meet the definition of essential medicines in terms of satisfying public health need.

The Expert Committee therefore decided not to recommend addition of gadopentate dimeglumine, with a square box symbol (as representative of the therapeutic class of Gd-CAs) to the EML or of gadoterate meglumine to the EML and EMLc.

Section 15: Disinfectants and antiseptics

15.2: Disinfectants

Alcohol-based hand rub (addition) – EML and EMLc

An application was submitted by Dr Benedetta Allegranzi, Service Delivery and Safety, HIS Cluster, WHO, Geneva, for inclusion of alcohol-based hand rub (ABHR) in the EML and EMLc to contribute to the establishment and maintenance of safe essential health services and prevention of infection in both patients and health workers.

Reviews of the application were prepared by two members of the Expert Committee. Comments in support of the application were received from the Infection Control Africa Network, Cape Town, South Africa.

Health-care-associated infections (HCAIs) are infections that patients acquire while receiving treatment for medical or surgical conditions and are the most frequent adverse event during care delivery (*981*). They are a major problem for patient safety and can result in prolonged hospital stays, long-term disability, increased resistance of microorganisms to antimicrobial agents, an additional financial burden for the health system, high costs for patients and their families, and excess deaths (*982*, *983*). This is a key public health problem, with a disproportionately high burden of disease in low- and middle-income countries (LMICs) (*983*).

Hand hygiene is the leading measure for preventing the transmission of HCAI pathogens and reducing HCAIs (*984*) and ABHR is considered the gold standard for hand hygiene in most clinical situations. The 2009 WHO guidelines on hand hygiene recommend ABHR for routine hand antisepsis in all clinical situations, except when hands are visibly dirty or visibly soiled with blood or other body fluids or after using the toilet, when they should be washed with soap and water (*985*). Organisms are removed more effectively and quickly by ABHR than by soap or other antiseptic agents and water (*986*). Moreover, hand-rubbing with alcohol-based products is better tolerated than hand-washing with soap and water.

The Expert Committee noted that, during the 2014 west African filovirus disease outbreak, WHO guidelines (*987*) made a strong recommendation – based on high-quality evidence – for the use of either ABHR or soap and water. The guidelines also recommended that ABHR, as the standard of care, be made available at every point of care. WHO provides a range of tools to support education on the use of ABHRs, to promote awareness of when AHBRs should be used, and for monitoring use of these products in practice (http://www.who.int/gpsc/en/).

The main ingredients of the WHO-recommended ABHR formulations are isopropyl alcohol 99.8% or ethanol 96%, formulated to produce final concentrations of 75% v/v and 80% v/v respectively (*985*). Commercially-

available products meeting WHO standards are produced mainly in Europe and the USA. Production and availability of ABHRs are lowest in African and south-east Asian regions. When ABHR is made locally, for example in hospitals rather than industrial settings, quality assurance is needed. This requires either that alcoholmeters be available on site or that a sample of the product be sent to an approved facility for testing.

The production cost per 100-mL bottle of ABHR was US$ 0.37 in Kenya, US$ 0.30 in Bangladesh and US$ 0.30 in Mali. Prices of some commercially available ABHRs may be much higher and vary greatly (*985*). Effective action to facilitate local procurement of some raw ingredients for the production of the WHO-recommended ABHR formulations would probably lead to a further reduction in the cost of the end product. The Committee noted United Kingdom estimates that cost–benefits could be achieved if use of ABHR resulted in HCAI rates being reduced by as little as 0.1% (*985*).

The Expert Committee acknowledged that health-care workers' hands are a frequent means of transmission of pathogens and agreed that hand hygiene measures and use of ABHR can lead to significant reductions in avoidable infections in both adults and children. Given the obvious public health need and the potential for promoting the availability of ABHR globally, the Expert Committee recommended the addition of ABHR to the WHO Model Lists of Essential Medicines for adults and children. ABHRs may be commercially available products (meeting recognized ASTM or EN standards for microbicidal efficacy) or WHO-recommended formulations for local production (ethanol 80% v/v, isopropyl alcohol 75% v/v).

Section 17: Gastrointestinal medicines

17.1: Antiulcer medicines

Omeprazole (new formulation) – EML

Omeprazole (as solid and liquid oral dose forms) is currently included on the EML and EMLc with a square box as representative of the therapeutic class of proton-pump inhibitors (PPIs). The need for a parenteral preparation of omeprazole was discussed at the 19th meeting of the Expert Committee in 2013 as part of a broader review of antiulcer medicines (histamine-2 receptor antagonists (H2RAs) and PPIs). In 2013, the Expert Committee considered that the most important and common indication for intravenous PPIs was peptic ulcer bleeding. However, no changes to the EML were recommended at that time and it was considered that a more extensive application would be needed to justify the addition of a parenteral PPI on the EML (*11*).

An application was submitted by Dr Grigorios Leontiadis and Dr Holger Schünemann, Departments of Clinical Epidemiology and Biostatistics & WHO Collaborating Centre for Evidence-Informed Policy, McMaster University, Hamilton, ON, Canada, for inclusion on the core list of the EML of a parenteral formulation of omeprazole for intravenous administration for:

- patients with severe suspected non-variceal upper gastrointestinal bleeding for whom endoscopy is unavailable or is expected to be delayed; and
- patients with endoscopically documented peptic ulcer bleeding with high risk for detrimental outcomes (active bleeding or a non-bleeding visible vessel), regardless of the application of endoscopic haemostatic treatment (which may not be widely available in low-resource settings).

Expert reviews of the application were prepared by two members of the Expert Committee. Comments in support of the application were received from Myriam Henkens, International Medical Coordinator, Médecins Sans Frontières.

In consideration of the application, the Expert Committee acknowledged that peptic ulcer bleeding is a common medical emergency and is associated with substantial morbidity, mortality and health-care costs (*988*). Haemostasis in the stomach and duodenum is antagonized by gastric acid and pepsin, which inhibit clot formation and promote lysis of previously formed clots. The Committee noted that, in a Cochrane systematic review of 24 randomized controlled trials comprising 4373 participants, PPIs improved clinical outcomes in patients with peptic ulcer bleeding compared with H2RAs or placebo (*989*). PPI treatment significantly reduced rebleeding (odds ratio (OR) 0.49; 95% CI: 0.37–0.65), surgical interventions (OR 0.61; 95% CI 0.48–0.78) and further

endoscopic haemostatic treatment (OR 0.32; 95% CI: 0.20–0.51). There was no evidence of an effect of PPI treatment on all-cause mortality rates (OR 1.01; 95% CI 0.74–1.40). However, PPI treatment significantly reduced mortality when the analysis was restricted to patients with high-risk endoscopic findings (active bleeding or a non-bleeding visible vessel) (OR 0.53; 95% CI: 0.31–0.91), and among trials that had been conducted in Asia (OR 0.35; 95% CI: 0.16–0.74).

In the current application, a literature search for clinical practice guidelines on the management of peptic ulcer bleeding or non-variceal upper gastrointestinal bleeding was performed. Of the seven guidelines identified (*990–996*), six recommended pre-endoscopic PPI treatment in patients with suspected non-variceal upper gastrointestinal bleeding and none recommended an exclusively oral route of administration. All seven guidelines recommended post-endoscopic PPI treatment of patients with endoscopically documented peptic ulcer bleeding. Again, none recommended an exclusively oral route of administration.

The application also presented an updated systematic review of 10 randomized controlled trials that compared oral with intravenous PPI treatment in patients with peptic ulcer bleeding (*997*). The pooled analysis showed no statistically significant differences in mortality rates, rebleeding rates or surgery rates between IV and oral PPI treatment, therefore suggesting equivalence. The summary of findings is presented in Table 10. The Expert Committee acknowledged the fact that biases related to study limitations (i.e. absence of blinding) postulated by Cochrane reviewers, which led to downgrading of the quality of evidence to low or very low, were unlikely to happen. Blinding of outcome assessors is less important for the assessment of all-cause mortality. It is possible that bleeding and surgery might be more vulnerable to biased judgments in unblinded RCTs. However the Expert Committee perceived these risks to be limited, while indirectness and imprecision might be more important limitations to overall quality of evidence.

Table 10

Intravenous PPI compared with oral PPI treatment for acute peptic ulcer bleeding: summary of clinical efficacy findings

Notes:

1. The basis for the *assumed risk* (e.g. the median control group risk across studies is provided in footnotes. The *corresponding risk* (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
2. RR = risk ratio; CI = confidence interval.
3. GRADE Working Group grades of evidence:
   High quality: further research is very unlikely to change our confidence in the estimate of effect.
   Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
   Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: we are very uncertain about the estimate.

Patients or population: patients with acute peptic ulcer bleeding
Settings: hospital
Intervention: intravenous PPI treatment
Comparison: oral PPI treatment

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Oral PPI	IV PPI				
Mortality	2 per 100	2 per 100 (0–4)[a]	RR 0.83 (0.27–2.53)	763 (8 studies)	⊕⊖⊖⊖ **Very low** [b, c, d]	
Rebleeding	7 per 100	7 per 100 (5–10)[a]	RR 1.07 (0.71–1.62)	1894 (10 studies)	⊕⊕⊖⊖ **Low** [e, f, g]	

Table 10 *continued*

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Oral PPI	IV PPI				
Surgery	2 per 100	2 per 100 (0–3)[a]	RR 1.33 (0.63–2.77)	1270 (9 studies)	⨁⨁⨀⨀ **Low** [e, f, g]	

[a] Pooled risk difference.

[b] Serious study limitations: All 8 trials included in the analysis on mortality had high risk of bias (largely because no trial was blinded).

[c] Very serious imprecision: very small number of events (11 in total); the 95% CI of the pooled RR does not exclude a clinically relevant benefit or harm.

[d] Serious indirectness: the low mortality rate (1.6% for the oral PPI group; 1.4% overall) suggests that the study populations included in this analysis are not representative of the patients with peptic ulcer bleeding seen in clinical practice.

[e] Serious study limitations: Nine out of 10 trials included in the analysis on rebleeding had high risk of bias (performance and detection bias due to lack of blinding). One trial had unclear risk of bias (possible attrition bias).

[f] Serious imprecision: Small number of events (84 in total). The 95% CI for the pooled effect does not exclude a clinically relevant benefit or harm.

[g] Possible indirectness: the low mortality rate (1.6% for the oral PPI group; 1.4% overall) among the 8 (of 10) studies that reported mortality rates suggests that the study populations included in this analysis are not representative of the patients with peptic ulcer bleeding seen in clinical practice.

With regard to safety, short-term treatment with PPIs (oral or IV) for the duration of therapy required for peptic ulcer bleeding (median 2–3 days) has not raised safety concerns (*998*). The 2006 Cochrane review that compared PPIs with placebo or H2RAs for peptic ulcer bleeding found that there were no serious adverse effects associated with PPI treatment (oral or IV) (*989*). The 10 trials included in the application's systematic review of IV versus oral PPI provided limited data on adverse effects.

While the data presented in the application were not specific to omeprazole, the Expert Committee was satisfied that the efficacy and safety of intravenous PPIs for peptic ulcer bleeding was acceptable. The Committee noted that other available parenteral PPIs include esomeprazole, lansoprazole and pantoprazole, and that there was no evidence to suggest significant differences in the efficacy and safety of omeprazole compared with other PPIs. This view was supported by the fact that oral dose forms of omeprazole were included in the Model Lists in 2009 with a square box symbol indicating similar clinical performance to other agents within the same pharmacological class.

No specific data on the cost of IV omeprazole were presented. The median supplier price for omeprazole 20 mg oral tablets/capsules is reported by the International Drug Price Indicator Guide as US$ 0.0213 per tablet/capsule. The Committee noted that the daily cost of IV pantoprazole (then on patent) was US$ 7.64 in the USA in 2003; since pantoprazole came off patent in 2007, it was likely that the cost would now have fallen significantly. The Committee considered that it was reasonable to estimate the cost of IV omeprazole to be similar to the cost of IV pantoprazole.

The Committee considered that, in settings where endoscopy was not easily and/or immediately available, treatment of suspected or documented peptic ulcer bleeding with IV PPIs represented a potentially life-saving intervention. However, the Committee agreed that PPI treatment and endoscopic haemostatic therapy are not substitutes for each other, and that both treatments are effective in reducing adverse clinical outcomes.

On the basis of the evidence presented, the Committee recommended inclusion of the parenteral formulation of omeprazole for IV administration on the core list of the EML for the treatment of adults with suspected peptic ulcer bleeding for whom endoscopy is unavailable or is expected to be delayed, and of patients with confirmed peptic ulcer bleeding with high risk for detrimental outcomes, regardless of the application of endoscopic haemostatic techniques. The Committee considered that it was appropriate for parenteral omeprazole to be listed with the square box symbol, indicative of similar within-class performance of PPIs and for consistency with the listed omeprazole oral dose forms.

The Committee also recommended that an application for inclusion of IV omeprazole on the Model List of Essential Medicines for Children should be sought, so that the suitability of the parenteral formulation for the treatment of children could be evaluated.

Section 18: Hormones, other endocrine medicines and contraceptives

During discussion on the addition of three new hormonal contraceptives to this section of the Model List, the Expert Committee acknowledged that:

- family planning contributes towards advancing maternal and child health and the UN Millennium Development Goal of improving maternal health;
- effective contraception reduces both unintended pregnancies and the need for abortion (particularly unsafe abortion);
- family planning reinforces people's rights to determine the number and spacing of their children.

The unmet need for contraception remains high in many settings and is highest among the most vulnerable in society – adolescents, the poor, those living in rural areas and urban slums, people with HIV infection, internally displaced people and refugees. In 2012, an estimated 222 million women had an unmet need for contraception (*999*). The Committee agreed with the WHO Reproductive Health and Research Department in strongly supporting the principle of choice for patients in the provision of family planning and contraception. The Committee considered that many factors can influence a person's choice and use of contraception, including cultural and religious values, individual preferences, medical conditions, delivery methods, cost and convenience.

The Committee noted that the three contraceptives for which inclusion in the EML was sought are all included in the WHO guidelines on medical eligibility criteria for contraceptive use (*1000*, *1001*). Further, the Committee noted the support of the WHO Reproductive Health and Research for inclusion of these products in the EML.

Details of the Expert Committee's consideration of each application are presented below.

18.3.3: Intrauterine devices

Levonorgestrel-releasing intrauterine system (new formulation) – EML

An application was submitted by Dr Petrus Steyn, Department of Reproductive Health and Research, WHO, Geneva, requesting the inclusion of a levonorgestrel-releasing intrauterine system (LNG-IUS) on the Model List to provide long-acting contraception in women of reproductive age. Compared to other contraceptives, LNG-IUS offers relevant advantages in women who are breastfeeding at least four times a day (from four weeks postpartum to one year) or have heavy menstrual bleeding. It is also suitable for use as endometrial protection during estrogen therapy for menopausal symptoms.

Reviews of the application were prepared by two members of the Expert Committee. Correspondence in support of the application was received from the WHO Reproductive Health and Research department.

A 2010 review classified the hierarchy of contraceptive effectiveness in descending order as: (i) female sterilization, long-acting hormonal contraceptives (LNG-IUS and implants); (ii) copper-containing intrauterine devices (Cu-IUDs) of ≥ 300 mm² surface area; (iii) Cu-IUDs of < 300 mm² surface area and short-acting hormonal contraceptives (injectables, oral contraceptives, the patch and vaginal ring); and (iv) barrier methods and natural methods (*1002*).

The LNG-IUS contraceptive method is included in WHO's *Medical eligibility criteria for contraceptive use* (*1000*, *1001*), *Selected practice recommendations for contraceptive use* (*1003*), and *Family planning: a global handbook for providers* (*1004*).

The contraceptive action of levonorgestrel released from the intrauterine system is associated with a thickening of cervical mucus, impedance of endocervical sperm transport, and alteration of the endometrium, preventing implantation. The LNG-IUS has high contraceptive efficacy, with reported first-year pregnancy rates of 0.1%. While it is approved for 5 years of contraceptive use, there is evidence of effectiveness for up to 7 years of continuous use. After removal there is rapid return to fertility.

A 2004 Cochrane systematic review compared the effectiveness, acceptability and tolerability of progestogen-releasing intrauterine systems with other reversible contraceptive methods (*1005*). No significant difference in the risk of unwanted pregnancy was observed between LNG-IUS and non-hormonal IUDs of > 250 mm² or levonorgestrel implant; however, the included studies may not have been sufficiently powered to detect a difference. The LNG-IUS was associated with a lower risk of pregnancy than non-hormonal IUDs of ≤ 250 mm². Women using the LNG-IUS were also more likely to experience an absence of menstrual bleeding.

Users report reduction in menstrual bleeding and 15–20% become amenorrhoeic one year after insertion. The LNG-IUS has been shown to be superior to oral treatments with either cyclic medroxyprogesterone acetate or combined oral contraceptives in reducing menstrual bleeding and in improving blood haemoglobin levels among women suffering from documented menorrhagia (*1006*).

A recent review of safety outcomes for LNG-IUS users concluded that there were no differences between LNG-IUS and Cu-IUDs in measures of bone mineral density, no clinically significant metabolic effects or effects on cardiovascular disease risk markers, no association with increased risks of venous or arterial thrombotic effects, and no evidence of increased incidence of bacterial vaginosis or cytological abnormalities (*1006*). The authors concluded

that current data support the view that there is no increased risk of primary diagnosis of breast cancer among premenopausal women who use the LNG-IUS, although the risk remains unknown in women using the LNG-IUS together with estrogens for hormone replacement therapy.

The Committee noted the higher cost of LNG-IUS compared with other contraceptive methods and devices.

The Committee considered that it was important for people to have a choice of contraceptive methods available to them, and that the addition of new, effective and safe contraceptive alternatives such as the LNG-IUS could lead to improved contraceptive use and resultant beneficial outcomes.

Based on the available evidence for effectiveness and safety, the Committee recommended the addition of the levonorgestrel-releasing intrauterine system to the core list of the EML for long-acting contraception in women of reproductive age. The Committee considered that this contraceptive option would be particularly useful in women with menorrhagia, given the observed reduction in menstrual bleeding. It is also a suitable contraceptive for women who are breastfeeding at least four times a day.

18.3.5: Implantable contraceptives

Etonogestrel-releasing implant (addition) – EML

An application was submitted by Merck Sharp & Dohme, Kenilworth, NJ, USA, for the inclusion of a long-acting etonogestrel-releasing subdermal implant on the Model List of Essential Medicines. It was proposed that the listing would complement the current listing of the levonorgestrel-releasing implant and allow countries to choose the implant best suited to local needs.

Expert reviews of the application were prepared by two members of the Expert Committee. Comments on the application were received from Dr Myriam Henkens, International Medical Coordinator, Médecins Sans Frontières. Correspondence in support of the application was also received from the WHO Reproductive Health and Research department.

Etonogestrel implants are widely available, including through government and international donor purchasing programmes. Both Implanon® and Implanon NXT® are WHO prequalified products. Implanon NXT® is bioequivalent to Implanon®; it includes an applicator to facilitate insertion and radiopaque barium sulfate to facilitate detection of the implant at the time of insertion and removal (*1007*). The preloaded, sterile, single-use applicator is suited to mobile clinics and environments with limited health infrastructure and avoids the need for incision required for manually-loaded two rod systems. The UN Commission on Life-Saving Commodities for Women and Children has prioritized implants as one of the 13 life-saving commodities for long-term contraception (*1008*).

Etonogestrel-releasing implants are included in WHO's *Medical eligibility criteria for contraceptive use* and are rated 1 (no restriction) or 2 (advantages outweigh theoretical or proven risks) for most of the conditions listed (*1000*, *1001*).

The etonogestrel-releasing implants, containing 68 mg of etonogestrel, provide up to three years' reversible contraception, with rapid return to fertility on implant removal (*1009*). Three contacts with health service providers are required – for insertion, for a 3-month check and for removal.

The application calculated event rates for efficacy end-points from pooled data from available studies (*1009–1021*), which showed a pregnancy rate of 0.15% (3 of 1995 subjects) and continuation rates of 86.5% at year 1, 77.4% at year 2 and 65.6% at year 3.

The application presented results of a meta-analysis of direct comparisons between etonogestrel-releasing implants and other long-acting reversible contraceptives (LARCs): levonorgestrel-releasing implants, depot medroxyprogesterone acetate (DMPA), levonorgestrel intrauterine devices (IUDs) and copper-containing IUDs. No significant differences were observed in rates of pregnancy between etonogestrel-releasing implants and other LARCs or in rates of continuation between etonogestrel- and levonorgestrel-releasing implants. Continuation rates for etonogestrel-releasing implants were significantly higher compared with DMPA within the first year of use, but no significant differences in continuation rates were observed between etonogestrel-releasing implants and copper-containing IUDs overall.

Tolerability end-points of amenorrhoea and bleeding patterns were examined from pooled data from the available studies. In patients using etonogestrel-releasing implants, rates of amenorrhoea were 32% at the end of year 1 and 35% at the end of year 2. Rates of bleeding at the end of years 1 and 2 respectively were: infrequent bleeding 27% and 24%; frequent bleeding 3% and 2%; and prolonged bleeding 8% and 5%. The percentages of patients using etonogestrel-releasing implants who discontinued as a result of bleeding issues over the duration of the studies were 0.07% (amenorrhoea) and 5.5% (any bleeding issue).

Meta-analysis results demonstrated that levonorgestrel-releasing implants were associated with less amenorrhoea at years 1 and 2 than etonogestrel-releasing implants. Etonogestrel-releasing implants were associated with less discontinuation due to heavy bleeding than copper-containing IUDs. Levonorgestrel IUD was associated with fewer discontinuations for frequent and prolonged bleeding than etonogestrel-releasing implant.

The Expert Committee noted the pricing agreement described in the application under which etonogestrel-releasing implants are available at reduced cost in targeted countries and with a differential pricing structure elsewhere. The Committee also noted the "Co-operation Agreement for the Receipt and

Use of Implanon" (CARUI) described in the application for family planning programmes in the developing world.

The Committee also noted that etonogestrel-releasing implants have been reported to be cost–effective in a variety of settings (*1022–1025*).

The Committee considered that it was important for people to have a choice of contraceptive methods available to them, and that the addition of new, effective and safe contraceptive alternatives such as the etonogestrel-releasing implants could lead to improved contraceptive use and resultant beneficial outcomes.

The Committee considered that etonogestrel implant was well-suited for use in low-resource settings, being highly effective and long-acting and offering the convenience of a preloaded applicator dosage form, making it particularly useful where infrastructure is limited.

Based on the evidence presented, the Expert Committee recommended that etonogestrel contraceptive implant (single rod, 68 mg) be added to the core list of the Model List of Essential Medicines for women of reproductive age. The Committee considered that contraceptive efficacy and safety of etonogestrel implant have been satisfactorily demonstrated in women aged 18–40 years.

18.3.6: Intravaginal contraceptives (new section)

Progesterone contraceptive vaginal ring (addition) – EML

An application was submitted by the Population Council, New York, for the inclusion of a progesterone contraceptive vaginal ring (PCVR) on the Model List to provide contraception for breastfeeding women.

Reviews of the application were prepared by two members of the Expert Committee. Correspondence in support of the application was also received from the WHO Reproductive Health and Research department.

In 2012, an estimated 222 million women had an unmet need for contraception and family planning globally (*999*). An analysis of survey data from 28 countries across Latin America, sub-Saharan Africa, Asia and the Middle East indicated that only approximately 30% of postpartum women are using a method of contraception. During their first year postpartum, 65% of women have an unmet need for contraception (*1026*).

Limited contraceptive choices are available for postpartum breastfeeding women. Progestogen-containing and copper-containing intrauterine devices (IUDs) and progestogen-containing implants are suitable for postpartum women but require the involvement of a skilled health-care provider for insertion, which can limit access and use in many developing countries. The progesterone contraceptive vaginal ring is an alternative contraceptive option for breastfeeding women.

The Expert Committee considered that, in addition to accessibility, the potential advantages of the PCVR include ease of use (user-controlled – women can insert and remove the ring themselves, following initial instruction), the fact that it does not require daily action, and its good acceptability among women.

In a multicentre study that evaluated the PCVR in comparison with the Copper T 380A IUD, the PCVR had a one-year pregnancy rate of 1.5 per 100, which did not differ significantly from the IUD ($P > 0.05$). More than half of the participants with a PCVR were continuing at 6 months post-admission and 23.5% were still using the PCVR and breastfeeding one year after admission. Women with the IUD, however, had higher continuation rates ($P < 0.001$) at both time points. PCVR users had more complaints of vaginal problems but had fewer vaginal disorders on examination (*1027*).

Three other studies confirm the contraceptive efficacy, acceptability and safety of the PCVR for contraceptive use by lactating women (*1028–1030*).

With regard to safety, no serious adverse events have been reported in the studies. The most frequent adverse events among PCVR users were vaginal complaints (e.g. discharge, nonspecific vaginitis, fungal or yeast infections, trichomonal infection and urinary discomfort); the rate was 3.5 per 100 women–months which was significantly higher than for IUD users (1.9 per 100 women–months) (*1030*).

Progesterone has a short half-life (3 to 90 minutes) and undergoes rapid absorption from the gastrointestinal tract and extensive hepatic metabolism; it is therefore unlikely that the small amount of progesterone excreted in breast milk can affect the infant. The PCVR has been shown to be safe for breastfed infants, with no differences in growth rate compared with infants breastfed by IUD users (*1031*).

The Expert Committee noted that a recommendation for use of a progesterone-releasing vaginal ring was added to WHO's *Medical eligibility criteria for contraceptive use* (MEC) as a new method in 2015. The fifth edition of the MEC includes a category 1 (without restriction) recommendation for use of PCVR by women who are actively breastfeeding and are at least 4 weeks postpartum (*1001*).

The Expert Committee considered that the PCVR is a safe and effective contraceptive method for breastfeeding women and confers a number of advantages. It contains the natural hormone progesterone. Systemic progesterone levels remain low in comparison with other orally administered progesterone-only contraceptives, which have a prolonged half-life. Its use does not interfere with the production of milk, the growth of the child or the health of the mother and child. In addition, following initial examination and instructions for use, the PCVR can be inserted and removed by the user without the intervention of a health-care provider. Finally, the PCVR does not require cold-chain storage or specialized facilities.

The Expert Committee noted that the Population Council has negotiated a cost-plus price agreement with the PCVR manufacturer for public-sector procurement. The aim of this agreement is to ensure public-sector availability of PVCR at the lowest possible cost.

The Expert Committee acknowledged that expanding the use of modern contraceptive methods among women who breastfeed is a public health concern. Based on the efficacy, safety, ease of use and user-control of the PCVR for contraceptive use by breastfeeding women, the Committee recommended that the PCVR be added to the core list of Model List of Essential Medicines for contraception in women who are actively breastfeeding at least four times a day during the first year postpartum.

The Committee recommended listing of PCVR in a new subsection of the Model List – 18.3.6, Intravaginal contraceptives.

The Committee considered that it was important for people to have a choice of contraceptive methods available to them, and that the addition of new, effective and safe contraceptive alternatives such as the PCVR for breastfeeding women could lead to improved contraceptive use and resultant beneficial outcomes.

Section 19: Immunologicals

19.3: Vaccines (review) – EML and EMLc

The EML Secretariat, with input from the WHO Immunization, Vaccines and Biologicals Department, proposed a slightly revised approach to the listing of vaccines on the EML and EMLc for consideration by the Expert Committee.

The revised approach involves the full alignment of vaccines on the Model Lists with current WHO immunization policy recommendations as published in vaccine position papers on the basis of recommendations made by the Strategic Advisory Group of Experts on Immunization (SAGE).

SAGE is the principal advisory group to WHO for vaccines and immunization. It is charged with advising WHO on overall global policies and strategies, ranging from vaccines and technology, research and development to delivery of immunization and its linkages with other health interventions in accordance with its mandate to provide guidance to Member States on health policy matters (http://www.who.int/immunization/policy/sage/en). SAGE consists of 15 internationally renowned independent experts in the field of immunization and is concerned not just with childhood vaccines and immunization but with all vaccine-preventable diseases. SAGE meets twice a year, generally in April and October. Working groups are established for detailed review of specific topics in advance of discussion by SAGE. Members of working groups review the evidence and prepare options for recommendations for discussion by the full SAGE group in an open forum. In developing recommendations, SAGE follows an evidence-based review process and applies GRADE. Processes follow the critical elements required by WHO's Guideline Review Committee in the development of WHO guidelines.

SAGE may decide to recommend specific vaccines to be used universally or to be used conditionally or to not use specific vaccines at a given point in time. These recommendations translate into WHO policy recommendations. WHO publishes its global vaccine policy recommendations as vaccine position papers within the Weekly Epidemiological Record, available on the WHO website at http://www.who.int/immunization/documents/positionpapers/en/index.html. The position papers summarize essential background information on diseases and vaccines, and conclude with the current WHO position concerning vaccine use in the global context. The papers are designed for use by national public health officials and immunization programme managers. They may also be of interest to international funding agencies, the vaccine manufacturing industry, the medical community, and the scientific media.

WHO position papers undergo a formal review process both internally and externally before publication. Processes for managing potential conflicts of interest and ensuring careful and critical appraisal of the best scientific evidence have become more rigorous in recent years. The need for updating vaccine

position papers is reviewed periodically and depends primarily on the availability of new scientific evidence and public health priorities. A brief update concerning a specific recommendation in a paper is released when warranted.

The Expert Committee agreed that the EML and EMLc should include those vaccines for which a WHO position paper exists (as at a specific publication date), with reference to the WHO immunization website for up-to-date recommendations at any point in time. The Committee also agreed that the EML and EMLc should specify whether vaccines are recommended for universal or conditional use (e.g. only in certain regions, populations, or in other specified circumstances), with reference to relevant WHO vaccine position papers for detail.

Section 21: Ophthalmological preparations

21.6: Anti-vascular endothelial growth factor (VEGF) preparations

Ranibizumab (addition) – EML

An application was submitted by Novartis Pharma AG, Basel, Switzerland for inclusion in the WHO Model List of Essential Medicines of ranibizumab for the treatment of neovascular (wet) age-related macular degeneration (nAMD), visual impairment due to diabetic macular oedema (DME), visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO), visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO) and visual impairment due to choroidal neovascularization (CNV) secondary to pathological myopia (PM).

Expert reviews of the application were prepared by two members of the Expert Committee. Public comments on the application were received from The European Alliance for Access to Safe Medicines, from Professor Andrzej Stankiewicz, President of AMD Association Poland, from The Hellenic Retina Society, from Professor Wojciech Omulecki, Head of the Department of Ophthalmology, Medical University of Lodz, Poland, and from the Chairmen of the Polish Ophthalmological Society, Retina Hong Kong and the Irish Patients' Association.

At its 19th meeting, the Expert Committee, while noting the absence of stringent regulatory authority approval for use for the indication of nAMD, recommended inclusion of bevacizumab (an alternative vascular endothelial growth factor (VEGF) inhibitor) in the EML for treatment of nAMD on the grounds of public health need, demonstrated safety and effectiveness, and favourable cost–effectiveness (*11*).

The pooled prevalence of nAMD, a progressive and chronic disease of the retina, at any stage is 8.7% (95% credible interval (CrI): 4.3–17.4%) and the prevalence of late-stage nAMD is 0.4% (95% CrI: 0.2–0.8%). Higher prevalence is observed in European than in Asian or African populations (*1032*). The condition is the leading cause of irreversible blindness in people over 50 years of age in developed countries (*1033*). As a result of increased life expectancy and the growth of the elderly population, the number of cases of nAMD is expected to increase drastically by 2020 (*1034*).

Diabetic retinopathy is one of the most frequent and severe complications of diabetes mellitus. DME is caused by the exudation and accumulation of extracellular fluid and proteins in the macula and is associated with blindness in the working-age population in developed countries (*1035*). Visual impairment due to DME has been reported to affect approximately 1–3% of the diabetic population (*1036*).

Retinal vein occlusion involves the narrowing or blockage of a retinal vein. It is classified by the site of venous occlusion as either central retinal vein

occlusion (CRVO) or branch retinal vein occlusion (BRVO). Approximately 16.4 million adults are affected worldwide, 13.9 million with BRVO and 2.5 million with CRVO; annual incidences of BRVO and CRVO are 0.12% and 0.03–0.04%, respectively (*1037–1039*).

Pathological myopia is a leading cause of vision loss, especially in a younger population (< 50 years of age). Population-based studies reported the prevalence of PM to be 0.9–3.1% and of visual impairment attributable to PM to range from 0.1% to 0.5% in European studies and 0.2% to 1.4% in Asian studies (*1040*). The prevalence of choroidal neovascularization in individuals with PM has been reported to be 5.2–11.3%; development of CNV is associated with visual impairment.

Numerous studies document the efficacy of ranibizumab for the treatment of nAMD, DME, BRVO, CRVO, CNV and PM.

In nAMD, the MARINA (*1041*), ANCHOR (*1042*) and FOCUS (*1043*) trials reported mean increases in visual acuity in the subgroups receiving intravitreal injections of 0.5 mg ranibizumab compared with sham photodynamic therapy (PDT), sham intravitreal injections and active verteporfin PDT.

The results of a Cochrane review of 12 randomized controlled trials (RCTs) including a total of 5496 participants with nAMD indicate that anti-VEGF agents (ranibizumab, bevacizumab and pegaptanib) are effective in terms of maintaining visual acuity; ranibizumab and bevacizumab were also shown to improve visual acuity (*1044*). Comparative efficacy for visual acuity (gain of 15 letters or more of visual acuity at one year) of ranibizumab compared with the currently EML-listed bevacizumab, expressed as risk ratio (RR), was 0.90 (95% CI: 0.73–1.11).

The RESOLVE and RESTORE studies assessed the efficacy and safety of ranibizumab in patients with visual impairment due to DME. The RESOLVE study showed that ranibizumab is effective in improving best corrected visual acuity (BCVA) and is well tolerated (*1045*). In the RESTORE study, ranibizumab monotherapy and ranibizumab combined with laser therapy proved to be superior to standard laser therapy in improving visual acuity (*1046*). Over three years, BCVA was maintained and the occurrence of ocular and non-ocular adverse events was limited (*1047*).

The results of a Cochrane review of 18 RCTs indicate that anti-VEGF agents (ranibizumab, aflibercept, bevacizumab and pegaptanib) are effective in terms of maintaining and improving visual acuity in patients with DME when compared with control treatments (i.e. no anti-VEGF agents) (*1048*). Regarding absolute benefit, 100 participants need to be treated with antiangiogenic therapy to allow 20 more people (95% CI: 13–29) to have markedly improved vision after one year. No significant subgroup difference between bevacizumab, ranibizumab and aflibercept was demonstrated. The comparative efficacy for visual acuity

(a gain of three or more lines at one year) of ranibizumab compared with the currently EML-listed bevacizumab, expressed as relative odds ratio (OR), was 1.15 (95% CI: 0.67–2.08). This analysis was based on direct and indirect comparisons, taking advantage of all available evidence.

More recently, a multicentre RCT of 660 patients with DME found aflibercept to be more effective than ranibizumab and bevacizumab at improving vision in patients with lower visual-acuity letter scores at baseline (*1049*). The Expert Committee considered that the results of this trial are of interest and that the comparative effectiveness of aflibercept in comparison with other anti-VEGF agents needs to be further explored.

The BRAVO study, a multi-centred RCT of 397 patients with macular oedema secondary to BRVO, compared monthly intravitreal ranibizumab injections (0.3 mg and 0.5 mg) with sham injections (*1050*). The study reported that ranibizumab appears to have a favourable effect on visual function. However, approximately 50% of the ranibizumab 0.3 mg group and 45% of the ranibizumab 0.5 mg group in the trial also received rescue laser photocoagulation therapy, which may have had a significant effect on the primary outcome (*1051*).

The CRUISE RCT followed a similar design to BRAVO, randomizing 392 patients with macular oedema secondary to CRVO to monthly intravitreal ranibizumab injections (0.3 mg and 0.5 mg) or sham injections (*1050*). The proportions of patients gaining three lines or more in BCVA were 46.2% in the 0.3 mg ranibizumab group, 47.7% in the 0.5 mg ranibizumab group, and 16.9% in those receiving sham injections. The ROCC study of 32 patients with macular oedema secondary to CRVO, randomized to monthly intravitreal ranibizumab (0.5 mg/0.05 mL) or sham injections for three consecutive months, also reported increased BCVA in the ranibizumab group compared with the sham injection group (*1052*).

The results of a Cochrane review of six RCTs including a total of 937 patients with CRVO indicated that anti-VEGF agents (ranibizumab, aflibercept, bevacizumab and pegaptanib) are effective in maintaining and improving visual acuity (*1053*). There were no statistically significant differences between the anti-VEGF agent subgroups. This comparison is limited by the paucity of studies and – in the absence of head-to-head randomized studies – the lack of direct comparison of anti-VEGFs. However, the Expert Committee considered that differences between bevacizumab and ranibizumab for this indication are unlikely, given the contextual evidence in similar diseases and the lack of a biological rationale for differences.

The 12-month randomized RADIANCE trial, including 277 patients with myopic CNV, assessed the efficacy and safety of ranibizumab, administered under two different schedules, guided by visual acuity stabilization or disease activity, compared with verteporfin PDT. Ranibizumab treatment provided

superior BCVA gains compared with verteporfin PDT in the first three months (*1054*); patients in the verteporfin PDT arm of the study were switched to ranibizumab thereafter.

Three additional RCTs compared ranibizumab and bevacizumab in patients with myopic choroidal neovascularization (mCNV) (*1055–1057*). Significant improvements in visual acuity were observed in both ranibizumab and bevacizumab groups. The differences in the final mean BCVA between the groups was not significant, although these studies had limited power. In a recent meta-analysis, the comparative efficacy for visual acuity (a gain of three or more lines at one year) of ranibizumab compared with the currently EML-listed bevacizumab, expressed as risk ratio, was 0.95 (95% CI: 0.67–1.32) (*1058*).

With regard to safety, the meta-analyses conducted for all antiangiogenic drugs compared with either sham therapy or photocoagulation showed no significant difference regarding all serious systemic adverse events, specific serious systemic adverse events such as arterial thromboembolic events (including myocardial infarction, stroke or cerebral infarction, ischaemic cardiomyopathy), and overall mortality (*1044*, *1048*, *1053*). Ocular inflammation and increased intraocular pressure after intravitreal injection were the most frequently reported serious ocular adverse events. Endophthalmitis was reported in less than 1% of anti-VEGF treated participants.

The occurrence of serious systemic adverse events was comparable across anti-VEGF-treated groups and control groups. In addition, a recent Cochrane systematic review assessing the systemic safety of intravitreal bevacizumab compared with ranibizumab in patients with nAMD in non-industry-sponsored RCTs found no relevant difference for deaths, serious adverse events, or specific subsets of serious adverse events, with the exception of gastrointestinal disorders, in the first two years of treatment (*1059*). Based on the event rates in the studies, the risk of death with ranibizumab is 3.4% and with bevacizumab 3.7% (95% CI: 2.7–5.3%), and the risk of serious adverse events with ranibizumab is 22.2% and with bevacizumab 24% (95% CI: 20–29.1%). These results suggest that if a difference does exist, it is likely to be small.

In consideration of costs, the Expert Committee noted that the National Institute for Health and Care Excellence (NICE) considers ranibizumab to be cost–effective for nAMD (20 000 – 25 000 patients/year in the United Kingdom) but not affordable for DME (100 000 patients/year) (*1060*). Ranibizumab is more expensive than bevacizumab, with each injection costing several hundred US dollars and less than US$ 100 US respectively (*1061*). In a large independent RCT based in the United Kingdom, the mean total cost per patient over the 2-year trial ranged from £18 590 (US$ 29 119) for monthly ranibizumab to £3002 (US$ 4702) for as-needed bevacizumab (*1062*). Drug cost accounted for 80–88% of the total cost for patients randomized to ranibizumab and 21–30% of the cost

for patients randomized to bevacizumab. Recent economic analyses investigated the cost–effectiveness of as-needed ranibizumab versus monthly bevacizumab: as-needed ranibizumab was more costly and produced negligible or no health gains compared with monthly bevacizumab (*1061*, *1062*).

Ranibizumab is currently registered in more than 100 countries worldwide for nAMD, DME, BRVO and CRVO and in more than 80 countries for mCNV. It is recommended by NICE as a possible treatment for these conditions (*1060*, *1063–1065*). Ranibizumab must be administered under aseptic conditions by a qualified ophthalmologist experienced in intravitreal injections. Adequate anaesthesia and a broad-spectrum topical microbicide to disinfect the skin, eyelid and ocular surface should be administered before the injection. Following intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection and tonometry within 30 minutes following the injection. Patients should be monitored during the week following the injection to permit early treatment if an infection occurs. Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography) (*1066*).

The Expert Committee noted that currently available formulations of bevacizumab are not specifically formulated for intravitreal injection. Bevacizumab is available as a sterile solution of 25 mg/mL (i.e. 1.25 mg per 0.05 mL) and therefore does not need to be diluted or reconstituted in any way for intravitreal injection. The Committee considered that reports of adverse events (such as endophthalmitis) resulting from compounding of doses from the currently available bevacizumab vial sizes for multiple intravitreal injections had been traced to inadequate sterility in the compounding process. The Committee therefore noted that safe use of bevacizumab as currently formulated requires that use may need to be restricted to a single patient per vial, notwithstanding the wastage. Any alternative approach to using a single vial for multiple patients would have to comply with appropriate safe and sterile injection practices, including any requirements for storage of the product, to ensure that there would be no possibility of contamination.

Bevacizumab is already included in the EML. The Expert Committee noted that the evidence resulting from well-conducted independent studies comparing ranibizumab and bevacizumab, critically appraised in several independent systematic reviews, is substantial. Overall, the evidence shows ranibizumab and bevacizumab to be similarly effective in nAMD, DME and mCNV. There was no direct comparative evidence for bevacizumab and ranibizumab in BRVO and CRVO, but the Expert Committee considered that differences have not been demonstrated, as the contextual evidence in similar

diseases supports similar effectiveness and safety of the two medicines. In cost–effectiveness analyses, as might be expected, bevacizumab is the preferable option since ranibizumab costs significantly more but offers no greater benefits.

The Committee was also concerned that inclusion of ranibizumab on the Model List for treatment of eye diseases might divert relevant resources from other interventions at country level.

The Committee considered the option of adding a square box to the existing listing of bevacizumab, thereby allowing selection of ranibizumab as a pharmacological alternative VEGF inhibitor. However, given the difference in current prices of the two products and the legislation relating to "off-label" use of medicines in many countries, the Committee decided that indicating interchangeability could well result in considerable additional expenditure at country level, without additional clinical benefit. The Committee considered that inclusion only of the less expensive bevacizumab on the EML might serve to facilitate its use (albeit off-label) for this indication.

While recognizing the importance of effective management strategies for neovascular eye diseases, and that ranibizumab is registered in many countries for these indications while bevacizumab is used off-label, the Expert Committee decided not to add ranibizumab to the EML.

Section 22: Oxytocics and antioxytocics

22.1: Oxytocics

The Expert Committee noted that 289 000 women died during and following pregnancy and childbirth in 2013 (*1067*). Haemorrhage accounted for more than one quarter of these maternal deaths, making it the most common direct cause of death among women and one of the main causes of maternal mortality globally (*1068*).

A 2014 systematic review of studies documenting causes of maternal death found that haemorrhage was the leading cause in southern Asia and the second most common cause in sub-Saharan Africa (*1068*). Major determinants of maternal deaths from postpartum haemorrhage (PPH) include delays in seeking and receiving appropriate care (*1069*). The Expert Committee agreed that it was important that delivery care attendants should have access to evidence-based interventions to treat PPH in a timely, effective and safe manner.

The Committee noted that the 2012 WHO *Recommendations for the prevention and treatment of postpartum haemorrhage* recommend that uterotonics be administered in the third stage of labour for all births to prevent PPH (*1070*). Oxytocin is the recommended uterotonic agent; where it is unavailable, other uterotonics (including misoprostol 600 μg) are recommended. In addition, in settings where skilled birth attendants are not present and oxytocin is unavailable, the administration of misoprostol (600 μg orally) by community health workers and lay health workers is recommended. Intravenous oxytocin is recommended for treatment of PPH; other uterotonics (including misoprostol 800 μg) are recommended in the event that oxytocin is unavailable or bleeding does not respond.

The Committee considered that reducing the risk of women dying from PPH was a global health need and would contribute to achievement of the UN Millennium Health Goal to improve maternal health.

Misoprostol (deletion) for PPH prevention – EML

An application was submitted by Professor Allyson Pollock and Dr Petra Sevcikova-Brhlikova, Barts and The London School of Medicine and Dentistry, London, England, for the deletion of the indication of misoprostol for the prevention of postpartum haemorrhage (PPH) from the WHO Model List of Essential Medicines on the basis of lack of evidence of efficacy.

Expert reviews of the application were prepared by two members of the Expert Committee. Comments supporting the retention of misoprostol on the EML for prevention of PPH were received from Dr Myriam Henkens, International Medical Coordinator, Médecins Sans Frontières. Correspondence was also received from the WHO Department of Reproductive Health and Research and Department of Maternal, Newborn, Child and Adolescent Health,

advising that the departments do not agree with the request to delete misoprostol for prevention of PPH.

In 2011, misoprostol was added to the core list of the EML for prevention of PPH in settings where parenteral uterotonics are not available or feasible (*738*). It was listed with a conditional note: "For prevention of postpartum haemorrhage where oxytocin is *not* available or *cannot* be safely used" (emphasis added).

In 2013, the Expert Committee had considered a similar application from Professor Pollock and Dr Sevcikova-Brhlikova for the deletion of misoprostol from the Model List. The Committee had expressed the view that no new clinical data had been presented and that the request was based on a reinterpretation of data previously presented. The Committee had concluded there was no basis for changing its previous decision to list misoprostol for the prevention of PPH only under circumstances where oxytocin is not available or cannot be safely used (*11*).

The current application reiterated the conclusions of the 2013 submission to the Expert Committee. No new clinical trials were cited to inform the discussion. The applicants expressed their concerns that most studies of misoprostol excluded women at risk and that the cost–benefit ratio for misoprostol women at low risk for PPH may not apply to the general population of women. The applicants were also concerned that temporal trends in randomized trials conducted in low-resource settings and factors other than misoprostol, such as training of birth attendants and comprehensiveness of care, influenced the study outcomes. However the Expert Committee noted that the use of the randomization process is a valuable protection against secular trends and other biases. Furthermore oral misoprostol was associated with large benefits (*1071*, *1072*): for instance in a large trial in rural India researchers found a significant reduction in the rate of acute postpartum haemorrhage (12.0% to 6.4%, $p < 0.0001$; relative risk 0.53 [95% CI 0.39-0.74]) and acute severe postpartum haemorrhage (1.2% to 0.2%, $p < 0.0001$; 0.20 [0.04-0.91]) in women randomised to receive misoprostol compared to placebo (*1071*). The second RCT, conducted in rural Pakistan, showed similar advantages associated with misoprostol (*1072*). The applicants concluded that it is not possible to estimate the overall efficacy of misoprostol, or its comparative efficacy, because of the significant heterogeneity in the design of existing studies and the fact that no effectiveness data are available. However this is true only for comparisons of misoprostol versus different strategies, where RCTs are scarce (*1073*).

The application discussed the safety profile of misoprostol, in particular fever greater than 38 °C, an adverse event associated with misoprostol use (*1074*). This may cause healthcare workers to be concerned about the risk of postpartum infection and initiate antibiotics unnecessarily.

The applicants reported that the number of programmes promoting use of misoprostol for the prevention of PPH is growing and contended that misoprostol is now being used extensively as the drug of choice and in place of oxytocin in a number of countries including Nepal and Uganda. It was claimed that this is diverting resources from proven effective measures such as oxytocin and trained birth attendants. Unpublished data from Uganda were provided to support the contention that misoprostol is replacing oxytocin even in settings where oxytocin use should be possible, that health-care providers lack training and that guidelines on misoprostol use are not available in health-care centres. A recent study conducted in Uganda supported the conclusion that oxytocin is superior to misoprostol for the prevention of PPH, is associated with fewer side-effects, and is the preferred treatment in settings where oxytocin is available (*1075*).

The Expert Committee noted that the current listing of misoprostol reflects a clear preference for oxytocin, relegating misoprostol to use in specific circumstances (i.e. "where oxytocin is *not* available or *cannot* be safely used"). However misoprostol, an inexpensive and heat stable prostaglandin E1 analogue that can be administered orally, vaginally, sublingually or rectally, effective at stimulating uterine contractions, is still a valuable option in those circumstances.

In consideration of the application, the Expert Committee noted that, as in 2013, no new trials were presented comparing the use of misoprostol and oxytocin for the prevention of PPH. The conclusions reached are unchanged from those of the 2013 Expert Committee: misoprostol is less effective than oxytocin infusion and is associated with adverse events (particularly vomiting and shivering). The circumstances of use have not changed; misoprostol remains an alternative for prevention of PPH in resource-poor, community and rural settings where intravenous oxytocin is not available, or cannot be safely administered. The Committee therefore concluded that the current listing for misoprostol for the prevention of PPH on the EML should remain unchanged.

Misoprostol (new indication – treatment of postpartum haemorrhage) – EML

An application was submitted by Gynuity Health Projects, New York, USA, for the inclusion on the Model List of misoprostol for the treatment of postpartum haemorrhage (PPH) in circumstances where oxytocin is not available, or cannot be safely administered. The application sought to reaffirm the need to improve access to intravenous oxytocin for treating PPH; however, misoprostol may be the only treatment option in some delivery situations. The application was supported by the WHO Department of Reproductive Health and Research (Dr O. Oladapo) and the Department of Maternal, Newborn, Child and Adolescent Health (Dr M. Mathai).

Reviews of the application were prepared by two members of the Expert Committee. A number of public comments were received in support of the application and are available on the WHO website.

In 2013, the Expert Committee had considered a similar application from Gynuity Health Projects for inclusion of misoprostol for the treatment of PPH (*11*). The 2013 Committee had noted clinical evidence showing that misoprostol was inferior to oxytocin for important clinical outcomes such as overall blood loss and WHO guidelines, which referred to the use of misoprostol as last-resort or "rescue" medication when oxytocin is not available. The 2013 Committee suggested that its listing for prevention of PPH would allow its availability for rescue purposes. Therefore it was decided not to add misoprostol for the treatment of PPH to the Model List.

Misoprostol (Hemoprostol®), administered sublingually at a dose of 800 µg (4 x 200 µg), was approved in 2014 by the European Medicines Agency (EMA) for treatment of PPH due to uterine atony where intravenous oxytocin is not available. The EMA regulatory authorities decided that, although less effective than oxytocin, misoprostol has been shown to be safe and of benefit in the treatment of women with PPH and concluded that this benefit outweighed any side-effects associated with the medicine. Because of the widespread availability of oxytocin within the European Union, Hemoprostol® is intended for sale only in markets outside the EU, where it is often less possible to provide oxytocin as cold storage and intravenous administration may not be feasible (*1076*).

A Cochrane systematic review of 10 randomized controlled trials (RCTs) of 4052 women assessed treatment of primary PPH (*1077*). Two double-blind RCTs included in the review (*1078*, *1079*) involved 1787 participants and compared 800 µg sublingual misoprostol with oxytocin (40 IU infusion) for the treatment of primary PPH among women who had a vaginal delivery with clinically diagnosed or measured blood loss of 700 mL or more within one hour of delivery. In the first RCT women were not exposed to oxytocin during labour while in the second RCT women received prophylactic oxytocin. There were no significant differences between treatments for the primary outcomes of maternal mortality (one maternal death reported for each treatment), hysterectomy, admission to intensive care unit and serious maternal morbidity. Compared with oxytocin infusion, sublingual misoprostol use was associated with a significant increase in the number of women who had blood loss of at least 1000 mL (relative risk RR 2.65; 95% CI 1.04–6.75) and blood transfusion (RR 1.47; 95% CI: 1.02–2.14) (*1077*). However, there were no significant differences between sublingual misoprostol and oxytocin infusion in blood loss of at least 500 mL (average RR 1.51; 95% CI: 01.14–2.00) and post-randomization

use of additional uterotonics to control bleeding (average RR 1.30; 95% CI 0.57–2.94). No significant differences were noted between the two groups in the number of women who required examination under anaesthesia, bimanual compression or surgical intervention to control bleeding. Misoprostol was associated with a significant increase in vomiting and shivering. The review concluded that oxytocin infusion is more effective than misoprostol and causes fewer adverse events when used as first-line therapy for the treatment of primary PPH. The authors suggested that efforts should be made to make injectable oxytocin available for use at deliveries occurring outside of facilities. The review conceded that misoprostol can be used for treatment of PPH in settings where cold chain storage and infusion facilities (as required for oxytocin) are not available, and the largest body of evidence available supports the safety and effectiveness of an 800 μg sublingual dose.

Concerns that inclusion of misoprostol for treatment of PPH might detract from efforts to ensure the availability of oxytocin were raised in the application from Professor Pollock and Dr Sevcikova-Brhlikova for the deletion of misoprostol from the Model List (see Misoprostol (deletion) for PPH prevention – EML). However, the application by Gynuity Health Projects concludes that there is no evidence to indicate that revising clinical protocols to allow treatment of PPH with misoprostol or recommendations in support of misoprostol have discouraged the use of oxytocin when it is available, or hampered efforts to promote institutional deliveries in low-resource settings. Furthermore recent studies have shown poor provider knowledge and adherence to protocols for use of oxytocin and low quality of oxytocin products that have sometimes been stored at room temperature (*1080*, *1081*). Even where oxytocin is available, supply shortages of syringes, needles and IV infusion sets have been identified as barriers to the provision of appropriate care (*1082*).

The Expert Committee noted that misoprostol is a WHO prequalified medicinal product, while oxytocin is not.

The Expert Committee noted that trials providing comparative data on the use of misoprostol and oxytocin for the treatment of PPH were presented in the application. The Committee, again, recognized that misoprostol is less effective than oxytocin infusion and is associated with more adverse events (particularly vomiting and shivering) and should be used only when oxytocin is not available; this is consistent with WHO guidelines.

The Expert Committee agreed that misoprostol can offer an alternative treatment where cold storage and properly skilled personnel are not available for the safe use of oxytocin. These circumstances hopefully should become increasingly rare. The Committee noted that misoprostol is included in many hospital protocols and treatment algorithms for the management of PPH, including hospitals in both high- and low-income countries.

The Committee therefore recommended that the listing for misoprostol 200 µg tablets on the EML be extended to include treatment of PPH where oxytocin is not available or cannot be safely used, and that this condition be specified in the listing, as is currently the case for misoprostol for prevention of PPH.

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Annex 1

19th WHO Model List of Essential Medicines (April 2015)

Explanatory notes

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

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

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

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

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

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

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

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

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

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

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

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

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

1. ANAESTHETICS	
1.1 General anaesthetics and oxygen	
1.1.1 ***Inhalational medicines***	
halothane	**Inhalation.**
isoflurane	**Inhalation.**
nitrous oxide	**Inhalation.**
oxygen	**Inhalation** (medicinal gas).
1.1.2 ***Injectable medicines***	
ketamine	**Injection:** 50 mg (as hydrochloride)/ mL in 10- mL vial.
propofol*	**Injection:** 10 mg/ mL; 20 mg/ mL. * Thiopental may be used as an alternative depending on local availability and cost.
1.2 Local anaesthetics	
☐ bupivacaine	**Injection:** 0.25%; 0.5% (hydrochloride) in vial. **Injection for spinal anaesthesia:** 0.5% (hydrochloride) in 4- mL ampoule to be mixed with 7.5% glucose solution.
☐ lidocaine	**Injection:** 1%; 2% (hydrochloride) in vial. **Injection for spinal anaesthesia:** 5% (hydrochloride) in 2- mL ampoule to be mixed with 7.5% glucose solution. **Topical forms:** 2% to 4% (hydrochloride).
lidocaine + epinephrine (adrenaline)	**Dental cartridge:** 2% (hydrochloride) + epinephrine 1:80 000. **Injection:** 1%; 2% (hydrochloride or sulfate) + epinephrine 1:200 000 in vial.
Complementary List	
ephedrine	***Injection:*** *30 mg (hydrochloride)/ mL in 1- mL ampoule.* *(For use in spinal anaesthesia during delivery, to prevent hypotension).*
1.3 Preoperative medication and sedation for short-term procedures	
atropine	**Injection:** 1 mg (sulfate) in 1- mL ampoule.

1. ANAESTHETICS *(continued)*	
☐ midazolam	**Injection:** 1 mg/ mL. **Oral liquid:** 2 mg/ mL [c]. **Tablet:** 7.5 mg; 15 mg.
morphine	**Injection:** 10 mg (sulfate **or** hydrochloride) in 1- mL ampoule.
2. MEDICINES FOR PAIN AND PALLIATIVE CARE	
2.1 Non-opioids and non-steroidal anti-inflammatory medicines (NSAIMs)	
acetylsalicylic acid	**Suppository:** 50 mg to 150 mg. **Tablet:** 100 mg to 500 mg.
ibuprofen [a]	**Oral liquid:** 200 mg/5 mL. **Tablet:** 200 mg; 400 mg; 600 mg. [a] Not in children less than 3 months.
paracetamol*	**Oral liquid:** 125 mg/5 mL. **Suppository:** 100 mg. **Tablet:** 100 mg to 500 mg. * Not recommended for anti-inflammatory use due to lack of proven benefit to that effect.
2.2 Opioid analgesics	
codeine	**Tablet:** 30 mg (phosphate).
☐ morphine*	**Granules (slow-release; to mix with water):** 20 mg–200 mg (morphine sulfate). **Injection:** 10 mg (morphine hydrochloride or morphine sulfate) in 1- mL ampoule. **Oral liquid:** 10 mg (morphine hydrochloride or morphine sulfate)/5 mL. **Tablet (slow release):** 10 mg–200mg (morphine hydrochloride or morphine sulfate). **Tablet (immediate release):** 10 mg (morphine sulfate). * Alternatives limited to hydromorphone and oxycodone
2.3 Medicines for other common symptoms in palliative care	
amitriptyline	**Tablet:** 10 mg; 25 mg; 75 mg.
cyclizine [c]	**Injection:** 50 mg/ mL. **Tablet:** 50 mg.

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

3. ANTIALLERGICS AND MEDICINES USED IN ANAPHYLAXIS	
dexamethasone	**Injection:** 4 mg/ mL in 1- mL ampoule (as disodium phosphate salt).
epinephrine (adrenaline)	**Injection:** 1 mg (as hydrochloride **or** hydrogen tartrate) in 1- mL ampoule.
hydrocortisone	**Powder for injection:** 100 mg (as sodium succinate) in vial.
☐ loratadine *	**Oral liquid:** 1 mg/ mL. **Tablet:** 10 mg. * *There may be a role for sedating antihistamines for limited indications (EMLc).*
☐ prednisolone	**Oral liquid:** 5 mg/ mL [c]. **Tablet:** 5 mg; 25 mg.
4. ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS	
4.1 Non-specific	
charcoal, activated	**Powder.**
4.2 Specific	
acetylcysteine	**Injection:** 200 mg/ mL in 10- mL ampoule. **Oral liquid:** 10% [c]; 20% [c].
atropine	**Injection:** 1 mg (sulfate) in 1- mL ampoule.
calcium gluconate	**Injection:** 100 mg/ mL in 10- mL ampoule.
methylthioninium chloride (methylene blue)	**Injection:** 10 mg/ mL in 10- mL ampoule.
naloxone	**Injection:** 400 micrograms (hydrochloride) in 1- mL ampoule.
penicillamine	**Solid oral dosage form:** 250 mg.
potassium ferric hexacyano-ferrate(II) -2H_2O(Prussian blue)	**Powder for oral administration.**
sodium nitrite	**Injection:** 30 mg/ mL in 10- mL ampoule.
sodium thiosulfate	**Injection:** 250 mg/ mL in 50- mL ampoule.
Complementary List	
deferoxamine	***Powder for injection:*** *500 mg (mesilate) in vial.*
dimercaprol	***Injection in oil:*** *50 mg/ mL in 2- mL ampoule.*

4. ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS *(continued)*	
fomepizole	***Injection:*** *5 mg/ mL (sulfate) in 20- mL ampoule or 1 g/ mL (base) in 1.5- mL ampoule.*
sodium calcium edetate	***Injection:*** *200 mg/ mL in 5- mL ampoule.*
succimer	***Solid oral dosage form:*** *100 mg.*
5. ANTICONVULSANTS/ANTIEPILEPTICS	
carbamazepine	**Oral liquid:** 100 mg/5 mL. **Tablet (chewable):** 100 mg; 200 mg. **Tablet (scored):** 100 mg; 200 mg.
diazepam	**Gel or rectal solution:** 5 mg/ mL in 0.5 mL; 2- mL; 4- mL tubes.
☐ lorazepam	**Parenteral formulation:** 2 mg/ mL in 1- mL ampoule; 4 mg/ mL in 1- mL ampoule.
magnesium sulfate*	**Injection:** 0.5g/ mL in 2- mL ampoule (equivalent to 1 g in 2 mL; 50% weight/volume); 0.5g/ mL in 10- mL ampoule (equivalent to 5 g in 10 mL; 50% weight/volume). * For use in eclampsia and severe pre-eclampsia and not for other convulsant disorders.
midazolam	**Solution for oromucosal administration:** 5 mg/mL; 10 mg/mL. **Ampoule*:** 1 mg/ mL; 10 mg/mL. * for buccal administration when solution for oromucosal administration is not available.
phenobarbital	**Injection:** 200 mg/ mL (sodium). **Oral liquid:** 15 mg/5 mL. **Tablet:** 15 mg to 100 mg.
phenytoin	**Injection:** 50 mg/ mL in 5- mL vial (sodium salt). **Oral liquid:** 25 mg to 30 mg/5 mL.* **Solid oral dosage form:** 25 mg; 50 mg; 100 mg (sodium salt). T**ablet (chewable):** 50 mg. * The presence of both 25 mg/5 mL and 30 mg/5 mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided.

5. ANTICONVULSANTS/ANTIEPILEPTICS *(continued)*	
valproic acid (sodium valproate)	**Oral liquid:** 200 mg/5 mL. **Tablet (crushable):** 100 mg. **Tablet (enteric-coated):** 200 mg; 500 mg (sodium valproate).
Complementary List	
ethosuximide	***Capsule:*** *250 mg.* ***Oral liquid:*** *250 mg/5 mL.*
valproic acid (sodium valproate)	***Injection:*** *100 mg/ mL in 4- mL ampoule; 100 mg/ mL in 10- mL ampoule.*
6. ANTI-INFECTIVE MEDICINES	
6.1 Anthelminthics	
6.1.1 ***Intestinal anthelminthics***	
albendazole	**Tablet (chewable):** 400 mg.
levamisole	**Tablet:** 50 mg; 150 mg (as hydrochloride).
mebendazole	**Tablet (chewable):** 100 mg; 500 mg.
niclosamide	**Tablet (chewable):** 500 mg.
praziquantel	**Tablet:** 150 mg; 600 mg.
pyrantel	**Oral liquid:** 50 mg (as embonate **or** pamoate)/ mL. **Tablet (chewable):** 250 mg (as embonate **or** pamoate).
6.1.2 ***Antifilarials***	
albendazole	**Tablet (chewable):** 400 mg.
diethylcarbamazine	**Tablet:** 50 mg; 100 mg (dihydrogen citrate).
ivermectin	**Tablet (scored):** 3 mg.
6.1.3 ***Antischistosomals and other antitrematode medicines***	
praziquantel	**Tablet:** 600 mg.
triclabendazole	**Tablet:** 250 mg.
Complementary List	
*oxamniquine**	**Capsule:** 250 mg. **Oral liquid:** 250 mg/5 mL. * *Oxamniquine is listed for use when praziquantel treatment fails.*

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.2 Antibacterials

6.2.1 ***Beta-lactam medicines***

amoxicillin	**Powder for oral liquid:** 125 mg (as trihydrate)/5 mL; 250 mg (as trihydrate)/5 mL [c] . **Solid oral dosage form:** 250 mg; 500 mg (as trihydrate).
amoxicillin + clavulanic acid	**Oral liquid:** 125 mg amoxicillin + 31.25 mg clavulanic acid/5 mL AND 250 mg amoxicillin + 62.5 mg clavulanic acid/5 mL [c] . **Tablet:** 500 mg (as trihydrate) + 125 mg (as potassium salt).
ampicillin	**Powder for injection:** 500 mg; 1 g (as sodium salt) in vial.
benzathine benzylpenicillin	**Powder for injection:** 900 mg benzylpenicillin (= 1.2 million IU) in 5- mL vial [c] ; 1.44 g benzylpenicillin (= 2.4 million IU) in 5- mL vial.
benzylpenicillin	**Powder for injection:** 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium **or** potassium salt) in vial.
cefalexin [c]	**Powder for reconstitution with water:** 125 mg/5 mL; 250 mg/5 mL (anhydrous). **Solid oral dosage form:** 250 mg (as monohydrate).
☐ cefazolin* [a]	**Powder for injection:** 1 g (as sodium salt) in vial. * For surgical prophylaxis. [a] >1 month.
cefixime*	**Capsule:** 400 mg (as trihydrate). * Listed only for single-dose treatment of uncomplicated anogenital gonorrhoea.
ceftriaxone* [a]	**Powder for injection:** 250 mg; 1 g (as sodium salt) in vial. * Do not administer with calcium and avoid in infants with hyperbilirubinaemia. [a] >41 weeks corrected gestational age.
☐ cloxacillin	**Capsule:** 500 mg; 1 g (as sodium salt). **Powder for injection:** 500 mg (as sodium salt) in vial. **Powder for oral liquid:** 125 mg (as sodium salt)/5 mL.

6. ANTI-INFECTIVE MEDICINES *(continued)*	
phenoxymethylpenicillin	**Powder for oral liquid:** 250 mg (as potassium salt)/5 mL. **Tablet:** 250 mg (as potassium salt).
procaine benzylpenicillin*	**Powder for injection:** 1 g (=1 million IU); 3 g (=3 million IU) in vial. * Procaine benzylpenicillin is not recommended as first-line treatment for neonatal sepsis except in settings with high neonatal mortality, when given by trained health workers in cases where hospital care is not achievable.
Complementary List	
*cefotaxime** [c]	***Powder for injection:** 250 mg per vial (as sodium salt).* * *3rd generation cephalosporin of choice for use in hospitalized neonates.*
ceftazidime	***Powder for injection:** 250 mg **or** 1 g (as pentahydrate) in vial.*
*imipenem** + *cilastatin**	***Powder for injection:** 250 mg (as monohydrate) + 250 mg (as sodium salt); 500 mg (as monohydrate) + 500 mg (as sodium salt) in vial.* * *Listed only for the treatment of life-threatening hospital-based infection due to suspected or proven multidrug-resistant infection.* *Meropenem is indicated for the treatment of meningitis and is licensed for use in children over the age of 3 months.*
6.2.2 *Other antibacterials*	
azithromycin*	**Capsule:** 250 mg; 500 mg (anhydrous). **Oral liquid:** 200 mg/5 mL. * Only listed for single-dose treatment of genital *Chlamydia trachomatis* and of trachoma.
chloramphenicol	**Capsule:** 250 mg. **Oily suspension for injection*:** 0.5 g (as sodium succinate)/ mL in 2- mL ampoule. * Only for the presumptive treatment of epidemic meningitis in children older than 2 years. **Oral liquid:** 150 mg (as palmitate)/5 mL. **Powder for injection:** 1 g (sodium succinate) in vial.

6. ANTI-INFECTIVE MEDICINES *(continued)*	
☐ ciprofloxacin*	**Oral liquid:** 250 mg/5 mL (anhydrous) [c]. **Solution for IV infusion:** 2 mg/ mL (as hyclate) [c]. **Tablet:** 250 mg (as hydrochloride). * Square box applies to adults only.
clarithromycin*	**Solid oral dosage form:** 500 mg. * For use in combination regimens for eradication of *H. Pylori* in adults.
doxycycline [a]	**Oral liquid:** 25 mg/5 mL [c]; 50 mg/5 mL (anhydrous) [c]. **Solid oral dosage form:** 50 mg [c]; 100 mg (as hyclate). [a] Use in children < 8 years only for life-threatening infections when no alternative exists.
☐ erythromycin	**Powder for injection:** 500 mg (as lactobionate) in vial. **Powder for oral liquid:** 125 mg/5 mL (as stearate **or** estolate **or** ethyl succinate). **Solid oral dosage form:** 250 mg (as stearate **or** estolate **or** ethyl succinate).
☐ gentamicin	**Injection:** 10 mg; 40 mg (as sulfate)/ mL in 2- mL vial.
☐ metronidazole	**Injection:** 500 mg in 100- mL vial. **Oral liquid:** 200 mg (as benzoate)/5 mL. **Suppository:** 500 mg; 1 g. **Tablet:** 200 mg to 500 mg.
nitrofurantoin	**Oral liquid:** 25 mg/5 mL [c]. **Tablet:** 100 mg.
spectinomycin	**Powder for injection:** 2 g (as hydrochloride) in vial.
sulfamethoxazole + trimethoprim	**Injection:** 80 mg + 16 mg/ mL in 5- mL ampoule; 80 mg + 16 mg/ mL in 10- mL ampoule. **Oral liquid:** 200 mg + 40 mg/5 mL. **Tablet:** 100 mg + 20 mg; 400 mg + 80 mg; 800 mg + 160 mg.
trimethoprim [a]	**Oral liquid:** 50 mg/5 mL [c]. **Tablet:** 100 mg; 200 mg. [a] >6 months.

6. ANTI-INFECTIVE MEDICINES *(continued)*

Complementary List

clindamycin	***Capsule:*** *150 mg (as hydrochloride).* ***Injection:*** *150 mg (as phosphate)/ mL.* ***Oral liquid:*** *75 mg/5 mL (as palmitate)* [c] .
vancomycin	***Powder for injection:*** *250 mg (as hydrochloride) in vial.*

6.2.3 ***Antileprosy medicines***

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

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

6.2.4 ***Antituberculosis medicines***

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

ethambutol	**Oral liquid:** 25 mg/ mL [c] . **Tablet:** 100 mg to 400 mg (hydrochloride).
ethambutol + isoniazid	**Tablet:** 400 mg + 150 mg.
ethambutol + isoniazid + pyrazinamide + rifampicin	**Tablet:** 275 mg + 75 mg + 400 mg + 150 mg.
ethambutol + isoniazid + rifampicin	**Tablet:** 275 mg + 75 mg + 150 mg.
isoniazid	**Oral liquid:** 50 mg/5 mL [c] . **Tablet:** 100 mg to 300 mg. **Tablet (scored):** 50 mg.
isoniazid + pyrazinamide + rifampicin	**Tablet:** 75 mg + 400 mg + 150 mg. 150 mg + 500 mg + 150 mg **(For intermittent use three times weekly)**.

6. ANTI-INFECTIVE MEDICINES *(continued)*

isoniazid + rifampicin	**Tablet:** 75 mg + 150 mg; 150 mg + 300 mg. 60 mg + 60 mg **(For intermittent use three times weekly)**. 150 mg + 150 mg **(For intermittent use three times weekly)**.
pyrazinamide	**Oral liquid:** 30 mg/ mL [c]. **Tablet:** 400 mg. **Tablet (dispersible):** 150 mg. **Tablet (scored):** 150 mg.
rifabutin	**Capsule:** 150 mg.* * For use only in patients with HIV receiving protease inhibitors.
rifampicin	**Oral liquid:** 20 mg/ mL [c]. **Solid oral dosage form:** 150 mg; 300 mg.
rifapentine*	**Tablet:** 150 mg. * For treatment of latent TB infection (LTBI) only.
streptomycin	**Powder for injection:** 1 g (as sulfate) in vial.

Complementary List

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

amikacin	***Powder for injection:** 100 mg; 500 mg; 1 g (as sulfate) in vial.*
bedaquiline	***Tablet:** 100 mg.*
capreomycin	***Powder for injection:** 1 g (as sulfate) in vial.*
*cycloserine**	***Solid oral dosage form:** 250 mg.* * *Terizidone may be an alternative.*
delamanid	***Tablet:** 50 mg.*
*ethionamide**	***Tablet:** 125 mg; 250 mg.* * *Protionamide may be an alternative.*
kanamycin	***Powder for injection:** 1 g (as sulfate) in vial.*
*levofloxacin**	***Tablet:** 250mg; 500 mg; 750 mg.* * *Ofloxacin and moxifloxacin may be alternatives based on availability and programme considerations.*

6. ANTI-INFECTIVE MEDICINES *(continued)*	
linezolid	***Injection for intravenous administration:*** *2 mg/ mL in 300 mL bag.* ***Powder for oral liquid:*** *100 mg/5 mL.* ***Tablet:*** *400 mg; 600 mg.*
p-aminosalicylic acid	***Granules:*** *4 g in sachet.* ***Tablet:*** *500 mg.*
streptomycin [c]	***Powder for injection:*** *1 g (as sulfate) in vial.*
6.3 Antifungal medicines	
amphotericin B	**Powder for injection:** 50 mg in vial (as sodium deoxycholate or liposomal complex).
clotrimazole	**Vaginal cream:** 1%; 10%. **Vaginal tablet:** 100 mg; 500 mg.
☐ fluconazole	**Capsule:** 50 mg. **Injection:** 2 mg/ mL in vial. **Oral liquid:** 50 mg/5 mL.
flucytosine	**Capsule:** 250 mg. **Infusion:** 2.5 g in 250 mL.
griseofulvin	**Oral liquid:** 125 mg/5 mL [c]. **Solid oral dosage form:** 125 mg; 250 mg.
nystatin	**Lozenge:** 100 000 IU. **Oral liquid:** 50 mg/5 mL [c]; 100 000 IU/ mL [c]. **Pessary:** 100 000 IU. **Tablet:** 100 000 IU; 500 000 IU.
Complementary List	
potassium iodide	***Saturated solution.***
6.4 Antiviral medicines	
6.4.1 ***Antiherpes medicines***	
☐ aciclovir	**Oral liquid:** 200 mg/5 mL [c]. **Powder for injection:** 250 mg (as sodium salt) in vial. **Tablet:** 200 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.4.2 ***Antiretrovirals***

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

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

6.4.2.1 ***Nucleoside/Nucleotide reverse transcriptase inhibitors***

abacavir (ABC)	**Oral liquid:** 100 mg (as sulfate)/5 mL. **Tablet:** 300 mg (as sulfate).
lamivudine (3TC)	**Oral liquid:** 50 mg/5 mL. **Tablet:** 150 mg.
stavudine (d4T)	**Capsule:** 15 mg; 20 mg; 30 mg. **Powder for oral liquid:** 5 mg/5 mL.
tenofovir disoproxil fumarate (TDF)	**Tablet:** 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil).
zidovudine (ZDV or AZT)	**Capsule:** 100 mg; 250 mg. **Oral liquid:** 50 mg/5 mL. **Solution for IV infusion injection:** 10 mg/ mL in 20- mL vial. **Tablet:** 300 mg.

6.4.2.2 ***Non-nucleoside reverse transcriptase inhibitors***

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

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.4.2.3 ***Protease inhibitors***

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

atazanavir [a]	**Solid oral dosage form:** 100 mg; 150 mg; 300 mg (as sulfate). [a] >25 kg.
darunavir [a]	**Tablet:** 75 mg; 400 mg; 600 mg; 800 mg. [a] >3 years.
lopinavir + ritonavir (LPV/r)	**Oral liquid:** 400 mg + 100 mg/5 mL. **Tablet (heat stable):** 100 mg + 25 mg; 200 mg + 50 mg.
ritonavir	**Oral liquid:** 400 mg/5 mL. **Tablet (heat stable):** 25 mg; 100 mg.
saquinavir (SQV) [a]	**Solid oral dosage form:** 200 mg; 500 mg (as mesilate). [a] >25 kg.
FIXED-DOSE COMBINATIONS	
abacavir + lamivudine	**Tablet (dispersible, scored):** 60 mg (as sulfate) + 30 mg.
efavirenz + emtricitabine* + tenofovir	**Tablet:** 600 mg + 200 mg + 300 mg (disoproxil fumarate equivalent to 245 mg tenofovir disoproxil). * Emtricitabine (FTC) is an acceptable alternative to 3TC, based on knowledge of the pharmacology, the resistance patterns and clinical trials of antiretrovirals.
emtricitabine* + tenofovir	**Tablet:** 200 mg + 300 mg (disoproxil fumarate equivalent to 245 mg tenofovir disoproxil). * Emtricitabine (FTC) is an acceptable alternative to 3TC, based on knowledge of the pharmacology, the resistance patterns and clinical trials of antiretrovirals.
lamivudine + nevirapine + stavudine	**Tablet:** 150 mg + 200 mg + 30 mg. **Tablet (dispersible):** 30 mg + 50 mg + 6 mg [c].
lamivudine + nevirapine + zidovudine	**Tablet:** 30 mg + 50 mg + 60 mg [c]; 150 mg + 200 mg + 300 mg.
lamivudine + zidovudine	**Tablet:** 30 mg + 60 mg [c]; 150 mg + 300 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.4.3 ***Other antivirals***

oseltamivir*	**Capsule:** 30 mg; 45 mg; 75 mg (as phosphate). **Oral powder:** 12 mg/ mL. * potentially severe or complicated illness due to confirmed or suspected influenza virus infection in accordance with WHO treatment guidelines.
ribavirin*	**Injection for intravenous administration:** 800 mg and 1 g in 10- mL phosphate buffer solution. **Solid oral dosage form:** 200 mg; 400 mg; 600 mg. * For the treatment of viral haemorrhagic fevers.
valganciclovir*	**Tablet:** 450 mg. * For the treatment of cytomegalovirus retinitis (CMVr).

6.4.4 ***Antihepatitis medicines***

6.4.4.1 ***Medicines for hepatitis B***

6.4.4.1.1 ***Nucleoside/Nucleotide reverse transcriptase inhibitors***

entecavir	**Oral liquid:** 0.05 mg/ mL. **Tablet:** 0.5 mg; 1 mg.
tenofovir disoproxil fumarate (TDF)	**Tablet:** 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil).

6.4.4.2 ***Medicines for hepatitis C***

Based on current evidence, medicines in the following classes of direct acting antiviral medicines are included as essential medicines for treatment of hepatitis C virus infection. WHO guidelines recommend specific combination therapy utilizing medicines from different classes.

6.4.4.2.1 ***Nucleotide polymerase inhibitors***

sofosbuvir	**Tablet:** 400 mg.

6.4.4.2.2 ***Protease inhibitors***

simeprevir	**Capsule:** 150 mg.

6.4.4.2.3 ***NS5A inhibitors***

daclatasvir	**Tablet:** 30 mg; 60 mg (as hydrochloride).

6.4.4.2.4 ***Non-nucleoside polymerase inhibitors***

dasabuvir	**Tablet:** 250 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.4.4.2.5 ***Other antivirals***

ribavirin*	**Injection for intravenous administration:** 800 mg and 1 g in 10- mL phosphate buffer solution. **Solid oral dosage form:** 200 mg; 400 mg; 600 mg. * For the treatment of hepatitis C, in combination with peginterferon and/or direct acting anti-viral medicines.
Complementary List	
*pegylated interferon alfa (2a or 2b)**	***Vial or prefilled syringe:*** *180 micrograms (peginterferon alfa-2a), 80 microgram, 100 microgram (peginterferon alfa-2b).* * *To be used in combination with ribavirin.*
FIXED-DOSE COMBINATIONS	
Alternative combinations of DAAs from different pharmacological classes are possible	
ledipasvir + sofosbuvir	**Tablet:** 90 mg + 400 mg.
ombitasvir + paritaprevir + ritonavir	**Tablet:** 12.5 mg + 75 mg + 50 mg.

6.5 Antiprotozoal medicines

6.5.1 ***Antiamoebic and antigiardiasis medicines***

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

6.5.2 ***Antileishmaniasis medicines***

amphotericin B	**Powder for injection:** 50 mg in vial (as sodium deoxycholate or liposomal complex).
miltefosine	**Solid oral dosage form:** 10 mg; 50 mg.
paromomycin	**Solution for intramuscular injection:** 750 mg of paromomycin base (as the sulfate).
sodium stibogluconate **or** meglumine antimoniate	**Injection:** 100 mg/ mL, 1 vial = 30 mL **or** 30%, equivalent to approximately 8.1% antimony (pentavalent) in 5- mL ampoule.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.5.3 ***Antimalarial medicines***

6.5.3.1 ***For curative treatment***

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

amodiaquine*	**Tablet:** 153 mg **or** 200 mg (as hydrochloride). * To be used in combination with artesunate 50 mg.
artemether*	**Oily injection:** 80 mg/ mL in 1- mL ampoule. * For use in the management of severe malaria.
artemether + lumefantrine*	**Tablet:** 20 mg + 120 mg. **Tablet (dispersible):** 20 mg + 120 mg [c]. * Not recommended in the first trimester of pregnancy **or** in children below 5 kg.
artesunate*	**Injection:** ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution. For use in the management of severe malaria. **Rectal dosage form:** 50 mg [c]; 200 mg capsules (for pre-referral treatment of severe malaria only; patients should be taken to an appropriate health facility for follow-up care) [c]. **Tablet:** 50 mg. * To be used in combination with either amodiaquine, mefloquine **or** sulfadoxine + pyrimethamine.
artesunate + amodiaquine*	**Tablet:** 25 mg + 67.5 mg; 50 mg + 135 mg; 100 mg + 270 mg. * Other combinations that deliver the target doses required such as 153 mg **or** 200 mg (as hydrochloride) with 50 mg artesunate can be alternatives.
artesunate + mefloquine	**Tablet:** 25 mg + 55 mg; 100 mg + 220 mg.
chloroquine*	**Oral liquid:** 50 mg (as phosphate **or** sulfate)/5 mL. **Tablet:** 100 mg; 150 mg (as phosphate **or** sulfate). * For use only for the treatment of *P. vivax* infection.

6. ANTI-INFECTIVE MEDICINES *(continued)*	
doxycycline*	**Capsule:** 100 mg (as hydrochloride **or** hyclate). **Tablet (dispersible):** 100 mg (as monohydrate). * For use only in combination with quinine.
mefloquine*	**Tablet:** 250 mg (as hydrochloride). * To be used in combination with artesunate 50 mg.
primaquine*	**Tablet:** 7.5 mg; 15 mg (as diphosphate). * Only for use to achieve radical cure of *P. vivax* and *P. ovale* infections, given for 14 days.
quinine*	**Injection:** 300 mg quinine hydrochloride/ mL in 2- mL ampoule. **Tablet:** 300 mg (quinine sulfate) **or** 300 mg (quinine bisulfate). * For use only in the management of severe malaria, and should be used in combination with doxycycline.
sulfadoxine + pyrimethamine*	**Tablet:** 500 mg + 25 mg. * Only in combination with artesunate 50 mg.
6.5.3.2 ***For prophylaxis***	
chloroquine*	**Oral liquid:** 50 mg (as phosphate **or** sulfate)/5 mL. **Tablet:** 150 mg (as phosphate **or** sulfate). * For use only in central American regions, for *P. vivax* infections.
doxycycline [a]	**Solid oral dosage form:** 100 mg (as hydrochloride **or** hyclate). [a] >8 years.
mefloquine [a]	**Tablet:** 250 mg (as hydrochloride). [a] >5 kg or >3 months.
proguanil*	**Tablet:** 100 mg (as hydrochloride). * For use only in combination with chloroquine.
6.5.4 ***Antipneumocystosis and antitoxoplasmosis medicines***	
pyrimethamine	**Tablet:** 25 mg.
sulfadiazine	**Tablet:** 500 mg.
sulfamethoxazole + trimethoprim	**Injection:** 80 mg + 16 mg/ mL in 5- mL ampoule; 80 mg + 16 mg/ mL in 10- mL ampoule. **Oral liquid:** 200 mg + 40 mg/5 mL [c]. **Tablet:** 100 mg + 20 mg; 400 mg + 80 mg [c].

6. ANTI-INFECTIVE MEDICINES *(continued)*	
Complementary List	
pentamidine	***Tablet:** 200 mg; 300 mg (as isethionate).*
6.5.5 *Antitrypanosomal medicines*	
6.5.5.1 *African trypanosomiasis*	
Medicines for the treatment of 1st stage African trypanosomiasis	
pentamidine*	**Powder for injection:** 200 mg (as isetionate) in vial. * To be used for the treatment of *Trypanosoma brucei gambiense* infection.
suramin sodium*	**Powder for injection:** 1 g in vial. * To be used for the treatment of the initial phase of *Trypanosoma brucei rhodesiense* infection.
Medicines for the treatment of 2nd stage African trypanosomiasis	
eflornithine*	**Injection:** 200 mg (hydrochloride)/ mL in 100- mL bottle. * To be used for the treatment of *Trypanosoma brucei gambiense* infection.
melarsoprol	**Injection:** 3.6% solution, 5- mL ampoule (180 mg of active compound).
nifurtimox*	**Tablet:** 120 mg. * Only to be used in combination with eflornithine, for the treatment of *Trypanosoma brucei gambiense* infection.
Complementary List [c]	
melarsoprol	***Injection:** 3.6% solution in 5- mL ampoule (180 mg of active compound).*
6.5.5.2 *American trypanosomiasis*	
benznidazole	**Tablet:** 12.5 mg [c] ;100 mg. **Tablet (scored):** 50 mg.
nifurtimox	**Tablet:** 30 mg; 120 mg; 250 mg.
7 ANTIMIGRAINE MEDICINES	
7.1 For treatment of acute attack	
acetylsalicylic acid	**Tablet:** 300 mg to 500 mg.
ibuprofen [c]	**Tablet:** 200 mg; 400 mg.

7 ANTIMIGRAINE MEDICINES *(continued)*	
paracetamol	**Oral liquid:** 125 mg/5 mL [c]. **Tablet:** 300 mg to 500 mg.
7.2 For prophylaxis	
☐ propranolol	**Tablet:** 20 mg; 40 mg (hydrochloride).
8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES	
8.1 Immunosuppressive medicines	
Complementary List	
azathioprine	***Powder for injection:*** *100 mg (as sodium salt) in vial.* ***Tablet (scored):*** *50 mg.*
ciclosporin	***Capsule:*** *25 mg.* ***Concentrate for injection:*** *50 mg/ mL in 1- mL ampoule for organ transplantation.*
8.2 Cytotoxic and adjuvant medicines	
Medicines listed below should be used according to protocols for treatment of the diseases.	
Complementary List	
all-trans retinoid acid (ATRA)	***Capsule:*** *10 mg.* – *Acute promyelocytic leukaemia.*
allopurinol [c]	***Tablet:*** *100 mg; 300 mg.*
asparaginase	***Powder for injection:*** *10 000 IU in vial.* – *Acute lymphoblastic leukaemia*
bendamustine	***Injection:*** *45 mg/0.5 mL; 180 mg/2 mL.* – *Chronic lymphocytic leukaemia* – *Follicular lymphoma*
bleomycin	***Powder for injection:*** *15 mg (as sulfate) in vial.* – *Hodgkin lymphoma* – *Kaposi sarcoma* – *Ovarian germ cell tumour* – *Testicular germ cell tumour*

8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES *(continued)*	
calcium folinate	***Injection:*** *3 mg/ mL in 10- mL ampoule.* ***Tablet:*** *15 mg.* – *Early stage colon cancer* – *Early stage rectal cancer* – *Gestational trophoblastic neoplasia* – *Metastatic colorectal cancer* – *Osteosarcoma* – *Burkitt lymphoma*
capecitabine	***Tablet:*** *150 mg; 500 mg.* – *Early stage colon cancer* – *Early stage rectal cancer* – *Metastatic breast cancer* – *Metastatic colorectal cancer*
carboplatin	***Injection:*** *50 mg/5 mL; 150 mg/15 mL; 450 mg/45 mL; 600 mg/60 mL.* – *Early stage breast cancer* – *Epithelial ovarian cancer* – *Nasopharyngeal cancer* – *Non-small cell lung cancer* – *Osteosarcoma* – *Retinoblastoma*
chlorambucil	***Tablet:*** *2 mg.* – *Chronic lymphocytic leukaemia*
cisplatin	***Injection:*** *50 mg/50 mL; 100 mg/100 mL.* – *Cervical cancer (as a radio-sensitizer)* – *Head and neck cancer (as a radio-sensitizer)* – *Nasopharyngeal cancer (as a radio-sensitizer)* – *Non-small cell lung cancer* – *Osteosarcoma* – *Ovarian germ cell tumour* – *Testicular germ cell tumour*

8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES *(continued)*	
cyclophosphamide	***Powder for injection:*** *500 mg in vial.* ***Tablet:*** *25 mg.* – *Chronic lymphocytic leukaemia* – *Diffuse large B-cell lymphoma* – *Early stage breast cancer* – *Gestational trophoblastic neoplasia* – *Hodgkin lymphoma* – *Follicular lymphoma* – *Rhabdomyosarcoma* – *Ewing sarcoma* – *Acute lymphoblastic leukaemia* – *Burkitt lymphoma* – *Metastatic breast cancer*
cytarabine	***Powder for injection:*** *100 mg in vial.* – *Acute myelogenous leukaemia* – *Acute lymphoblastic leukaemia* – *Acute promyelocytic leukaemia* – *Burkitt lymphoma*
dacarbazine	***Powder for injection:*** *100 mg in vial.* – *Hodgkin lymphoma*
dactinomycin	***Powder for injection:*** *500 micrograms in vial.* – *Gestational trophoblastic neoplasia* – *Rhabdomyosarcoma* – *Wilms tumour*
daunorubicin	***Powder for injection:*** *50 mg (hydrochloride) in vial.* – *Acute lymphoblastic leukaemia* – *Acute myelogenous leukaemia* – *Acute promyelocytic leukaemia*
docetaxel	***Injection:*** *20 mg/ mL; 40 mg/ mL.* – *Early stage breast cancer* – *Metastatic breast cancer* – *Metastatic prostate cancer*

8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES *(continued)*	
doxorubicin	***Powder for injection:*** *10 mg; 50 mg (hydrochloride) in vial.* – *Diffuse large B-cell lymphoma* – *Early stage breast cancer* – *Hodgkin lymphoma* – *Kaposi sarcoma* – *Follicular lymphoma* – *Metastatic breast cancer* – *Osteosarcoma* – *Ewing sarcoma* – *Acute lymphoblastic leukaemia* – *Wilms tumour* – *Burkitt lymphoma*
etoposide	***Capsule:*** *100 mg.* ***Injection:*** *20 mg/ mL in 5- mL ampoule.* – *Testicular germ cell tumour* – *Gestational trophoblastic neoplasia* – *Hodgkin lymphoma* – *Non-small cell lung cancer* – *Ovarian germ cell tumour* – *Retinoblastoma* – *Ewing sarcoma* – *Acute lymphoblastic leukaemia* – *Burkitt lymphoma*
fludarabine	***Powder for injection:*** *50 mg (phosphate) in vial.* ***Tablet:*** *10 mg.* – *Chronic lymphocytic leukaemia*
fluorouracil	***Injection:*** *50 mg/ mL in 5- mL ampoule.* – *Early stage breast cancer* – *Early stage colon cancer* – *Early stage rectal cancer* – *Metastatic colorectal cancer* – *Nasopharyngeal cancer*

8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES *(continued)*	
filgrastim	***Injection:*** *120 micrograms/0.2 mL; 300 micrograms/0.5 mL; 480 micrograms/0.8 mL in pre-filled syringe 300 micrograms/mL in 1- mL vial, 480 mg/1.6 mL in 1.6- mL vial.* – *Primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy* – *Secondary prophylaxis for patients who have experienced neutropenia following prior myelotoxic chemotherapy* – *To facilitate administration of dose dense chemotherapy regimens*
gemcitabine	***Powder for injection:*** *200 mg in vial, 1 g in vial.* – *Epithelial ovarian cancer* – *Non-small cell lung cancer*
hydroxycarbamide	***Solid oral dosage form:*** *200 mg; 250 mg; 300 mg; 400 mg; 500 mg; 1 g.* – *Chronic myeloid leukaemia*
ifosfamide	***Powder for injection:*** *500 mg vial; 1-g vial; 2-g vial.* – *Testicular germ cell tumour* – *Ovarian germ cell tumour* – *Osteosarcoma* – *Rhabdomyosarcoma* – *Ewing sarcoma*
imatinib	***Tablet:*** *100 mg; 400 mg.* – *Chronic myeloid leukaemia* – *Gastrointestinal stromal tumour*
irinotecan	***Injection:*** *40 mg/2 mL in 2- mL vial; 100 mg/5 mL in 5- mL vial; 500 mg/25 mL in 25- mL vial.* – *Metastatic colorectal cancer*
mercaptopurine	***Tablet:*** *50 mg.* – *Acute lymphoblastic leukaemia* – *Acute promyelocytic leukaemia*

8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES *(continued)*	
mesna	***Injection:*** *100 mg/ mL in 4- mL and 10- mL ampoules.* ***Tablet:*** *400 mg; 600 mg.* – *Testicular germ cell tumour* – *Ovarian germ cell tumour* – *Osteosarcoma* – *Rhabdomyosarcoma* – *Ewing sarcoma*
methotrexate	***Powder for injection:*** *50 mg (as sodium salt) in vial.* ***Tablet:*** *2.5 mg (as sodium salt).* – *Early stage breast cancer* – *Gestational trophoblastic neoplasia* – *Osteosarcoma* – *Acute lymphoblastic leukaemia* – *Acute promyelocytic leukaemia*
oxaliplatin	***Injection:*** *50 mg/10 mL in 10- mL vial; 100 mg/20 mL in 20- mL vial; 200 mg/40 mL in 40- mL vial.* ***Powder for injection:*** *50 mg, 100 mg in vial.* – *Early stage colon cancer* – *Metastatic colorectal cancer*
paclitaxel	***Powder for injection:*** *6 mg/ mL.* – *Epithelial ovarian cancer* – *Early stage breast cancer* – *Metastatic breast cancer* – *Kaposi sarcoma* – *Nasopharyngeal cancer* – *Non-small cell lung cancer* – *Ovarian germ cell tumour*
procarbazine	***Capsule:*** *50 mg (as hydrochloride).*
rituximab	***Injection:*** *100 mg/10 mL in 10- mL vial; 500 mg/50 mL in 50- mL vial.* – *Diffuse large B-cell lymphoma* – *Chronic lymphocytic leukaemia* – *Follicular lymphoma*
tioguanine **[c]**	***Solid oral dosage form:*** *40 mg.* – *Acute lymphoblastic leukaemia*
trastuzumab	***Powder for injection:*** *60 mg; 150 mg; 440 mg in vial* – *Early stage HER2 positive breast cancer* – *Metastatic HER2 positive breast cancer*

8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES *(continued)*	
vinblastine	***Powder for injection:*** *10 mg (sulfate) in vial.* – *Hodgkin lymphoma* – *Kaposi sarcoma* – *Testicular germ cell tumour* – *Ovarian germ cell tumour*
vincristine	***Powder for injection:*** *1 mg; 5 mg (sulfate) in vial.* – *Diffuse large B-cell lymphoma* – *Gestational trophoblastic neoplasia* – *Hodgkin lymphoma* – *Kaposi sarcoma* – *Follicular lymphoma* – *Retinoblastoma* – *Rhabdomyosarcoma* – *Ewing sarcoma* – *Acute lymphoblastic leukaemia* – *Wilms tumour* – *Burkitt lymphoma*
vinorelbine	***Injection:*** *10 mg/mL in 1- mL vial; 50 mg/5 mL in 5- mL vial.* – *Non-small cell lung cancer* – *Metastatic breast cancer*

8.3 Hormones and antihormones

Complementary List

☐ *anastrozole*	***Tablet:*** *1 mg.* – *Early stage breast cancer* – *Metastatic breast cancer*
☐ *bicalutamide*	***Tablet:*** *50 mg.* – *Metastatic prostate cancer*
dexamethasone	***Injection:*** *4 mg/ mL in 1- mL ampoule (as disodium phosphate salt).* ***Oral liquid:*** *2 mg/5 mL* **[c]**. – *Acute lymphoblastic leukaemia*
☐ *leuprorelin*	***Injection:*** *7.5 mg; 22.5 mg in pre-filled syringe.* – *Early stage breast cancer* – *Metastatic prostate cancer*

8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES *(continued)*	
hydrocortisone	***Powder for injection:*** *100 mg (as sodium succinate) in vial.* – *Acute lymphoblastic leukaemia*
methylprednisolone [c]	***Injection:*** *40 mg/ mL (as sodium succinate) in 1- mL single-dose vial and 5- mL multi-dose vials; 80 mg/ mL (as sodium succinate) in 1- mL single-dose vial.* – *Acute lymphoblastic leukamia*
☐ *prednisolone*	***Oral liquid:*** *5 mg/ mL* [c] *.* ***Tablet:*** *5 mg; 25 mg.* – *Chronic lymphocytic leukaemia* – *Diffuse large B-cell lymphoma* – *Hodgkin lymphoma* – *Follicular lymphoma* – *Acute lymphoblastic leukaemia* – *Burkitt lymphoma*
tamoxifen	***Tablet:*** *10 mg; 20 mg (as citrate).* – *Early stage breast cancer* – *Metastatic breast cancer*
9. ANTIPARKINSONISM MEDICINES	
☐ biperiden	**Injection:** 5 mg (lactate) in 1- mL ampoule. **Tablet:** 2 mg (hydrochloride).
levodopa + ☐ carbidopa	**Tablet:** 100 mg + 10 mg; 100 mg + 25 mg; 250 mg + 25 mg.
10. MEDICINES AFFECTING THE BLOOD	
10.1 Antianaemia medicines	
ferrous salt	**Oral liquid:** equivalent to 25 mg iron (as sulfate)/ mL. **Tablet:** equivalent to 60 mg iron.
ferrous salt + folic acid	**Tablet:** equivalent to 60 mg iron + 400 micrograms folic acid (nutritional supplement for use during pregnancy).
folic acid	**Tablet:** 400 micrograms*; 1 mg; 5 mg. * periconceptual use for prevention of first occurrence of neural tube defects.
hydroxocobalamin	**Injection:** 1 mg (as acetate, as hydrochloride or as sulfate) in 1- mL ampoule.

10. MEDICINES AFFECTING THE BLOOD *(continued)*

10.2 Medicines affecting coagulation

☐ enoxaparin*	**Injection:** ampoule or pre-filled syringe 20 mg/0.2 mL; 40 mg/0.4 mL; 60 mg/0.6 mL; 80 mg/0.8 mL; 100 mg/1 mL; 120 mg/0.8 mL; 150 mg/1 mL. * Alternatives are limited to nadroparin and dalteparin.
heparin sodium	**Injection:** 1000 IU/ mL; 5000 IU/ mL; 20 000 IU/ mL in 1- mL ampoule.
phytomenadione	**Injection:** 1 mg/ mL [c]; 10 mg/ mL in 5- mL ampoule. **Tablet:** 10 mg.
protamine sulfate	**Injection:** 10 mg/ mL in 5- mL ampoule.
tranexamic acid	**Injection:** 100 mg/ mL in 10- mL ampoule.
☐ warfarin	**Tablet:** 1 mg; 2 mg; 5 mg (sodium salt).
Complementary List *[c]*	
desmopressin	***Injection:*** *4 micrograms/ mL (as acetate) in 1- mL ampoule.* ***Nasal spray:*** *10 micrograms (as acetate) per dose.*
heparin sodium	***Injection:*** *1000 IU/ mL; 5000 IU/ mL in 1- mL ampoule.*
protamine sulfate	***Injection:*** *10 mg/ mL in 5- mL ampoule.*
☐ *warfarin*	***Tablet:*** *0.5 mg; 1 mg; 2 mg; 5 mg (sodium salt).*

10.3 Other medicines for haemoglobinopathies

Complementary List	
*deferoxamine**	***Powder for injection:*** *500 mg (mesilate) in vial.* * *Deferasirox oral form may be an alternative, depending on cost and availability.*
hydroxycarbamide	***Solid oral dosage form:*** *200 mg; 500 mg; 1 g.*

11. BLOOD PRODUCTS OF HUMAN ORIGIN AND PLASMA SUBSTITUTES

11.1 Blood and blood components

In accordance with the World Health Assembly resolution WHA63.12, WHO recognizes that achieving self-sufficiency, unless special circumstances preclude it, in the supply of safe blood components based on voluntary, non-remunerated blood donation, and the security of that supply are important national goals to prevent blood shortages and meet the transfusion requirements of the patient population. All preparations should comply with the WHO requirements.

fresh–frozen plasma

platelets

red blood cells

whole blood

11.2 Plasma-derived medicines

All human plasma-derived medicines should comply with the WHO requirements.

11.2.1 *Human immunoglobulins*

anti-D immunoglobulin	**Injection:** 250 micrograms in single-dose vial.
Anti-rabies immunoglobulin	**Injection:** 150 IU/ mL in vial.
Anti-tetanus immunoglobulin	**Injection:** 500 IU in vial.
Complementary List	
normal immunoglobulin	***Intramuscular administration:*** *16% protein solution.** ***Intravenous administration:*** *5%; 10% protein solution.*** ***Subcutaneous administration:*** *15%; 16% protein solution.** * *Indicated for primary immune deficiency.* ** *Indicated for primary immune deficiency and Kawasaki disease.*

11.2.2 *Blood coagulation factors*

Complementary List	
☐ *coagulation factor VIII*	***Powder for injection:*** *500 IU/vial.*
☐ *coagulation factor IX*	***Powder for injection:*** *500 IU/vial, 1000 IU/vial.*

11.3 Plasma substitutes

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

12. CARDIOVASCULAR MEDICINES

12.1 Antianginal medicines

☐ bisoprolol*	**Tablet:** 1.25 mg; 5 mg. * ☐ includes metoprolol and carvedilol as alternatives.
glyceryl trinitrate	**Tablet (sublingual):** 500 micrograms.
☐ isosorbide dinitrate	**Tablet (sublingual):** 5 mg.
verapamil	**Tablet:** 40 mg; 80 mg (hydrochloride).

12.2 Antiarrhythmic medicines

☐ bisoprolol*	**Tablet:** 1.25 mg; 5 mg. * ☐ includes metoprolol and carvedilol as alternatives.
digoxin	**Injection:** 250 micrograms/ mL in 2- mL ampoule. **Oral liquid:** 50 micrograms/ mL. **Tablet:** 62.5 micrograms; 250 micrograms.
epinephrine (adrenaline)	**Injection:** 100 micrograms/ mL (as acid tartrate **or** hydrochloride) in 10- mL ampoule.
lidocaine	**Injection:** 20 mg (hydrochloride)/ mL in 5- mL ampoule.
verapamil	**Injection:** 2.5 mg (hydrochloride)/ mL in 2- mL ampoule. **Tablet:** 40 mg; 80 mg (hydrochloride).
Complementary List	
amiodarone	***Injection:*** *50 mg/ mL in 3- mL ampoule (hydrochloride).* ***Tablet:*** *100 mg; 200 mg; 400 mg (hydrochloride).*

12.3 Antihypertensive medicines

☐ amlodipine	**Tablet:** 5 mg (as maleate, mesylate **or** besylate).
☐ bisoprolol*	**Tablet:** 1.25 mg; 5 mg. * includes atenolol, metoprolol and carvedilol as alternatives. Atenolol should not be used as a first-line agent in uncomplicated hypertension in patients >60 years.
☐ enalapril	**Tablet:** 2.5 mg; 5 mg (as hydrogen maleate).

12. CARDIOVASCULAR MEDICINES *(continued)*	
hydralazine*	**Powder for injection:** 20 mg (hydrochloride) in ampoule. **Tablet:** 25 mg; 50 mg (hydrochloride). * Hydralazine is listed for use only in the acute management of severe pregnancy-induced hypertension. Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines.
☐ hydrochlorothiazide	**Oral liquid:** 50 mg/5 mL. Solid oral dosage form: 12.5 mg; 25 mg.
methyldopa*	**Tablet:** 250 mg. * Methyldopa is listed for use only in the management of pregnancy-induced hypertension. Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines.
Complementary List	
sodium nitroprusside	***Powder for infusion:*** *50 mg in ampoule.*
12.4 Medicines used in heart failure	
☐ bisoprolol*	**Tablet:** 1.25 mg; 5 mg. * ☐ includes metoprolol and carvedilol as alternatives.
digoxin	**Injection:** 250 micrograms/ mL in 2- mL ampoule. **Oral liquid:** 50 micrograms/ mL. **Tablet:** 62.5 micrograms; 250 micrograms.
☐ enalapril	**Tablet:** 2.5 mg; 5 mg (as hydrogen maleate).
☐ furosemide	**Injection:** 10 mg/ mL in 2- mL ampoule. **Oral liquid:** 20 mg/5 mL [c]. **Tablet:** 40 mg.
☐ hydrochlorothiazide	**Oral liquid:** 50 mg/5 mL. **Solid oral dosage form:** 25 mg.
spironolactone	**Tablet:** 25 mg.
Complementary List	
dopamine	***Injection:*** *40 mg/ mL (hydrochloride) in 5- mL vial.*

12. CARDIOVASCULAR MEDICINES *(continued)*	
12.5 Antithrombotic medicines	
12.5.1 ***Anti-platelet medicines***	
acetylsalicylic acid	**Tablet:** 100 mg.
clopidogrel	**Tablet:** 75 mg; 300 mg.
12.5.2 ***Thrombolytic medicines***	
Complementary List	
streptokinase	***Powder for injection:*** *1.5 million IU in vial.*
12.6 Lipid-lowering agents	
☐ simvastatin*	**Tablet:** 5 mg; 10 mg; 20 mg; 40 mg. * For use in high-risk patients.
13. DERMATOLOGICAL MEDICINES (topical)	
13.1 Antifungal medicines	
☐ miconazole	**Cream or ointment:** 2% (nitrate).
selenium sulfide	**Detergent-based suspension:** 2%.
sodium thiosulfate	**Solution:** 15%.
terbinafine	**Cream:** 1% **or Ointment:** 1% terbinafine hydrochloride.
13.2 Anti-infective medicines	
mupirocin	**Cream (as mupirocin calcium):** 2%. **Ointment:** 2%.
potassium permanganate	**Aqueous solution:** 1:10 000.
silver sulfadiazine [a]	**Cream:** 1%. [a] >2 months.
13.3 Anti-inflammatory and antipruritic medicines	
☐ betamethasone [a]	**Cream or ointment:** 0.1% (as valerate). [a] Hydrocortisone preferred in neonates.
☐ calamine	**Lotion.**
☐ hydrocortisone	**Cream or ointment:** 1% (acetate).

13. DERMATOLOGICAL MEDICINES (topical) *(continued)*	
13.4 Medicines affecting skin differentiation and proliferation	
benzoyl peroxide	**Cream or lotion:** 5%.
coal tar	**Solution:** 5%.
fluorouracil	**Ointment:** 5%.
☐ podophyllum resin	**Solution:** 10% to 25%.
salicylic acid	**Solution:** 5%.
urea	**Cream or ointment:** 5%; 10%.
13.5 Scabicides and pediculicides	
☐ benzyl benzoate [a]	**Lotion:** 25%. [a] >2 years.
permethrin	**Cream:** 5%. **Lotion:** 1%.
14. DIAGNOSTIC AGENTS	
14.1 Ophthalmic medicines	
fluorescein	**Eye drops:** 1% (sodium salt).
☐ tropicamide	**Eye drops:** 0.5%.
14.2 Radiocontrast media	
☐ amidotrizoate	**Injection:** 140 mg to 420 mg iodine (as sodium **or** meglumine salt)/ mL in 20- mL ampoule.
barium sulfate	**Aqueous suspension.**
☐ iohexol	**Injection:** 140 mg to 350 mg iodine/ mL in 5- mL; 10- mL; 20- mL ampoules.
Complementary List	
barium sulfate [c]	***Aqueous suspension.***
☐ *meglumine iotroxate*	***Solution:*** *5 g to 8 g iodine in 100 mL to 250 mL.*
15. DISINFECTANTS AND ANTISEPTICS	
15.1 Antiseptics	
☐ chlorhexidine	**Solution:** 5% (digluconate).
☐ ethanol	**Solution:** 70% (denatured).

15. DISINFECTANTS AND ANTISEPTICS *(continued)*	
☐ povidone iodine	**Solution:** 10% (equivalent to 1% available iodine).
15.2 Disinfectants	
alcohol based hand rub	**Solution** containing ethanol 80% volume /volume. **Solution** containing isopropyl alcohol 75% volume/ volume.
☐ chlorine base compound	**Powder:** (0.1% available chlorine) for solution.
☐ chloroxylenol	**Solution:** 4.8%.
glutaral	**Solution:** 2%.
16. DIURETICS	
amiloride	**Tablet:** 5 mg (hydrochloride).
☐ furosemide	**Injection:** 10 mg/ mL in 2- mL ampoule. **Oral liquid:** 20 mg/5 mL [c]. **Tablet:** 10 mg [c]; 20 mg [c]; 40 mg.
☐ hydrochlorothiazide	**Solid oral dosage form:** 25 mg.
mannitol	**Injectable solution:** 10%; 20%.
spironolactone	**Tablet:** 25 mg.
Complementary List *[c]*	
☐ *hydrochlorothiazide*	***Tablet (scored):*** *25 mg.*
mannitol	***Injectable solution:*** *10%; 20%.*
spironolactone	***Oral liquid:*** *5 mg/5 mL; 10 mg/5 mL; 25 mg/5 mL.* ***Tablet:*** *25 mg.*
17. GASTROINTESTINAL MEDICINES	
Complementary List *[c]*	
☐ *pancreatic enzymes*	*Age-appropriate formulations and doses including lipase, protease and amylase.*
17.1 Antiulcer medicines	
☐ omeprazole	**Powder for injection:** 40 mg in vial. **Powder for oral liquid:** 20 mg; 40 mg sachets. **Solid oral dosage form:** 10 mg; 20 mg; 40 mg.

17. GASTROINTESTINAL MEDICINES *(continued)*	
☐ ranitidine	**Injection:** 25 mg/ mL (as hydrochloride) in 2- mL ampoule. **Oral liquid:** 75 mg/5 mL (as hydrochloride). **Tablet:** 150 mg (as hydrochloride).
17.2 Antiemetic medicines	
dexamethasone	**Injection:** 4 mg/ mL in 1- mL ampoule (as disodium phosphate salt). **Oral liquid:** 0.5 mg/5 mL; 2 mg/5 mL. **Solid oral dosage form:** 0.5 mg; 0.75 mg; 1.5 mg; 4 mg.
metoclopramide [a]	**Injection:** 5 mg (hydrochloride)/ mL in 2- mL ampoule. **Oral liquid:** 5 mg/5 mL [c]. **Tablet:** 10 mg (hydrochloride). [a] Not in neonates.
ondansetron [a]	**Injection:** 2 mg base/ mL in 2- mL ampoule (as hydrochloride). **Oral liquid:** 4 mg base/5 mL. **Solid oral dosage form:** Eq 4 mg base; Eq 8 mg base; Eq 24 mg base. [a] >1 month.
17.3 Anti-inflammatory medicines	
☐ sulfasalazine	**Retention enema.** **Suppository:** 500 mg. **Tablet:** 500 mg.
Complementary List	
☐ *hydrocortisone*	***Retention enema.*** ***Suppository:*** *25 mg (acetate).* (the ☐ only applies to hydrocortisone retention enema).
17.4 Laxatives	
☐ senna	**Tablet:** 7.5 mg (sennosides) (or traditional dosage forms).

17. GASTROINTESTINAL MEDICINES *(continued)*

17.5 Medicines used in diarrhoea

17.5.1 *Oral rehydration*

oral rehydration salts

Powder for dilution in 200 mL; 500 mL; 1 L.

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

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

17.5.2 *Medicines for diarrhoea*

zinc sulfate*

Solid oral dosage form: 20 mg [c].

* In acute diarrhoea zinc sulfate should be used as an adjunct to oral rehydration salts.

18. HORMONES, OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES

18.1 Adrenal hormones and synthetic substitutes

fludrocortisone — **Tablet:** 100 micrograms (acetate).

hydrocortisone — **Tablet:** 5 mg; 10 mg; 20 mg.

18.2 Androgens

Complementary List

testosterone — ***Injection:*** *200 mg (enanthate) in 1- mL ampoule.*

18.3 Contraceptives

18.3.1 *Oral hormonal contraceptives*

☐ ethinylestradiol + ☐ levonorgestrel — **Tablet:** 30 micrograms + 150 micrograms.

18. HORMONES, OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES *(continued)*	
☐ ethinylestradiol + ☐ norethisterone	**Tablet:** 35 micrograms + 1 mg.
levonorgestrel	**Tablet:** 30 micrograms; 750 micrograms (pack of two); 1.5 mg.
18.3.2 ***Injectable hormonal contraceptives***	
estradiol cypionate + medroxyprogesterone acetate	**Injection:** 5 mg + 25 mg.
medroxyprogesterone acetate	**Depot injection:** 150 mg/ mL in 1- mL vial.
norethisterone enantate	**Oily solution:** 200 mg/ mL in 1- mL ampoule.
18.3.3 ***Intrauterine devices***	
copper-containing device	
levonorgestrel-releasing intrauterine system	Intrauterine system with reservoir containing 52 mg of levonorestrel.
18.3.4 ***Barrier methods***	
condoms	
diaphragms	
18.3.5 ***Implantable contraceptives***	
etonogestrel-releasing implant	Single-rod etonogestrel-releasing implant, containing 68 mg of etonogestrel.
levonorgestrel-releasing implant	Two-rod levonorgestrel-releasing implant, each rod containing 75 mg of levonorgestrel (150 mg total).
18.3.6 ***Intravaginal contraceptives***	
progesterone vaginal ring*	Progesterone-releasing vaginal ring containing 2.074 g of micronized progesterone. * For use in women actively breastfeeding at least 4 times per day.
18.4 Estrogens	
18.5 Insulins and other medicines used for diabetes	
☐ gliclazide*	**Solid oral dosage form:** (controlled-release tablets) 30 mg; 60 mg; 80 mg. * glibenclamide not suitable above 60 years.
glucagon	**Injection:** 1 mg/ mL.

18. HORMONES, OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES *(continued)*	
insulin injection (soluble)	**Injection:** 40 IU/ mL in 10- mL vial; 100 IU/ mL in 10- mL vial.
intermediate-acting insulin	**Injection:** 40 IU/ mL in 10- mL vial; 100 IU/ mL in 10- mL vial (as compound insulin zinc suspension **or** isophane insulin).
metformin	Tablet: 500 mg (hydrochloride).
Complementary List [c]	
metformin	***Tablet:*** *500 mg (hydrochloride).*
18.6 Ovulation inducers	
Complementary List	
clomifene	***Tablet:*** *50 mg (citrate).*
18.7 Progestogens	
☐ medroxyprogesterone acetate	**Tablet:** 5 mg.
18.8 Thyroid hormones and antithyroid medicines	
levothyroxine	**Tablet:** 25 micrograms [c]; 50 micrograms; 100 micrograms (sodium salt).
potassium iodide	**Tablet:** 60 mg.
☐ propylthiouracil	**Tablet:** 50 mg.
Complementary List [c]	
Lugol's solution	***Oral liquid:*** *about 130 mg total iodine/ mL.*
potassium iodide	***Tablet:*** *60 mg.*
propylthiouracil	***Tablet:*** *50 mg.*
19. IMMUNOLOGICALS	
19.1 Diagnostic agents	
All tuberculins should comply with the WHO requirements for tuberculins.	
tuberculin, purified protein derivative (PPD)	**Injection.**

19. IMMUNOLOGICALS *(continued)*

19.2 Sera and immunoglobulins

All plasma fractions should comply with the WHO requirements.

Anti-venom immunoglobulin*	**Injection.** * Exact type to be defined locally.
diphtheria antitoxin	**Injection:** 10 000 IU; 20 000 IU in vial.

19.3 Vaccines

WHO immunization policy recommendations are published in vaccine position papers on the basis of recommendations made by the Strategic Advisory Group of Experts on Immunization (SAGE).

WHO vaccine position papers are updated three to four times per year. The list below details the vaccines for which there is a recommendation from SAGE and a corresponding WHO position paper as at **27 February 2015**. The most recent versions of the WHO position papers, reflecting the current evidence related to a specific vaccine and the related recommendations, can be accessed at any time on the WHO website at: http://www.who.int/immunization/documents/positionpapers/en/index.html.

Vaccine recommendations may be universal or conditional (e.g., in certain regions, in some high-risk populations or as part of immunization programmes with certain characteristics). Details are available in the relevant position papers, and in the Summary Tables of WHO Routine Immunization Recommendations available on the WHO website at: http://www.who.int/immunization/policy/immunization_tables/en/index.html.

Selection of vaccines from the Model List will need to be determined by each country after consideration of international recommendations, epidemiology and national priorities.

All vaccines should comply with the WHO requirements for biological substances.

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

Recommendations for all

BCG vaccine

diphtheria vaccine

Haemophilus influenzae type b vaccine

hepatitis B vaccine

HPV vaccine

measles vaccine

19. IMMUNOLOGICALS *(continued)*	
pertussis vaccine	
pneumococcal vaccine	
poliomyelitis vaccine	
rotavirus vaccine	
rubella vaccine	
tetanus vaccine	
Recommendations for certain regions	
Japanese encephalitis vaccine	
yellow fever vaccine	
tick-borne encephalitis vaccine	
Recommendations for some high-risk populations	
cholera vaccine	
hepatitis A vaccine	
meningococcal meningitis vaccine	
rabies vaccine	
typhoid vaccine	
Recommendations for immunization programmes with certain characteristics	
influenza vaccine (seasonal)	
mumps vaccine	
varicella vaccine	
20. MUSCLE RELAXANTS (PERIPHERALLY-ACTING) AND CHOLINESTERASE INHIBITORS	
☐ atracurium	**Injection:** 10 mg/ mL (besylate).
neostigmine	**Injection:** 500 micrograms in 1- mL ampoule; 2.5 mg (metilsulfate) in 1- mL ampoule. **Tablet:** 15 mg (bromide).
suxamethonium	**Injection:** 50 mg (chloride)/ mL in 2- mL ampoule. **Powder for injection** (chloride), in vial.
☐ vecuronium [c]	**Powder for injection:** 10 mg (bromide) in vial.

20. MUSCLE RELAXANTS (PERIPHERALLY-ACTING) AND CHOLINESTERASE INHIBITORS *(continued)*	
Complementary List	
pyridostigmine	***Injection:*** *1 mg in 1- mL ampoule.* ***Tablet:*** *60 mg (bromide).*
☐ *vecuronium*	***Powder for injection:*** *10 mg (bromide) in vial.*
21. OPHTHALMOLOGICAL PREPARATIONS	
21.1 Anti-infective agents	
aciclovir	**Ointment:** 3% W/W.
azithromycin	**Solution (eye drops):** 1.5%.
☐ gentamicin	**Solution (eye drops):** 0.3% (sulfate).
☐ ofloxacin	**Solution (eye drops):** 0.3%.
☐ tetracycline	**Eye ointment:** 1% (hydrochloride).
21.2 Anti-inflammatory agents	
☐ prednisolone	**Solution (eye drops):** 0.5% (sodium phosphate).
21.3 Local anaesthetics	
☐ tetracaine [a]	**Solution (eye drops):** 0.5% (hydrochloride). [a] Not in preterm neonates.
21.4 Miotics and antiglaucoma medicines	
acetazolamide	**Tablet:** 250 mg.
latanoprost	**Solution (eye drops):** latanoprost 50 micrograms/mL.
☐ pilocarpine	**Solution (eye drops):** 2%; 4% (hydrochloride **or** nitrate).
☐ timolol	**Solution (eye drops):** 0.25%; 0.5% (as hydrogen maleate).
21.5 Mydriatics	
atropine* [a]	**Solution (eye drops):** 0.1%; 0.5%; 1% (sulfate). * [c] **Or** homatropine (hydrobromide) **or** cyclopentolate (hydrochloride). [a] >3 months.
Complementary List	
epinephrine (adrenaline)	***Solution (eye drops):*** *2% (as hydrochloride).*

21. OPHTHALMOLOGICAL PREPARATIONS *(continued)*	
21.6 Anti-vascular endothelial growth factor (VEGF) preparations	
Complementary List	
bevacizumab	***Injection:*** *25 mg/ mL.*
22. OXYTOCICS AND ANTIOXYTOCICS	
22.1 Oxytocics	
☐ ergometrine	**Injection:** 200 micrograms (hydrogen maleate) in 1- mL ampoule.
misoprostol	**Tablet:** 200 micrograms. – Management of incomplete abortion and miscarriage; – Prevention and treatment of postpartum haemorrhage where oxytocin is not available or cannot be safely used. **Vaginal tablet:** 25 micrograms.* * Only for use for induction of labour where appropriate facilities are available.
oxytocin	**Injection:** 10 IU in 1- mL.
Complementary List	
mifepristone – misoprostol** *Where permitted under national law and where culturally acceptable.*	***Tablet*** *200 mg –* ***tablet*** *200 micrograms.* * *Requires close medical supervision.*
22.2 Antioxytocics (tocolytics)	
nifedipine	**Immediate-release capsule:** 10 mg.
23. PERITONEAL DIALYSIS SOLUTION	
Complementary List	
intraperitoneal dialysis solution (of appropriate composition)	***Parenteral solution.***

24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS

24.1 Medicines used in psychotic disorders

☐ chlorpromazine	**Injection:** 25 mg (hydrochloride)/ mL in 2- mL ampoule. **Oral liquid:** 25 mg (hydrochloride)/5 mL. **Tablet:** 100 mg (hydrochloride).
☐ fluphenazine	**Injection:** 25 mg (decanoate or enantate) in 1- mL ampoule.
☐ haloperidol	**Injection:** 5 mg in 1- mL ampoule. **Tablet:** 2 mg; 5 mg.
risperidone	**Solid oral dosage form:** 0.25 mg to 6.0 mg.
Complementary List	
chlorpromazine [c]	***Injection:*** *25 mg (hydrochloride)/ mL in 2- mL ampoule.* ***Oral liquid:*** *25 mg (hydrochloride)/5 mL.* ***Tablet:*** *10 mg; 25 mg; 50 mg; 100 mg (hydrochloride).*
clozapine	***Solid oral dosage form:*** *25 to 200 mg.*
haloperidol [c]	***Injection:*** *5 mg in 1- mL ampoule.* ***Oral liquid:*** *2 mg/ mL.* ***Solid oral dosage form:*** *0.5 mg; 2 mg; 5 mg.*

24.2 Medicines used in mood disorders

24.2.1 *Medicines used in depressive disorders*

☐ amitriptyline	**Tablet:** 25 mg; 75mg. (hydrochloride).
fluoxetine	**Solid oral dosage form:** 20 mg (as hydrochloride).
Complementary List [c]	
fluoxetine [a]	***Solid oral dosage form:*** *20 mg (as hydrochloride).* [a] >8 years.

24.2.2 *Medicines used in bipolar disorders*

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

24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS *(continued)*	
24.3 Medicines for anxiety disorders	
☐ diazepam	**Tablet (scored):** 2 mg; 5 mg.
24.4 Medicines used for obsessive compulsive disorders	
clomipramine	**Capsule:** 10 mg; 25 mg (hydrochloride).
24.5 Medicines for disorders due to psychoactive substance use	
nicotine replacement therapy (NRT)	**Chewing gum:** 2 mg; 4 mg (as polacrilex). **Transdermal patch:** 5 mg to 30 mg/16 hrs; 7 mg to 21 mg/24 hrs.
Complementary List	
☐ *methadone**	**Concentrate for oral liquid:** 5 mg/ mL; 10 mg/ mL (hydrochloride). **Oral liquid:** 5 mg/5 mL; 10 mg/5 mL (hydrochloride). * The square box is added to include buprenorphine. The medicines should only be used within an established support programme.
25. MEDICINES ACTING ON THE RESPIRATORY TRACT	
25.1 Antiasthmatic and medicines for chronic obstructive pulmonary disease	
☐ beclometasone	**Inhalation (aerosol):** 50 micrograms (dipropionate) per dose; 100 micrograms (dipropionate) per dose (as CFC free forms).
☐ budesonide [c]	**Inhalation (aerosol):** 100 micrograms per dose; 200 micrograms per dose.
epinephrine (adrenaline)	**Injection:** 1 mg (as hydrochloride **or** hydrogen tartrate) in 1- mL ampoule.
ipratropium bromide	**Inhalation (aerosol):** 20 micrograms/metered dose.
☐ salbutamol	**Inhalation (aerosol):** 100 micrograms (as sulfate) per dose. **Injection:** 50 micrograms (as sulfate)/ mL in 5- mL ampoule. **Metered dose inhaler (aerosol):** 100 micrograms (as sulfate) per dose. **Respirator solution for use in nebulizers:** 5 mg (as sulfate)/ mL.

26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID–BASE DISTURBANCES	
26.1 Oral	
oral rehydration salts	See section 17.5.1.
potassium chloride	**Powder for solution.**
26.2 Parenteral	
glucose	Injectable solution: 5% (isotonic); 10% (hypertonic); 50% (hypertonic).
glucose with sodium chloride	**Injectable solution:** 4% glucose, 0.18% sodium chloride (equivalent to Na+ 30 mmol/L, Cl- 30 mmol/L). **Injectable solution:** 5% glucose, 0.9% sodium chloride (equivalent to Na+ 150 mmol/L and Cl- 150 mmol/L); 5% glucose, 0.45% sodium chloride (equivalent to Na+ 75 mmol/L and Cl- 75 mmol/L) [c].
potassium chloride	**Solution:** 11.2% in 20- mL ampoule (equivalent to K+ 1.5 mmol/ mL, Cl- 1.5 mmol/ mL). **Solution for dilution:** 7.5% (equivalent to K 1 mmol/ mL and Cl 1 mmol/ mL) [c]; 15% (equivalent to K 2 mmol/ mL and Cl 2 mmol/ mL) [c].
sodium chloride	**Injectable solution:** 0.9% isotonic (equivalent to Na+ 154 mmol/L, Cl- 154 mmol/L).
sodium hydrogen carbonate	**Injectable solution:** 1.4% isotonic (equivalent to Na+ 167 mmol/L, HCO_3- 167 mmol/L). **Solution:** 8.4% in 10- mL ampoule (equivalent to Na+ 1000 mmol/L, HCO_3-1000 mmol/L).
☐ sodium lactate, compound solution	**Injectable solution.**
26.3 Miscellaneous	
water for injection	2- mL; 5- mL; 10- mL ampoules.
27. VITAMINS AND MINERALS	
ascorbic acid	**Tablet:** 50 mg.
calcium	**Tablet:** 500 mg (elemental).

27. VITAMINS AND MINERALS *(continued)*	
cholecalciferol* [c]	**Oral liquid:** 400 IU/ mL. **Solid oral dosage form:** 400 IU; 1000 IU. * Ergocalciferol can be used as an alternative.
☐ ergocalciferol	**Oral liquid:** 250 micrograms/ mL (10 000 IU/ mL). **Solid oral dosage form:** 1.25 mg (50 000 IU).
iodine	**Capsule:** 200 mg. **Iodized oil:** 1 mL (480 mg iodine); 0.5 mL (240 mg iodine) in ampoule (oral or injectable); 0.57 mL (308 mg iodine) in dispenser bottle.
☐ nicotinamide	**Tablet:** 50 mg.
pyridoxine	**Tablet:** 25 mg (hydrochloride).
retinol	**Capsule:** 50 000 IU; 100 000 IU; 200 000 IU (as palmitate). **Oral oily solution:** 100 000 IU (as palmitate)/ mL in multidose dispenser. **Tablet (sugar-coated):** 10 000 IU (as palmitate). Water-miscible injection: 100 000 IU (as palmitate) in 2- mL ampoule.
riboflavin	**Tablet:** 5 mg.
sodium fluoride	In any appropriate topical formulation.
thiamine	**Tablet:** 50 mg (hydrochloride).
Complementary List	
calcium gluconate	***Injection:*** *100 mg/ mL in 10- mL ampoule.*
28. EAR, NOSE AND THROAT MEDICINES [c]	
acetic acid	**Topical:** 2%, in alcohol.
☐ budesonide	**Nasal spray:** 100 micrograms per dose.
☐ ciprofloxacin	**Topical:** 0.3% drops (as hydrochloride).
☐ xylometazoline [a]	**Nasal spray:** 0.05%. [a] Not in children less than 3 months.

29. SPECIFIC MEDICINES FOR NEONATAL CARE	
29.1 Medicines administered to the neonate [c]	
caffeine citrate	**Injection:** 20 mg/ mL (equivalent to 10 mg caffeine base/ mL). **Oral liquid:** 20 mg/ mL (equivalent to 10 mg caffeine base/ mL).
Chlorhexidine	**Solution or gel:** 7.1% (digluconate) delivering 4% chlorhexidine (for umbilical cord care) [c].
Complementary List	
☐ *ibuprofen*	***Solution for injection:*** *5 mg/ mL.*
☐ *prostaglandin E*	***Solution for injection:*** ***Prostaglandin E1:*** *0.5 mg/ mL in alcohol.* ***Prostaglandin E 2:*** *1 mg/ mL.*
surfactant	***Suspension for intratracheal instillation:*** *25 mg/ mL* **or** *80 mg/ mL.*
29.2 Medicines administered to the mother	
dexamethasone	**Injection:** 4 mg/ mL dexamethasone phosphate (as disodium salt).
30. MEDICINES FOR DISEASES OF JOINTS	
30.1 Medicines used to treat gout	
allopurinol	**Tablet:** 100 mg.
30.2 Disease-modifying agents used in rheumatoid disorders (DMARDs)	
chloroquine	**Tablet:** 100 mg; 150 mg (as phosphate **or** sulfate).
Complementary List	
azathioprine	***Tablet:*** *50 mg.*
hydroxychloroquine [c]	***Solid oral dosage form:*** *200 mg (as sulfate).*
methotrexate	***Tablet:*** *2.5 mg (as sodium salt).*
penicillamine	***Solid oral dosage form:*** *250 mg.*
sulfasalazine	***Tablet:*** *500 mg.*
30.3 Juvenile joint diseases	
acetylsalicylic acid* (acute or chronic use)	**Suppository:** 50 mg to 150 mg. **Tablet:** 100 mg to 500 mg. * For use for rheumatic fever, juvenile arthritis, Kawasaki disease.

Table 1.1: Medicines with age or weight restrictions

atazanavir	>25 kg
atropine	>3 months
benzyl benzoate	>2 years
betamethasone topical preparations	hydrocortisone preferred in neonates
cefazolin	>1 month
ceftriaxone	>41 weeks corrected gestational age
darunavir	>3 years
diloxanide	>25 kg
doxycycline	>8 years (except for serious infections e.g. cholera)
efavirenz	>3 years or >10 kg
fluoxetine	>8 years
ibuprofen	>3 months (except IV form for patent ductus arteriosus)
mefloquine	>5 kg or >3 months
metoclopramide	Not in neonates
nevirapine	>6 weeks
ondansetron	>1 month
saquinavir	>25 kg
silver sulfadiazine	>2 months
tetracaine	Not in preterm neonates
trimethoprim	>6 months
xylometazoline	>3 months

Table 1.2: Explanation of dosage forms

A. Principal dosage forms used in EML – oral administration

Term	Definition
Solid oral dosage form	Refers to tablets or capsules or other solid dosage forms such as 'melts' that are immediate-release preparations. It implies that there is no difference in clinical efficacy or safety between the available dosage forms, and countries should therefore choose the form(s) to be listed depending on quality and availability. The term 'solid oral dosage form' is never intended to allow any type of modified-release tablet.
Tablets	Refers to: • uncoated or coated (film-coated or sugar-coated) tablets that are intended to be swallowed whole; • unscored and scored*; • tablets that are intended to be chewed before being swallowed; • tablets that are intended to be dispersed or dissolved in water or another suitable liquid before being swallowed; • tablets that are intended to be crushed before being swallowed. The term 'tablet' without qualification is never intended to allow any type of modified-release tablet.
Tablets (qualified)	Refers to a specific type of tablet: chewable - tablets that are intended to be chewed before being swallowed; dispersible - tablets that are intended to be dispersed in water or another suitable liquid before being swallowed; soluble - tablets that are intended to be dissolved in water or another suitable liquid before being swallowed; crushable - tablets that are intended to be crushed before being swallowed; scored - tablets bearing a break mark or marks where sub-division is intended in order to provide doses of less than one tablet; sublingual - tablets that are intended to be placed beneath the tongue.

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

Table 1.2 *continued*

Term	Definition
	The term 'tablet' is *always* qualified with an additional term (in parentheses) in entries where one of the following types of tablet is intended: gastro-resistant (such tablets may sometimes be described as enteric-coated or as delayed-release), prolonged-release or another modified-release form.
Capsules	Refers to hard or soft capsules. The term 'capsule' without qualification is never intended to allow any type of modified-release capsule.
Capsules (qualified)	The term 'capsule' with qualification refers to gastro-resistant (such capsules may sometimes be described as enteric-coated or as delayed-release), prolonged-release or another modified-release form.
Granules	Preparations that are issued to patient as granules to be swallowed without further preparation, to be chewed, or to be taken in or with water or another suitable liquid. The term 'granules' without further qualification is *never* intended to allow any type of modified-release granules.
Oral powder	Preparations that are issued to patient as powder (usually as single-dose) to be taken in or with water or another suitable liquid.
Oral liquid	Liquid preparations intended to be *swallowed* i.e. oral solutions, suspensions, emulsions and oral drops, including those constituted from powders or granules, but *not* those preparations intended for *oromucosal administration* e.g. gargles and mouthwashes. Oral liquids presented as powders or granules may offer benefits in the form of better stability and lower transport costs. If more than one type of oral liquid is available on the same market (e.g. solution, suspension, granules for reconstitution), they may be interchanged and in such cases should be bioequivalent. It is preferable that oral liquids do not contain sugar and that solutions for children do not contain alcohol.

B. Principal dosage forms used in EMLc – parenteral administration

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

C. Other dosage forms

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

Annex 2

5th WHO Model List of Essential Medicines for Children (April 2015)

Explanatory notes

This Model List is intended for use for children up to 12 years of age.

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

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

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

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

The format and numbering of the 18th WHO Model List of Essential Medicines have been retained but, as indicated in the text, some sections have been deleted because they contain medicines that are not relevant for children.

[a] indicates that there is an age or weight restriction on use of the medicines; the details for each medicine are in Table 1.1 of Annex 1.

The presence of an entry on the Essential Medicines List carries no assurance as to pharmaceutical quality. It is the responsibility of the relevant national or regional drug regulatory authority to ensure that each product is of appropriate pharmaceutical quality (including stability) and that when relevant, different products are interchangeable.

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

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

The main terms used for dosage forms in the Essential Medicines List can be found in Table 1.2 of Annex 1.

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

1. ANAESTHETICS	
1.1 General anaesthetics and oxygen	
1.1.1 ***Inhalational medicines***	
halothane	**Inhalation.**
isoflurane	**Inhalation.**
nitrous oxide	**Inhalation.**
oxygen	**Inhalation** (medicinal gas).
1.1.2 ***Injectable medicines***	
ketamine	**Injection:** 50 mg (as hydrochloride)/mL in 10-mL vial.
propofol*	**Injection:** 10 mg/mL; 20 mg/mL. * Thiopental may be used as an alternative depending on local availability and cost.
1.2 Local anaesthetics	
☐ bupivacaine	**Injection:** : 0.25%; 0.5% (hydrochloride) in vial. **Injection for spinal anaesthesia:** 0.5% (hydrochloride) in 4-mL ampoule to be mixed with 7.5% glucose solution.
☐ lidocaine	**Injection:** 1%; 2% (hydrochloride) in vial. **Injection for spinal anaesthesia:** 5% (hydrochloride) in 2-mL ampoule to be mixed with 7.5% glucose solution. **Topical forms:** 2% to 4% (hydrochloride).
lidocaine + epinephrine (adrenaline)	**Dental cartridge:** 2% (hydrochloride) + epinephrine 1:80 000. **Injection:** 1%; 2% (hydrochloride or sulfate) + epinephrine 1:200 000 in vial.
1.3 Preoperative medication and sedation for short-term procedures	
atropine	**Injection:** 1 mg (sulfate) in 1-mL ampoule.
☐ midazolam	**Injection:** 1 mg/mL. **Oral liquid:** 2 mg/mL. **Tablet:** 7.5 mg; 15 mg.
morphine	**Injection:** 10 mg (sulfate **or** hydrochloride) in 1-mL ampoule.

2. MEDICINES FOR PAIN AND PALLIATIVE CARE

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

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

2.2 Opioid analgesics

☐ morphine*	**Granules (slow release; to mix with water):** 20 mg to 200 mg (morphine sulfate). **Injection:** 10 mg (morphine hydrochloride or morphine sulfate) in 1-mL ampoule. **Oral liquid:** 10 mg (morphine hydrochloride or morphine sulfate)/5 mL. **Tablet (slow release):** 10 mg – 200mg (morphine hydrochloride or morphine sulfate). **Tablet (immediate release):** 10 mg (morphine sulfate). * Alternatives limited to hydromorphone and oxycodone.

2.3 Medicines for other symptoms common in palliative care

amitriptyline	**Tablet:** 10 mg; 25 mg.
cyclizine	**Injection:** 50 mg/mL. **Tablet:** 50 mg.
dexamethasone	**Injection:** 4 mg/mL in 1-mL ampoule (as disodium phosphate salt). **Oral liquid:** 2 mg/5 mL. **Tablet:** 2 mg.
diazepam	**Injection:** 5 mg/mL. **Oral liquid:** 2 mg/5 mL. **Rectal solution:** 2.5 mg; 5 mg; 10 mg. **Tablet:** 5 mg; 10 mg.
docusate sodium	**Capsule:** 100 mg. **Oral liquid:** 50 mg/5 mL.

2. MEDICINES FOR PAIN AND PALLIATIVE CARE *(continued)*	
fluoxetine [a]	**Solid oral dosage form:** 20 mg (as hydrochloride). [a] >8 years.
hyoscine hydrobromide	**Injection:** 400 micrograms/mL; 600 micrograms/mL. **Transdermal patches:** 1 mg/72 hours.
lactulose	**Oral liquid:** 3.1–3.7 g/5 mL.
midazolam	**Injection:** 1 mg/mL; 5 mg/mL. **Oral liquid:** 2mg/mL. **Solid oral dosage form:** 7.5 mg; 15 mg.
ondansetron [a]	**Injection:** 2 mg base/mL in 2-mL ampoule (as hydrochloride). **Oral liquid:** 4 mg base/5 mL. **Solid oral dosage form:** Eq 4 mg base; Eq 8 mg base. [a] >1 month.
senna	**Oral liquid:** 7.5 mg/5 mL.
3. ANTIALLERGICS AND MEDICINES USED IN ANAPHYLAXIS	
dexamethasone	**Injection:** 4 mg/mL in 1-mL ampoule (as disodium phosphate salt).
epinephrine (adrenaline)	**Injection:** 1 mg (as hydrochloride or hydrogen tartrate) in 1-mL ampoule.
hydrocortisone	**Powder for injection:** 100 mg (as sodium succinate) in vial.
☐ loratadine *	**Oral liquid:** 1 mg/mL. **Tablet:** 10 mg. * There may be a role for sedating antihistamines for limited indications.
☐ prednisolone	**Oral liquid:** 5 mg/mL. **Tablet:** 5 mg; 25 mg.
4. ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS	
4.1 Non-specific	
charcoal, activated	**Powder.**
4.2 Specific	
acetylcysteine	**Injection:** 200 mg/mL in 10-mL ampoule. **Oral liquid:** 10%; 20%.

4. ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS *(continued)*	
atropine	**Injection:** 1 mg (sulfate) in 1-mL ampoule.
calcium gluconate	**Injection:** 100 mg/mL in 10-mL ampoule.
naloxone	**Injection:** 400 micrograms (hydrochloride) in 1-mL ampoule.
Complementary List	
deferoxamine	***Powder for injection:*** *500 mg (mesilate) in vial.*
dimercaprol	***Injection in oil:*** *50 mg/mL in 2-mL ampoule.*
fomepizole	***Injection:*** *5 mg/mL (sulfate) in 20-mL ampoule or 1 g/mL (base) in 1.5-mL ampoule.*
sodium calcium edetate	***Injection:*** *200 mg/mL in 5-mL ampoule.*
succimer	***Solid oral dosage form:*** *100 mg.*
5. ANTICONVULSANTS/ANTIEPILEPTICS	
carbamazepine	**Oral liquid:** 100 mg/5 mL. **Tablet (chewable):** 100 mg; 200 mg. **Tablet (scored):** 100 mg; 200 mg.
diazepam	**Gel or rectal solution:** 5 mg/mL in 0.5 mL; 2-mL; 4-mL tubes.
☐ lorazepam	**Parenteral formulation:** 2 mg/mL in 1-mL ampoule; 4 mg/mL in 1-mL ampoule.
midazolam	**Solution for oromucosal administration:** 5 mg/mL; 10 mg/mL. **Ampoule*:** 1 mg/ mL; 10 mg/mL. * for buccal administration when solution for oromucosal administration is not available.
phenobarbital	**Injection:** 200 mg/mL (sodium). **Oral liquid:** 15 mg/5 mL. **Tablet:** 15 mg to 100 mg.

5. ANTICONVULSANTS/ANTIEPILEPTICS *(continued)*	
phenytoin	**Injection:** 50 mg/mL in 5-mL vial (sodium salt). **Oral liquid:** 25 mg to 30 mg/5 mL.* **Solid oral dosage form:** 25 mg; 50 mg; 100 mg (sodium salt). **Tablet (chewable):** 50 mg. * The presence of both 25 mg/5 mL and 30 mg/5 mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided.
valproic acid (sodium valproate)	**Oral liquid:** 200 mg/5 mL. **Tablet (crushable):** 100 mg. **Tablet (enteric-coated):** 200 mg; 500 mg (sodium valproate).
Complementary List	
ethosuximide	***Capsule:*** *250 mg.* ***Oral liquid:*** *250 mg/5 mL.*
valproic acid (sodium valproate)	***Injection:*** *100 mg/ mL in 4- mL ampoule; 100 mg/ mL in 10- mL ampoule.*
6. ANTI-INFECTIVE MEDICINES	
6.1 Anthelminthics	
6.1.1 ***Intestinal anthelminthics***	
albendazole	**Tablet (chewable):** 400 mg.
levamisole	**Tablet:** 50 mg; 150 mg (as hydrochloride).
mebendazole	**Tablet (chewable):** 100 mg; 500 mg.
niclosamide	**Tablet (chewable):** 500 mg.
praziquantel	**Tablet:** 150 mg; 600 mg.
pyrantel	**Oral liquid:** 50 mg (as embonate **or** pamoate)/mL. **Tablet (chewable):** 250 mg (as embonate **or** pamoate).
6.1.2 ***Antifilarials***	
albendazole	**Tablet (chewable):** 400 mg.
diethylcarbamazine	**Tablet:** 50 mg; 100 mg (dihydrogen citrate).
ivermectin	**Tablet (scored):** 3 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*	
6.1.3 ***Antischistosomals and other antitrematode medicines***	
praziquantel	**Tablet:** 600 mg.
triclabendazole	**Tablet:** 250 mg.
Complementary List	
*oxamniquine**	***Capsule:*** *250 mg.* ***Oral liquid:*** *250 mg/5 mL.* * *Oxamniquine is listed for use when praziquantel treatment fails.*
6.2 Antibacterials	
6.2.1 ***Beta-lactam medicines***	
amoxicillin	**Powder for oral liquid:** 125 mg (as trihydrate)/5 mL; 250 mg (as trihydrate)/5 mL. **Solid oral dosage form:** 250 mg; 500 mg (as trihydrate).
amoxicillin + clavulanic acid	**Oral liquid:** 125 mg amoxicillin + 31.25 mg clavulanic acid/5 mL AND 250 mg amoxicillin + 62.5 mg clavulanic acid/5 mL. **Tablet:** 500 mg (as trihydrate) + 125 mg (as potassium salt).
ampicillin	**Powder for injection:** 500 mg; 1 g (as sodium salt) in vial.
benzathine benzylpenicillin	**Powder for injection:** 900 mg benzylpenicillin (= 1.2 million IU) in 5-mL vial; 1.44 g benzylpenicillin (= 2.4 million IU) in 5-mL vial.
benzylpenicillin	**Powder for injection:** 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial.
cefalexin	**Powder for reconstitution with water:** 125 mg/5 mL; 250 mg/5 mL (anhydrous). **Solid oral dosage form:** 250 mg (as monohydrate).
☐ cefazolin* [a]	**Powder for injection:** 1 g (as sodium salt) in vial. * For surgical prophylaxis. [a] >1 month.

6. ANTI-INFECTIVE MEDICINES *(continued)*	
ceftriaxone* [a]	**Powder for injection:** 250 mg; 1 g (as sodium salt) in vial. * Do not administer with calcium and avoid in infants with hyperbilirubinaemia. [a] >41 weeks corrected gestational age.
☐ cloxacillin	**Capsule:** 500 mg; 1 g (as sodium salt). **Powder for injection:** 500 mg (as sodium salt) in vial. **Powder for oral liquid:** 125 mg (as sodium salt)/5 mL.
phenoxymethylpenicillin	**Powder for oral liquid:** 250 mg (as potassium salt)/5 mL. **Tablet:** 250 mg (as potassium salt).
procaine benzylpenicillin*	**Powder for injection:** 1 g (=1 million IU); 3 g (=3 million IU) in vial. * Procaine benzylpenicillin is not recommended as first-line treatment for neonatal sepsis except in settings with high neonatal mortality, when given by trained health workers in cases where hospital care is not achievable.
Complementary List	
*cefotaxime**	***Powder for injection:** 250 mg per vial (as sodium salt).* * *3rd generation cephalosporin of choice for use in hospitalized neonates.*
ceftazidime	***Powder for injection:** 250 mg or 1 g (as pentahydrate) in vial.*
imipenem + cilastatin**	***Powder for injection:** 250 mg (as monohydrate) + 250 mg (as sodium salt); 500 mg (as monohydrate) + 500 mg (as sodium salt) in vial.* * *Only listed for the treatment of life-threatening hospital-based infection due to suspected or proven multidrug-resistant infection. Meropenem is indicated for the treatment of meningitis and is licensed for use in children over the age of 3 months.*
6.2.2 *Other antibacterials*	
azithromycin*	**Capsule:** 250 mg; 500 mg (anhydrous). **Oral liquid:** 200 mg/5 mL. * Listed only for trachoma.

6. ANTI-INFECTIVE MEDICINES *(continued)*	
chloramphenicol	**Capsule:** 250 mg. **Oily suspension for injection*:** 0.5 g (as sodium succinate)/mL in 2-mL ampoule. * Only for the presumptive treatment of epidemic meningitis in children older than 2 years. **Oral liquid:** 150 mg (as palmitate)/5 mL. **Powder for injection:** 1 g (sodium succinate) in vial.
ciprofloxacin	**Oral liquid:** 250 mg/5 mL (anhydrous). **Solution for IV infusion:** 2 mg/mL (as hyclate). **Tablet:** 250 mg (as hydrochloride).
doxycycline [a]	**Oral liquid:** 25 mg/5 mL; 50 mg/5 mL (anhydrous). **Solid oral dosage form:** 50 mg; 100 mg (as hyclate). [a] Use in children <8 years only for life-threatening infections when no alternative exists.
erythromycin	**Powder for oral liquid:** 125 mg/5 mL (as stearate **or** estolate **or** ethyl succinate). **Solid oral dosage form:** 250 mg (as stearate **or** estolate **or** ethyl succinate).
☐ gentamicin	**Injection:** 10 mg; 40 mg (as sulfate)/mL in 2-mL vial.
metronidazole	**Injection:** 500 mg in 100-mL vial. **Oral liquid:** 200 mg (as benzoate)/5 mL. **Tablet:** 200 mg to 500 mg.
nitrofurantoin	**Oral liquid:** 25 mg/5 mL. **Tablet:** 100 mg.
sulfamethoxazole + trimethoprim	**Injection:** 80 mg + 16 mg/mL in 5-mL ampoule; 80 mg + 16 mg/mL in 10-mL ampoule. **Oral liquid:** 200 mg + 40 mg/5 mL. **Tablet:** 100 mg + 20 mg; 400 mg + 80 mg.
trimethoprim [a]	**Oral liquid:** 50 mg/5 mL. **Tablet:** 100 mg; 200 mg. [a] >6 months.

6. ANTI-INFECTIVE MEDICINES *(continued)*

Complementary List

clindamycin	***Capsule:*** *150 mg (as hydrochloride).* ***Injection:*** *150 mg (as phosphate)/mL.* ***Oral liquid:*** *75 mg/5 mL (as palmitate).*
vancomycin	***Powder for injection:*** *250 mg (as hydrochloride) in vial.*

6.2.3 ***Antileprosy medicines***

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

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

6.2.4 ***Antituberculosis medicines***

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

ethambutol	**Oral liquid:** 25 mg/mL. **Tablet:** 100 mg; 400 mg (hydrochloride).
isoniazid	**Oral liquid:** 50 mg/5 mL. **Tablet:** 100 mg to 300 mg. **Tablet (scored):** 50 mg.
pyrazinamide	**Oral liquid:** 30 mg/mL. **Tablet:** 400 mg. **Tablet (dispersible):** 150 mg. **Tablet (scored):** 150 mg.
rifampicin	**Oral liquid:** 20 mg/mL. **Solid oral dosage form:** 150 mg; 300 mg.
rifapentine*	**Tablet:** 150 mg. * For treatment of latent TB infection (LTBI) only.

6. ANTI-INFECTIVE MEDICINES *(continued)*	
Complementary List	
Reserve second-line drugs for the treatment of multidrug-resistant tuberculosis (MDR-TB) should be used in specialized centres adhering to WHO standards for TB control.	
amikacin	***Powder for injection**: 100 mg; 500 mg; 1 g (as sulfate) in vial.*
capreomycin	***Powder for injection:** 1 g (as sulfate) in vial.*
cycloserine	***Solid oral dosage form:** 250 mg.*
*ethionamide**	***Tablet:** 125 mg; 250 mg.* ** Protionamide may be used as an alternative.*
kanamycin	***Powder for injection:** 1 g (as sulfate) in vial.*
*levofloxacin**	***Tablet:** 250 mg: 500 mg.* ** Ofloxacin and moxifloxacin may be used as alternatives based on availability and programme considerations.*
linezolid	***Injection for intravenous administration:** 2 mg/ mL in 300 mL bag.* ***Powder for oral liquid:** 100 mg/5 mL.* ***Tablet:** 400 mg; 600 mg.*
p-aminosalicylic acid	***Granules:** 4 g in sachet.* ***Tablet:** 500 mg.*
streptomycin	***Powder for injection:** 1 g (as sulfate) in vial.*
6.3 Antifungal medicines	
amphotericin B	**Powder for injection:** 50 mg in vial (as sodium deoxycholate or liposomal complex).
☐ fluconazole	**Capsule:** 50 mg. **Injection:** 2 mg/mL in vial. **Oral liquid:** 50 mg/5 mL.
flucytosine	**Capsule:** 250 mg. **Infusion:** 2.5 g in 250 mL.
griseofulvin	**Oral liquid:** 125 mg/5 mL. **Solid oral dosage form:** 125 mg; 250 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*	
nystatin	**Lozenge:** 100 000 IU. **Oral liquid:** 50 mg/5 mL; 100 000 IU/mL. **Tablet**: 100 000 IU; 500 000 IU.
Complementary List	
potassium iodide	***Saturated solution.***

6.4 Antiviral medicines

6.4.1 ***Antiherpes medicines***

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

6.4.2 ***Antiretrovirals***

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

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

6.4.2.1 ***Nucleoside/Nucleotide reverse transcriptase inhibitors***

abacavir (ABC)	**Oral liquid:** 100 mg (as sulfate)/5 mL.
lamivudine (3TC)	**Oral liquid:** 50 mg/5 mL. **Tablet:** 150 mg.
stavudine (d4T)	**Capsule:** 15 mg; 20 mg; 30 mg. **Powder for oral liquid:** 5 mg/5 mL.
zidovudine (ZDV or AZT)	**Capsule:** 100 mg. **Oral liquid:** 50 mg/5 mL.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.4.2.2 ***Non-nucleoside reverse transcriptase inhibitors***

efavirenz (EFV or EFZ) [a]	**Capsule:** 50 mg; 100 mg; 200 mg. **Tablet:** 200 mg (scored). [a] >3 years **or** >10 kg.
nevirapine (NVP) [a]	**Oral liquid:** 50 mg/5 mL. **Tablet:** 50 mg (dispersible); 200 mg. [a] >6 weeks.

6.4.2.3 ***Protease inhibitors***

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

atazanavir [a]	**Solid oral dosage form:** 100 mg; 150 mg (as sulfate). [a] >25 kg.
darunavir [a]	**Tablet:** 75 mg. [a] >3 years.
lopinavir + ritonavir (LPV/r)	**Oral liquid:** 400 mg + 100 mg/5 mL. **Tablet (heat stable):** 100 mg + 25 mg.
ritonavir	**Oral liquid:** 400 mg/5 mL. **Tablet (heat stable):** 25 mg; 100 mg.
FIXED-DOSE COMBINATIONS	
abacavir + lamivudine	**Tablet (dispersible, scored):** 60 mg (as sulfate) + 30 mg.
lamivudine + nevirapine + stavudine	**Tablet (dispersible):** 30 mg + 50 mg + 6 mg.
lamivudine + nevirapine + zidovudine	**Tablet:** 30 mg + 50 mg + 60 mg.
lamivudine + zidovudine	**Tablet:** 30 mg + 60 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*	
6.4.3 ***Other antivirals***	
oseltamivir*	**Capsule:** 30 mg; 45 mg; 75 mg (as phosphate). **Oral powder:** 12 mg/mL. * potentially severe or complicated illness due to confirmed or suspected influenza virus infection in accordance with WHO treatment guidelines.
ribavirin*	**Injection for intravenous administration:** 800 mg and 1 g in 10-mL phosphate buffer solution. **Solid oral dosage form:** 200 mg; 400 mg; 600 mg. * For the treatment of viral haemorrhagic fevers only.
Complementary List	
*valganciclovir**	***Powder for oral solution:*** *50 mg/mL* ***Tablet:*** *450 mg.* **For the treatment of cytomegalovirus retinitis (CMVr).*
6.4.4 ***Antihepatitis medicines***	
6.4.4.1 ***Medicines for hepatitis B***	
6.4.4.1.1 ***Nucleoside/Nucleotide reverse transcriptase inhibitors***	
entecavir	**Oral liquid:** 0.05 mg/ mL. **Tablet:** 0.5 mg; 1 mg.
~~**6.4.4.2** ***Medicines for hepatitis C***~~	
~~**6.4.4.2.1** ***Nucleotide polymerase inhibitors***~~	
~~**6.4.4.2.2** ***Protease inhibitors***~~	
~~**6.4.4.2.3** ***NS5A inhibitors***~~	
~~**6.4.4.2.4** ***Non-nucleoside polymerase inhibitors***~~	
~~**6.4.4.2.5** ***Other antivirals***~~	
~~***FIXED-DOSE COMBINATIONS***~~	
6.5 Antiprotozoal medicines	
6.5.1 ***Antiamoebic and antigiardiasis medicines***	
diloxanide [a]	**Tablet:** 500 mg (furoate). [a] >25 kg.
☐ metronidazole	**Injection:** 500 mg in 100-mL vial. **Oral liquid:** 200 mg (as benzoate)/5 mL. **Tablet:** 200 mg to 500 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.5.2 ***Antileishmaniasis medicines***

amphotericin B	**Powder for injection:** 50 mg in vial. As sodium deoxycholate **or** liposomal complex.
miltefosine	**Solid oral dosage form:** 10 mg; 50 mg.
paromomycin	**Solution for intramuscular injection:** 750 mg of paromomycin base (as the sulfate).
sodium stibogluconate **or** meglumine antimoniate	**Injection:** 100 mg/mL, 1 vial = 30 mL **or** 30%, equivalent to approximately 8.1% antimony (pentavalent) in 5-mL ampoule.

6.5.3 ***Antimalarial medicines***

6.5.3.1 ***For curative treatment***

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

amodiaquine*	**Tablet:** 153 mg or 200 mg (as hydrochloride). * To be used in combination with artesunate 50 mg.
artemether*	**Oily injection:** 80 mg/mL in 1-mL ampoule. * For use in the management of severe malaria.
artemether + lumefantrine*	**Tablet:** 20 mg + 120 mg. **Tablet (dispersible):** 20 mg + 120 mg. * Not recommended in the first trimester of pregnancy or in children below 5 kg.
artesunate*	**Injection:** ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution. For use in the management of severe malaria. **Rectal dosage form:** 50 mg; 200 mg capsules (for pre-referral treatment of severe malaria only; patients should be taken to an appropriate health facility for follow-up care). **Tablet:** 50 mg. * To be used in combination with either amodiaquine, mefloquine **or** sulfadoxine + pyrimethamine.

6. ANTI-INFECTIVE MEDICINES *(continued)*	
artesunate + amodiaquine *	**Tablet:** 25 mg + 67.5 mg; 50 mg + 135 mg; 100 mg + 270 mg. * Other combinations that deliver the target doses required such as 153 mg **or** 200 mg (as hydrochloride) with 50 mg artesunate can be alternatives.
artesunate + mefloquine	**Tablet:** 25 mg + 55 mg; 100 mg + 220 mg.
chloroquine*	**Oral liquid:** 50 mg (as phosphate **or** sulfate)/5 mL. **Tablet:** 100 mg; 150 mg (as phosphate **or** sulfate). * For use only for the treatment of *P. vivax* infection.
doxycycline*	**Capsule:** 100 mg (as hydrochloride **or** hyclate). **Tablet (dispersible):** 100 mg (as monohydrate). * For use only in combination with quinine.
mefloquine*	**Tablet:** 250 mg (as hydrochloride). * To be used in combination with artesunate 50 mg.
primaquine*	**Tablet:** 7.5 mg; 15 mg (as diphosphate). * Only for use to achieve radical cure of *P. vivax* and *P. ovale* infections, given for 14 days.
quinine*	**Injection:** 300 mg quinine hydrochloride/mL in 2-mL ampoule. **Tablet:** 300 mg (quinine sulfate) **or** 300 mg (quinine bisulfate). * For use only in the management of severe malaria, and should be used in combination with doxycycline.
sulfadoxine + pyrimethamine*	**Tablet:** 500 mg + 25 mg. * Only in combination with artesunate 50 mg.
6.5.3.2 ***For prophylaxis***	
chloroquine*	**Oral liquid:** 50 mg (as phosphate or sulfate)/5 mL. **Tablet:** 150 mg (as phosphate **or** sulfate). * For use only for the treatment of *P. vivax* infection.
doxycycline [a]	**Solid oral dosage form:** 100 mg (as hydrochloride **or** hyclate). [a] >8 years.
mefloquine [a]	**Tablet:** 250 mg (as hydrochloride). [a] >5 kg **or** >3 months.
proguanil*	**Tablet:** 100 mg (as hydrochloride). * For use only in combination with chloroquine.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.5.4 ***Antipneumocystosis and antitoxoplasmosis medicines***

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

6.5.5 ***Antitrypanosomal medicines***

6.5.5.1 ***African trypanosomiasis***

Medicines for the treatment of 1st stage African trypanosomiasis.

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

Medicines for the treatment of 2nd stage African trypanosomiasis

eflornithine*	**Injection:** 200 mg (hydrochloride)/mL in 100-mL bottle. * To be used for the treatment of *Trypanosoma brucei gambiense* infection.
nifurtimox*	**Tablet:** 120 mg. * Only to be used in combination with eflornithine, for the treatment of *Trypanosoma brucei gambiense* infection.

Complementary List

melarsoprol	***Injection:*** *3.6% solution in 5-mL ampoule (180 mg of active compound).*

6.5.5.2 ***American trypanosomiasis***

benznidazole	**Tablet:** 12.5 mg; 100 mg. **Tablet (scored):** 50 mg.
nifurtimox	**Tablet:** 30 mg; 120 mg; 250 mg.

7. ANTIMIGRAINE MEDICINES

7.1 For treatment of acute attack

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

7.2 For prophylaxis

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

8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES

8.1 Immunosuppressive medicines

Complementary List

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

8.2 Cytotoxic and adjuvant medicines

Medicines listed below should be used according to protocols for treatment of the diseases.

Complementary List

allopurinol	***Tablet:*** *100 mg; 300 mg.*
asparaginase	***Powder for injection:*** *10 000 IU in vial.* – *Acute lymphoblastic leukaemia*
bleomycin	***Powder for injection:*** *15 mg (as sulfate) in vial.* – *Hodgkin lymphoma* – *Testicular germ cell tumours* – *Ovarian germ cell tumours*
calcium folinate	***Injection:*** *3 mg/ mL in 10- mL ampoule.* ***Tablet:*** *15 mg.* – *Osteosarcoma* – *Burkitt lymphoma*

8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES *(continued)*	
carboplatin	***Injection:*** *50 mg/5 mL; 150 mg/15 mL; 450 mg/45 mL; 600 mg/60 mL.* – *Osteosarcoma* – *Retinoblastoma*
cisplatin	***Injection:*** *50 mg/50 mL; 100 mg/100 mL.* – *Osteosarcoma* – *Testicular germ cell tumours* – *Ovarian germ cell tumours*
cyclophosphamide	***Powder for injection:*** *500 mg in vial.* ***Tablet:*** *25 mg.* – *Rhabdomyosarcoma* – *Ewing sarcoma* – *Acute lymphoblastic leukaemia* – *Burkitt lymphoma* – *Hodgkin lymphoma*
cytarabine	***Powder for injection:*** *100 mg in vial.* – *Acute lymphoblastic leukaemia* – *Burkitt lymphoma*
dacarbazine	***Powder for injection:*** *100 mg in vial.* – *Hodgkin lymphoma*
dactinomycin	***Powder for injection:*** *500 micrograms in vial.* – *Rhabdomyosarcoma* – *Wilms tumour*
daunorubicin	***Powder for injection:*** *50 mg (hydrochloride) in vial.* – *Acute lymphoblastic leukaemia*
doxorubicin	***Powder for injection:*** *10 mg; 50 mg (hydrochloride) in vial.* – *Osteosarcoma* – *Ewing sarcoma* – *Acute lymphoblastic leukaemia* – *Wilms tumour* – *Burkitt lymphoma* – *Hodgkin lymphoma*

8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES *(continued)*	
etoposide	***Capsule:*** *100 mg.* ***Injection:*** *20 mg/ mL in 5- mL ampoule.* – *Retinoblastoma* – *Ewing sarcoma* – *Acute lymphoblastic leukaemia* – *Burkitt lymphoma* – *Hodgkin lymphoma* – *Testicular germ cell tumours* – *Ovarian germ cell tumours*
filgrastim	***Injection:*** *120 micrograms/0.2 mL; 300 micrograms/ 0.5 mL; 480 micrograms/0.8 mL in pre-filled syringe 300 micrograms/mL in 1- mL vial, 480 mg/1.6 mL in 1.6- mL vial.* – *Primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy* – *Secondary prophylaxis for patients who have experienced neutropenia following prior myelotoxic chemotherapy* – *To facilitate administration of dose dense chemotherapy regimens*
ifosfamide	***Powder for injection:*** *500 mg vial 1-g vial; 2-g vial.* – *Osteosarcoma* – *Rhabdomyosarcoma* – *Ewing sarcoma* – *Testicular germ cell tumours* – *Ovarian germ cell tumours*
mercaptopurine	***Tablet:*** *50 mg.* – *Acute lymphoblastic leukaemia*
mesna	***Injection:*** *100 mg/ mL in 4- mL and 10- mL ampoules.* ***Tablet:*** *400 mg; 600 mg.* – *Osteosarcoma* – *Rhabdomyosarcoma* – *Ewing sarcoma.* – *Testicular germ cell tumours* – *Ovarian germ cell tumours*

8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES *(continued)*	
methotrexate	***Powder for injection:*** *50 mg (as sodium salt) in vial.* ***Tablet:*** *2.5 mg (as sodium salt).* – *Osteosarcoma* – *Acute lymphoblastic leukaemia*
paclitaxel	***Powder for injection:*** *6 mg/ mL.* – *Ovarian germ cell tumours*
tioguanine	***Solid oral dosage form:*** *40 mg.* – *Acute lymphoblastic leukaemia*
vinblastine	***Powder for injection:*** *10 mg (sulfate) in vial.* – *Testicular germ cell tumours* – *Ovarian germ cell tumours* – *Hodgkin lymphoma*
vincristine	***Powder for injection:*** *1 mg; 5 mg (sulfate) in vial.* – *Retinoblastoma* – *Rhabdomyosarcoma* – *Ewing sarcoma* – *Acute lymphoblastic leukaemia* – *Wilms tumour* – *Burkitt lymphoma* – *Hodgkin lymphoma*
8.3 Hormones and antihormones	
Complementary List	
dexamethasone	***Oral liquid:*** *2 mg/5 mL.* – *Acute lymphoblastic leukaemia*
hydrocortisone	***Powder for injection:*** *100 mg (as sodium succinate) in vial.* – *Acute lymphoblastic leukaemia*
methylprednisolone	***Injection:*** *40 mg/ mL (as sodium succinate) in 1- mL single-dose vial and 5- mL multi-dose vials; 80 mg/ mL (as sodium succinate) in 1- mL single-dose vial.* – *Acute lymphoblastic leukamia*

8. ANTINEOPLASTICS AND IMMUNOSUPPRESSIVES *(continued)*	
☐ *prednisolone*	***Oral liquid:*** *5 mg/ mL.* ***Tablet:*** *5 mg; 25 mg.* – *Acute lymphoblastic leukaemia* – *Burkitt lymphoma* – *Hodgkin lymphoma*
~~**9. ANTIPARKINSONISM MEDICINES**~~	
10. MEDICINES AFFECTING THE BLOOD	
10.1 Antianaemia medicines	
ferrous salt	**Oral liquid:** equivalent to 25 mg iron (as sulfate)/mL. **Tablet:** equivalent to 60 mg iron.
folic acid	**Tablet:** 1 mg; 5 mg.
hydroxocobalamin	**Injection:** 1 mg (as acetate, as hydrochloride or as sulfate) in 1-mL ampoule.
10.2 Medicines affecting coagulation	
phytomenadione	**Injection:** 1 mg/mL; 10 mg/mL in 5-mL ampoule. **Tablet:** 10 mg.
Complementary List	
desmopressin	***Injection:*** *4 micrograms/ mL (as acetate) in 1- mL ampoule.* ***Nasal spray:*** *10 micrograms (as acetate) per dose.*
heparin sodium	***Injection:*** *1000 IU/mL; 5000 IU/mL in 1-mL ampoule.*
protamine sulfate	***Injection:*** *10 mg/mL in 5-mL ampoule.*
☐ *warfarin*	***Tablet:*** *0.5 mg; 1 mg; 2 mg; 5 mg (sodium salt).*
10.3 Other medicines for haemoglobinopathies	
Complementary List	
deferoxamine*	**Powder for injection:** 500 mg (mesilate) in vial. * Deferasirox oral form may be an alternative, depending on cost and availability.
hydroxycarbamide	**Solid oral dosage form:** 200 mg; 500 mg; 1 g.

11. BLOOD PRODUCTS OF HUMAN ORIGIN AND PLASMA SUBSTITUTES

11.1 Blood and blood components

In accordance with the World Health Assembly resolution WHA63.12, WHO recognizes that achieving self-sufficiency, unless special circumstances preclude it, in the supply of safe blood components based on voluntary, non-remunerated blood donation, and the security of that supply are important national goals to prevent blood shortages and meet the transfusion requirements of the patient population. All preparations should comply with the WHO requirements.

fresh–frozen plasma

platelet

red blood cells

whole blood

11.2 Plasma-derived medicines

All human plasma-derived medicines should comply with the WHO requirements.

11.2.1 *Human immunoglobulins*

anti-rabies immunoglobulin	**Injection:** 150 IU/ mL in vial.
anti-tetanus immunoglobulin	**Injection:** 500 IU in vial.
Complementary List	
normal immunoglobulin	***Intramuscular administration:*** *16% protein solution.**
	Intravenous administration: *5%; 10% protein solution.***
	Subcutaneous administration: *15%; 16% protein solution.**

* *Indicated for primary immune deficiency.*
** *Indicated for primary immune deficiency and Kawasaki disease.*

11.2.2 *Blood coagulation factors*

Complementary List	
☐ *coagulation factor VIII*	***Powder for injection:*** *500 IU/vial.*
☐ *coagulation factor IX*	***Powder for injection:*** *500 IU/vial, 1000 IU/vial.*

11.3 Plasma substitutes

☐ dextran 70*	**Injectable solution:** 6%.

* Polygeline, injectable solution, 3.5% is considered as equivalent.

12. CARDIOVASCULAR MEDICINES

~~**12.1 Antianginal medicines**~~

~~**12.2 Antiarrhythmic medicines**~~

12.3 Antihypertensive medicines

☐ enalapril	**Tablet:** 2.5 mg; 5 mg (as hydrogen maleate).

12.4 Medicines used in heart failure

digoxin	**Injection:** 250 micrograms/mL in 2-mL ampoule. **Oral liquid:** 50 micrograms/mL. **Tablet:** 62.5 micrograms; 250 micrograms.
furosemide	**Injection:** 10 mg/mL in 2-mL ampoule. **Oral liquid:** 20 mg/5 mL. **Tablet:** 40 mg.
Complementary List	
dopamine	***Injection:** 40 mg (hydrochloride) in 5-mL vial.*

~~**12.5 Antithrombotic medicines**~~

~~**12.5.1 *Anti-platelet medicines***~~

~~**12.5.2 *Thrombolytic medicines***~~

~~**12.6 Lipid-lowering agents**~~

13. DERMATOLOGICAL MEDICINES (topical)

13.1 Antifungal medicines

☐ miconazole	**Cream or ointment:** 2% (nitrate).
terbinafine	**Cream:** 1% **or Ointment:** 1% terbinafine hydrochloride.

13.2 Anti-infective medicines

mupirocin	**Cream (as mupirocin calcium):** 2%. **Ointment:** 2%.
potassium permanganate	**Aqueous solution:** 1:10 000.
silver sulfadiazine [a]	**Cream:** 1%. [a] >2 months.

13. DERMATOLOGICAL MEDICINES (topical) *(continued)*	
13.3 Anti-inflammatory and antipruritic medicines	
☐ betamethasone [a]	**Cream or ointment:** 0.1% (as valerate). [a] Hydrocortisone preferred in neonates.
calamine	**Lotion.**
hydrocortisone	**Cream or ointment:** 1% (acetate).
13.4 Medicines affecting skin differentiation and proliferation	
benzoyl peroxide	**Cream or lotion:** 5%.
coal tar	**Solution:** 5%.
☐ podophyllum resin	**Solution:** 10% to 25%.
salicylic acid	**Solution:** 5%.
urea	**Cream or ointment:** 5%; 10%.
13.5 Scabicides and pediculicides	
☐ benzyl benzoate [a]	**Lotion:** 25%. [a] >2 years.
permethrin	**Cream:** 5%. **Lotion:** 1%.
14. DIAGNOSTIC AGENTS	
14.1 Ophthalmic medicines	
fluorescein	**Eye drops:** 1% (sodium salt).
☐ tropicamide	**Eye drops:** 0.5%.
14.2 Radiocontrast media	
Complementary List	
barium sulfate	***Aqueous suspension.***
15. DISINFECTANTS AND ANTISEPTICS	
15.1 Antiseptics	
☐ chlorhexidine	**Solution:** 5% (digluconate). **Gel:** 4%.
☐ ethanol	**Solution:** 70% (denatured).
☐ povidone iodine	**Solution:** 10% (equivalent to 1% available iodine).

15. DISINFECTANTS AND ANTISEPTICS *(continued)*	
15.2 Disinfectants	
alcohol based hand rub	**Solution** containing ethanol 80% volume /volume. **Solution** containing isopropyl alcohol 75% volume/ volume.
☐ chlorine base compound	**Powder:** (0.1% available chlorine) for solution.
☐ chloroxylenol	**Solution:** 4.8%.
glutaral	**Solution:** 2%.
16. DIURETICS	
furosemide	**Injection:** 10 mg/mL in 2-mL ampoule. **Oral liquid:** 20 mg/5 mL. **Tablet:** 10 mg; 20 mg; 40 mg.
Complementary List	
☐ *hydrochlorothiazide*	***Tablet (scored):** 25 mg.*
mannitol	***Injectable solution:** 10%; 20%.*
spironolactone	***Oral liquid:** 5 mg/5 mL; 10 mg/5 mL; 25 mg/5 mL.* ***Tablet:** 25 mg.*
17. GASTROINTESTINAL MEDICINES	
Complementary List	
☐ *pancreatic enzymes*	*Age-appropriate formulations and doses including lipase, protease and amylase.*
17.1 Antiulcer medicines	
☐ omeprazole	**Powder for oral liquid:** 20-mg; 40-mg sachets. **Solid oral dosage form:** 10 mg; 20 mg; 40 mg.
☐ ranitidine	**Injection:** 25 mg/mL (as hydrochloride) in 2-mL ampoule. **Oral liquid:** 75 mg/5 mL (as hydrochloride). **Tablet:** 150 mg (as hydrochloride).

17. GASTROINTESTINAL MEDICINES *(continued)*

17.2 Antiemetic medicines

dexamethasone	**Injection:** 4 mg/mL in 1-mL ampoule (as disodium phosphate salt). **Oral liquid:** 0.5 mg/5 mL; 2 mg/5 mL. **Solid oral dosage form:** 0.5 mg; 0.75 mg; 1.5 mg; 4 mg.
metoclopramide [a]	**Injection:** 5 mg (hydrochloride)/mL in 2-mL ampoule. **Oral liquid:** 5 mg/5 mL. **Tablet:** 10 mg (hydrochloride). [a] Not in neonates.
ondansetron [a]	**Injection:** 2 mg base/mL in 2-mL ampoule (as hydrochloride). **Oral liquid:** 4 mg base/5 mL. **Solid oral dosage form:** Eq 4 mg base; Eq 8 mg base. [a] >1 month.

~~**17.3 Anti-inflammatory medicines**~~

~~**17.4 Laxatives**~~

17.5 Medicines used in diarrhoea

17.5.1 ***Oral rehydration***

oral rehydration salts

Powder for dilution in 200 mL; 500 mL; 1 L.

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

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

17. GASTROINTESTINAL MEDICINES *(continued)*	
17.5.2 ***Medicines for diarrhoea***	
zinc sulfate*	**Solid oral dosage form:** 20 mg. * In acute diarrhoea zinc sulfate should be used as an adjunct to oral rehydration salts.
18. HORMONES, OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES	
18.1 Adrenal hormones and synthetic substitutes	
fludrocortisone	**Tablet:** 100 micrograms (acetate).
hydrocortisone	**Tablet:** 5 mg; 10 mg; 20 mg.
~~**18.2 Androgens**~~	
~~**18.3 Contraceptives**~~	
~~***18.3.1 Oral hormonal contraceptives***~~	
~~***18.3.2 Injectable hormonal contraceptives***~~	
~~***18.3.3 Intrauterine devices***~~	
~~***18.3.4 Barrier methods***~~	
~~***18.3.5 Implantable contraceptives***~~	
~~***18.3.6 Intravaginal contraceptices***~~	
~~**18.4 Estrogens**~~	
18.5 Insulins and other medicines used for diabetes	
glucagon	**Injection:** 1 mg/mL.
insulin injection (soluble)	**Injection:** 100 IU/mL in 10-mL vial.
intermediate-acting insulin	**Injection:** 100 IU/mL in 10-mL vial (as compound insulin zinc suspension **or** isophane insulin).
Complementary List	
metformin	***Tablet:*** *500 mg (hydrochloride).*
~~**18.6 Ovulation inducers**~~	
~~**18.7 Progestogens**~~	
18.8 Thyroid hormones and antithyroid medicines	
levothyroxine	**Tablet:** 25 micrograms; 50 micrograms; 100 micrograms (sodium salt).

18. HORMONES, OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES *(continued)*	
Complementary List	
Lugol's solution	***Oral liquid:*** *about 130 mg total iodine/mL.*
potassium iodide	***Tablet:*** *60 mg.*
propylthiouracil	***Tablet:*** *50 mg.*

19. IMMUNOLOGICALS

19.1 Diagnostic agents

All tuberculins should comply with the WHO requirements for tuberculins.

tuberculin, purified protein derivative (PPD)	**Injection.**

19.2 Sera and immunoglobulins

All plasma fractions should comply with the WHO requirements.

Anti-venom immunoglobulin*	**Injection.** * Exact type to be defined locally.
diphtheria antitoxin	**Injection:** 10 000 IU; 20 000 IU in vial.

19.3 Vaccines

WHO immunization policy recommendations are published in vaccine position papers on the basis of recommendations made by the Strategic Advisory Group of Experts on Immunization (SAGE).

WHO vaccine position papers are updated three to four times per year. The list below details the vaccines for which there is a recommendation from SAGE and a corresponding WHO position paper as at **27 February 2015**. The most recent versions of the WHO position papers, reflecting the current evidence related to a specific vaccine and the related recommendations, can be accessed at any time on the WHO website at: http://www.who.int/immunization/documents/positionpapers/en/index.html.

Vaccine recommendations may be universal or conditional (e.g., in certain regions, in some high-risk populations or as part of immunization programmes with certain characteristics). Details are available in the relevant position papers, and in the Summary Tables of WHO Routine Immunization Recommendations available on the WHO website at: http://www.who.int/immunization/policy/immunization_tables/en/index.html.

Selection of vaccines from the Model List will need to be determined by each country after consideration of international recommendations, epidemiology and national priorities.

All vaccines should comply with the WHO requirements for biological substances.

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

19. IMMUNOLOGICALS *(continued)*

Recommendations for all

BCG vaccine

diphtheria vaccine

Haemophilus influenzae type b vaccine

hepatitis B vaccine

HPV vaccine

measles vaccine

pertussis vaccine

pneumococcal vaccine

poliomyelitis vaccine

rotavirus vaccine

rubella vaccine

tetanus vaccine

Recommendations for certain regions

Japanese encephalitis vaccine

yellow fever vaccine

tick-borne encephalitis vaccine

Recommendations for some high-risk populations

cholera vaccine

hepatitis A vaccine

meningococcal meningitis vaccine

rabies vaccine

typhoid vaccine

Recommendations for immunization programmes with certain characteristics

influenza vaccine (seasonal)

mumps vaccine

varicella vaccine

20. MUSCLE RELAXANTS (PERIPHERALLY-ACTING) AND CHOLINESTERASE INHIBITORS	
neostigmine	**Injection:** 500 micrograms in 1-mL ampoule; 2.5 mg (metilsulfate) in 1-mL ampoule. **Tablet:** 15 mg (bromide).
suxamethonium	**Injection:** 50 mg (chloride)/mL in 2-mL ampoule. **Powder for injection:** (chloride), in vial.
☐ vecuronium	**Powder for injection:** 10 mg (bromide) in vial.
Complementary List	
pyridostigmine	***Injection:*** *1 mg in 1-mL ampoule.* ***Tablet:*** *60 mg (bromide).*
21. OPHTHALMOLOGICAL PREPARATIONS	
21.1 Anti-infective agents	
aciclovir	**Ointment:** 3% W/W.
azithromycin	**Solution (eye drops):** 1.5%.
☐ gentamicin	**Solution (eye drops):** 0.3% (sulfate).
☐ ofloxacin	**Solution (eye drops):** 0.3%.
☐ tetracycline	**Eye ointment:** 1% (hydrochloride).
21.2 Anti-inflammatory agents	
☐ prednisolone	**Solution (eye drops):** 0.5% (sodium phosphate).
21.3 Local anaesthetics	
☐ tetracaine [a]	**Solution (eye drops):** 0.5% (hydrochloride). [a] Not in preterm neonates.
~~**21.4 Miotics and antiglaucoma medicines**~~	
21.5 Mydriatics	
atropine* [a]	**Solution (eye drops):** 0.1%; 0.5%; 1% (sulfate). * Or homatropine (hydrobromide) or cyclopentolate (hydrochloride). [a] >3 months.
Complementary List	
epinephrine (adrenaline)	***Solution (eye drops):*** *2% (as hydrochloride).*

21. OPHTHALMOLOGICAL PREPARATIONS *(continued)*

~~**21.6 Anti-vascular endothelial growth factor (VEGF) preparations**~~

~~**22. OXYTOCICS AND ANTIOXYTOCICS**~~

~~**22.1 Oxytocics**~~

~~**22.2 Antioxytocics (tocolytics)**~~

23. PERITONEAL DIALYSIS SOLUTION

Complementary List

intraperitoneal dialysis solution (of appropriate composition)	***Parenteral solution.***

24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS

24.1 Medicines used in psychotic disorders

Complementary List

chlorpromazine	***Injection:*** *25 mg (hydrochloride)/mL in 2-mL ampoule.* ***Oral liquid:*** *25 mg (hydrochloride)/5 mL.* ***Tablet:*** *10 mg; 25 mg; 50 mg; 100 mg (hydrochloride).*
haloperidol	***Injection:*** *5 mg in 1-mL ampoule.* ***Oral liquid:*** *2 mg/mL.* ***Solid oral dosage form:*** *0.5 mg; 2 mg; 5 mg.*

24.2 Medicines used in mood disorders

24.2.1 ***Medicines used in depressive disorders***

Complementary List

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

~~***24.2.2 Medicines used in bipolar disorders***~~

~~**24.3 Medicines for anxiety disorders**~~

~~**24.4 Medicines used for obsessive compulsive disorders**~~

~~**24.5 Medicines for disorders due to psychoactive substance use**~~

25. MEDICINES ACTING ON THE RESPIRATORY TRACT	
25.1 Antiasthmatic medicines	
☐ budesonide	**Inhalation (aerosol):** 100 micrograms per dose; 200 micrograms per dose.
epinephrine (adrenaline)	**Injection:** 1 mg (as hydrochloride or hydrogen tartrate) in 1-mL ampoule.
☐ salbutamol	**Injection:** 50 micrograms (as sulfate)/mL in 5-mL ampoule. **Metered dose inhaler (aerosol):** 100 micrograms (as sulfate) per dose. **Respirator solution for use in nebulizers:** 5 mg (as sulfate)/mL.
26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID–BASE DISTURBANCES	
26.1 Oral	
oral rehydration salts	See section 17.5.1.
potassium chloride	**Powder for solution.**
26.2 Parenteral	
glucose	**Injectable solution:** 5% (isotonic); 10% (hypertonic); 50% (hypertonic).
glucose with sodium chloride	**Injectable solution:** 5% glucose, 0.9% sodium chloride (equivalent to Na+ 150 mmol/L and Cl- 150 mmol/L); 5% glucose, 0.45% sodium chloride (equivalent to Na+ 75 mmol/L and Cl- 75 mmol/L).
potassium chloride	**Solution for dilution:** 7.5% (equivalent to K+ 1 mmol/mL and Cl- 1 mmol/mL); 15% (equivalent to K+ 2 mmol/mL and Cl- 2 mmol/mL).
sodium chloride	**Injectable solution:** 0.9% isotonic (equivalent to Na+ 154 mmol/L, Cl- 154 mmol/L).
sodium hydrogen carbonate	**Injectable solution:** 1.4% isotonic (equivalent to Na+167 mmol/L, HCO_3- 167 mmol/L). **Solution:** 8.4% in 10-mL ampoule (equivalent to Na+ 1000 mmol/L, HCO_3-1000 mmol/L).
☐ sodium lactate, compound solution	**Injectable solution.**

26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID–BASE DISTURBANCES *(continued)*	
26.3 Miscellaneous	
water for injection	2-mL; 5-mL; 10-mL ampoules.
27. VITAMINS AND MINERALS	
ascorbic acid	**Tablet:** 50 mg.
cholecalciferol*	**Oral liquid:** 400 IU/mL. **Solid oral dosage form:** 400 IU; 1000 IU. * Ergocalciferol can be used as an alternative.
iodine	**Capsule:** 200 mg. **Iodized oil:** 1 mL (480 mg iodine); 0.5 mL (240 mg iodine) in ampoule (oral or injectable); 0.57 mL (308 mg iodine) in dispenser bottle.
pyridoxine	**Tablet:** 25 mg (hydrochloride).
retinol	**Capsule:** 100 000 IU; 200 000 IU (as palmitate). **Oral oily solution:** 100 000 IU (as palmitate)/mL in multidose dispenser. **Tablet (sugar-coated):** 10 000 IU (as palmitate). **Water-miscible injection:** 100 000 IU (as palmitate) in 2-mL ampoule.
riboflavin	**Tablet:** 5 mg.
sodium fluoride	In any appropriate topical formulation.
thiamine	**Tablet:** 50 mg (hydrochloride).
Complementary List	
calcium gluconate	***Injection:** 100 mg/mL in 10-mL ampoule.*
28. EAR, NOSE AND THROAT MEDICINES	
acetic acid	**Topical:** 2%, in alcohol.
☐ budesonide	**Nasal spray:** 100 micrograms per dose.
☐ ciprofloxacin	**Topical:** 0.3% drops (as hydrochloride).
☐ xylometazoline [a]	**Nasal spray:** 0.05%. [a] Not in children less than 3 months.

29. SPECIFIC MEDICINES FOR NEONATAL CARE	
29.1 Medicines administered to the neonate	
caffeine citrate	**Injection:** 20 mg/mL (equivalent to 10 mg caffeine base/mL). **Oral liquid:** 20 mg/mL (equivalent to 10 mg caffeine base/mL).
chlorhexidine	**Solution or gel:** 7.1% (digluconate) delivering 4% chlorhexidine (for umbilical cord care).
Complementary List	
☐ *ibuprofen*	***Solution for injection:*** *5 mg/mL.*
☐ *prostaglandin E*	***Solution for injection:*** ***Prostaglandin E1:*** *0.5 mg/mL in alcohol.* ***Prostaglandin E2:*** *1 mg/mL.*
surfactant	***Suspension for intratracheal instillation:*** *25 mg/mL* ***or*** *80 mg/mL.*
~~**29.2 Medicines administered to the mother**~~	
30. MEDICINES FOR DISEASES OF JOINTS	
~~**30.1 Medicines used to treat gout**~~	
30.2 Disease-modifying agents used in rheumatoid disorders (DMARDs)	
Complementary List	
hydroxychloroquine	***Solid oral dosage form:*** *200 mg (as sulfate).*
methotrexate	***Tablet:*** *2.5 mg (as sodium salt).*
30.3 Juvenile joint diseases	
acetylsalicylic acid* (acute or chronic use)	**Suppository:** 50 mg to 150 mg. **Tablet:** 100 mg to 500 mg. * For use for rheumatic fever, juvenile arthritis, Kawasaki disease.

Annex 3

The Anatomical Therapeutic Chemical (ATC) Classification System

The following list provides the corresponding Anatomical Therapeutic Chemical (ATC) classification codes for all items on the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children, sorted by ATC code number.

ATC code	ATC group/medicine or item	Section
A	**ALIMENTARY TRACT AND METABOLISM**	
A02	**Drugs for acid related disorders**	
A02B	Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)	
A02BA	*H2-receptor antagonists*	
A02BA02	ranitidine	17.1
A02BC	*Proton pump inhibitors*	
A02BC01	omeprazole	17.1
A03	**Drugs for functional gastrointestinal disorders**	
A03B	Belladonna and derivatives, plain	
A03BA	*Belladonna alkaloids, tertiary amines*	
A03BA01	atropine	1.3; 4.2
A03BB	*Belladonna alkaloids, semisynthetic, quaternary ammonium compounds*	
A03BB01	hyoscine butylbromide*	2.3
A03F	Propulsives	
A03FA	*Propulsives*	
A03FA01	metoclopramide	2.3; 17.2
A04	**Antiemetics and antinauseants**	
A04A	Antiemetics and antinauseants	
A04AA	*Serotonin (5HT3) antagonists*	
A04AA01	ondansetron	17.2
A04AD	*Other antiemetics*	
A04AD01	hyoscine hydrobromide*	2.3

ATC code	ATC group/medicine or item	Section
A06	**Laxatives**	
A06A	Laxatives	
A06AA	*Softeners, emollients*	
A06AA02	docusate sodium	2.3
A06AB	*Contact laxatives*	
A06AB06	senna glycosides*	17.4
A06AD	*Osmotically acting laxatives*	
A06AD11	lactulose	2.3
A07	**Antidiarrheals, intestinal antiinflammatory/antiinfective agents**	
A07A	Intestinal antiinfectives	
A07AA	*Antibiotics*	
A07AA06	paromomycin	6.5.2
A07B	Intestinal adsorbents	
A07BA	*Charcoal preparations*	
A07BA01	medicinal charcoal*	4.1
A07C	Electrolytes with carbohydrates	
A07CA	*Oral rehydration salt formulations**	17.5.1; 26.1
A07DA	*Antipropulsives*	
A07DA03	loperamide	2.3
A07E	Intestinal antiinflammatory agents	
A07EA	*Corticosteroids for local use*	
A07EA02	hydrocortisone	17.3
A07EC	*Aminosalicylic acid and similar agents*	
A07EC01	sulfasalazine	17.3; 30.2
A09	**Digestives, incl. enzymes**	
A09A	Digestives, incl. enzymes	
A09AA	*Enzyme preparations*	
A09AA02	multienzymes (lipase, protease, etc.)*	17
A10	**Drugs used in diabetes**	
A10A	Insulins and analogues	
A10AB	*Insulins and analogues for injection, fast-acting*	
A10AB	insulin injection (soluble)*	18.5
A10AC	*Insulins and analogues for injection, intermediate-acting*	
A10AC	insulin, intermediate-acting*	18.5

ATC code	ATC group/medicine or item	Section
A10B	Blood glucose lowering drugs, excl. insulins	
A10BA	*Biguanides*	
A10BA02	metformin	18.5
A10BB	*Sulfonamides, urea derivatives*	
A10BB01	glibenclamide	18.5
A10BB09	gliclazide	18.5
A11	**Vitamins**	
A11C	Vitamin A and D, incl. combinations of the two	
A11CA	*Vitamin A, plain*	
A11CA01	retinol	27
A11CC	*Vitamin D and analogues*	
A11CC01	ergocalciferol	27
A11CC05	cholecalciferol*	27
A11D	Vitamin B1, plain and in combination with vitamin B6 and B12	
A11DA	*Vitamin B1, plain*	
A11DA01	thiamine	27
A11G	Ascorbic acid (vitamin C), incl. combinations	
A11GA	*Ascorbic acid (vitamin C), plain*	
A11GA01	ascorbic acid	27
A11H	Other plain vitamin preparations	
A11HA	*Other plain vitamin preparations*	
A11HA01	nicotinamide	27
A11HA02	pyridoxine	27
A11HA04	riboflavin	27
A12	**Mineral supplements**	
A12A	Calcium	
A12AA	*Calcium*	
A12AA03	calcium gluconate	4.2; 27
A12C	Other mineral supplements	
A12CB	*Zinc*	
A12CB01	zinc sulfate	17.5.2
A12CD	*Fluoride*	
A12CD01	sodium fluoride	27
A12CX	*Other mineral products**	27

ATC code	ATC group/medicine or item	Section
B	**BLOOD AND BLOOD FORMING ORGANS**	
B01	**Antithrombotic agents**	
B01A	Antithrombotic agents	
B01AA	*Vitamin K antagonists*	
B01AA03	warfarin	10.2
B01AB	*Heparin group*	
B01AB01	heparin*	10.2
B01AB04	dalteparin	10.2
B01AB05	enoxaparin	10.2
B01AB06	nadroparin	10.2
B01AC	*Platelet aggregation inhibitors excl. heparin*	
B01AC04	clopidogrel	12.5.1
B01AC06	acetylsalicylic acid	7.1; 12.5.1; 30.3
B01AD	*Enzymes*	
B01AD01	streptokinase	12.5.2
B02	**Antihemorrhagics**	
B02A	Antifibrinolytics	
B02AA	*Amino acids*	
B02AA02	tranexamic acid	10.2
B02B	Vitamin K and other hemostatics	
B02BA	*Vitamin K*	
B02BA01	phytomenadione	10.2
B02BD	*Blood coagulation factors*	
B02BD01	coagulation factor IX, II, VII and X in combination*	11.2.2
B02BD02	coagulation factor VIII*	11.2.2
B03	**Antianemic preparations**	
B03A	Iron preparations	10.1
B03AA	*Iron bivalent, oral preparations**	10.1
B03AB	*Iron trivalent, oral preparations**	10.1
B03AD	*Iron in combination with folic acid**	10.1
B03B	Vitamin B12 and folic acid	
B03BA	*Vitamin B12 (cyanocobalamin and analogues)*	
B03BA03	hydroxocobalamin	10.1

ATC code	ATC group/medicine or item	Section
B03BB	*Folic acid and derivatives*	
B03BB01	folic acid	10.1
B05	**Blood substitutes and perfusion solutions**	
B05A	Blood and related products	
B05A	platelet concentrates	11.1
B05A	whole blood*	11.1
B05AA	*Blood substitutes and plasma protein fractions*	
B05AA05	dextran*	11.3
B05AX	*Other blood products*	
B05AX01	red blood cells*	11.1
B05AX03	fresh frozen plasma*	11.1
B05B	I.V. solutions	
B05BA	*Solutions for parenteral nutrition*	
B05BA03	carbohydrates*	26.2
B05BB	*Solutions affecting the electrolyte balance*	
B05BB01	electrolytes*	26.2
B05BB02	electrolytes with carbohydrates*	26.2
B05BC	*Solutions producing osmotic diuresis*	
B05BC01	mannitol	16
B05D	Peritoneal dialytics	
B05DA	*Isotonic solutions**	23
B05X	I.V. solution additives	
B05XA	*Electrolyte solutions*	
B05XA01	potassium chloride	26.1; 26.2
B05XA02	sodium bicarbonate*	26.2
B05XA03	sodium chloride	26.2
B05XA05	magnesium sulfate	5
C	**CARDIOVASCULAR SYSTEM**	
C01	**Cardiac therapy**	
C01A	Cardiac glycosides	
C01AA	*Digitalis glycosides*	
C01AA05	digoxin	12.2; 12.4

ATC code	ATC group/medicine or item	Section
C01B	Antiarrhythmics, class I and III	
C01BB	*Antiarrhythmics, class Ib*	
C01BB01	lidocaine	12.2
C01BD	*Antiarrhythmics, class III*	
C01BD01	amiodarone	12.2
C01C	Cardiac stimulants excl. cardiac glycosides	
C01CA	*Adrenergic and dopaminergic agents*	
C01CA04	dopamine	12.4
C01CA24	epinephrine (adrenaline)	3; 12.2; 25.1
C01CA26	ephedrine	1.2
C01D	Vasodilators used in cardiac diseases	
C01DA	*Organic nitrates*	
C01DA02	glyceryl trinitrate	12.1
C01DA08	isosorbide dinitrate	12.1
C02	**Antihypertensives**	
C02A	Antiadrenergic agents, centrally acting	
C02AB	*Methyldopa*	
C02AB01	methyldopa (levorotatory)*	12.3
C02D	Arteriolar smooth muscle, agents acting on	
C02DB	*Hydrazinophthalazine derivatives*	
C02DB02	hydrazaline	12.3
C02DD	*Nitroferricyanide derivatives*	
C02DD01	nitroprusside*	12.3
C03	**Diuretics**	
C03A	Low-ceiling diuretics, thiazides	
C03AA	*Thiazides, plain*	
C03AA03	hydrochlorothiazide	12.3; 12.4; 16
C03C	High-ceiling diuretics	
C03CA	*Sulfonamides, plain*	
C03CA01	furosemide	12.4; 16
C03D	Potassium-sparing agents	
C03DA	*Aldosterone antagonists*	
C03DA01	spironolactone	12.4; 16
C03DB	*Other potassium-sparing agents*	
C03DB01	amiloride	16

ATC code	ATC group/medicine or item	Section
C07	**Beta blocking agents**	
C07A	Beta blocking agents	
C07AA	*Beta blocking agents, non-selective*	
C07AA05	propranolol	7.2
C07AB	*Beta blocking agents, selective*	
C07AB02	metoprolol	12.1; 12.2; 12.3; 12.4
C07AB03	atenolol	12.3
C07AB07	bisoprolol	12.1; 12.2; 12.3; 12.4
C07AG	*Alpha and beta blocking agents*	
C07AG02	carvedilol	12.1; 12.2; 12.3; 12.4
C08	**Calcium channel blockers**	
C08C	Selective calcium channel blockers with mainly vascular effects	
C08CA	*Dihydropyridine derivatives*	
C08CA01	amlodipine	12.3
C08CA05	nifedipine	22.2
C08D	Selective calcium channel blockers with direct cardiac effects	
C08DA	*Phenylalkylamine derivatives*	
C08DA01	verapamil	12.1; 12.2
C09	**Agents acting on the renin-angiotensin system**	
C09A	ACE inhibitors, plain	
C09AA	*ACE inhibitors, plain*	
C09AA02	enalapril	12.3; 12.4
C10	**Lipid modifying agents**	
C10A	Lipid modifying agents, plain	
C10AA	*HMG CoA reductase inhibitors*	
C10AA01	simvastatin	12.6
D	**DERMATOLOGICALS**	
D01	**Antifungals for dermatological use**	
D01A	Antifungals for topical use	
D01AA	*Antibiotics*	
D01AA01	nystatin	6.3

ATC code	ATC group/medicine or item	Section
D01AC	*Imidazole and triazole derivatives*	
D01AC02	miconazole	13.1
D01AE	*Other antifungals for topical use*	
D01AE12	salicylic acid	13.4
D01AE13	selenium sulfide	13.1
D01B	Antifungals for systemic use	
D01BA	*Antifungals for systemic use*	
D01BA01	griseofulvin	6.3
D01BA02	terbinafine	13.1
D02	**Emollients and protectives**	
D02A	Emollients and protectives	
D02AB	*Zinc products**	13.3
D02AE	*Carbamide products*	
D02AE01	*carbamide**	13.4
D05	**Antipsoriatics**	
D05A	Antipsoriatics for topical use	
D06	**Antibiotics and chemotherapeutics for dermatological use**	
D06A	Antibiotics for topical use	
D06AX	*Other antibiotics for topical use*	
D06AX09	mupirocin	13.2
D06B	Chemotherapeutics for topical use	
D06BA	*Sulfonamides*	
D06BA01	silver sulfadiazine	13.2
D06BB	*Antivirals*	
D06BB04	podophyllotoxin*	13.4
D07	**Corticosteroids, dermatological preparations**	
D07A	Corticosteroids, plain	
D07AA	*Corticosteroids, weak (group I)*	
D07AA02	hydrocortisone	13.3
D07AC	*Corticosteroids, potent (group III)*	
D07AC01	betamethasone	13.3

ATC code	ATC group/medicine or item	Section
D08	**Antiseptics and disinfectants**	
D08A	Antiseptics and disinfectants	
D08AC	*Biguanides and amidines*	
D08AC02	chlorhexidine	15.1; 29.1
D08AE	*Phenol and derivatives*	
D08AE05	chloroxylenol	15.2
D08AG	*Iodine products*	
D08AG02	povidone-iodine	15.1
D08AX	*Other antiseptics and disinfectants**	15
D08AX05	isopropanol*	15.2
D08AX06	potassium permanganate	13.2
D08AX08	ethanol	15.1; 15.2
D10	**Anti-acne preparations**	
D10A	Anti-acne preparations for topical use	
D10AE	*Peroxides*	
D10AE01	benzoyl peroxide	13.4
G	**GENITO URINARY SYSTEM AND SEX HORMONES**	
G01	**Gynecological antiinfectives and antiseptics**	
G01A	Antiinfectives and antiseptics, excl. combinations with corticosteroids	
G01AF	*Imidazole derivatives*	
G01AF02	clotrimazole	6.3
G02	**Other gynecologicals**	
G02A	Oxytocics	
G02AB	*Ergot alkaloids*	
G02AB03	ergometrine	22.1
G02AD	*Prostaglandins*	
G02AD06	misoprostol	22.1
G02B	Contraceptives for topical use	
G02BA	*Intrauterine contraceptives*	
G02BA02	plastic IUD with copper*	18.3.3
G02BA03	plastic IUD with progesteron*	18.3.3
G02BB	*Intravaginal contraceptives**	18.3.4; 18.3.6

ATC code	ATC group/medicine or item	Section
G03	**Sex hormones and modulators of the genital system**	
G03A	Hormonal contraceptives for systemic use	
G03AA	*Progestogens and estrogens, fixed combinations*	
G03AA05	norethisterone and ethinylestradiol	18.3.1
G03AA07	levonorgestrel and ethinylestradiol	18.3.1
G03AA08	medroxyprogesterone and estrogen*	18.3.2
G03AB	*Progestogens and estrogens, sequential preparations*	
G03AB03	levonorgestrel and estrogen*	18.3.1
G03AC	*Progestogens*	
G03AC01	norethisterone*	18.3.2
G03AC03	levonorgestrel	18.3.1; 18.3.3; 18.3.5
G03AC06	medroxyprogesterone*	18.3.2; 18.7
G03AC08	etonorgestrel	18.3.5
G03AD	*Emergency contraceptives*	
G03AD01	levonorgestrel	18.3.1
G03B	Androgens	
G03BA	*3-oxoandrosten (4) derivatives*	
G03BA03	testosterone	18.2
G03D	Progestogens	
G03DA	*Pregnen (4) derivatives*	
G03DA04	progesterone	18.3.6
G03G	Gonadotropins and other ovulation stimulants	
G03GB	*Ovulation stimulants, synthetic*	
G03GB02	clomifene	18.6
G03X	Other sex hormones and modulators of the genital system	
G03XB	*Antiprogesterons*	
G03XB01	mifepristone	22.1
H	**SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS**	
H01	**Pituitary, hypothalamic hormones and analogues**	
H01B	Posterior pituitary lobe hormones	
H01BA	*Vasopressin and analogues*	
H01BA02	desmopressin	10.2

ATC code	ATC group/medicine or item	Section
H01BB	*Oxytocin and analogues*	
H01BB02	oxytocin	22.1
H02	**Corticosteroids for systemic use**	
H02A	Corticosteroids for systemic use, plain	
H02AA	*Mineralocorticoids*	
H02AA02	fludrocortisone	18.1
H02AB	*Glucocorticoids*	
H02AB02	dexamethasone	2.3; 3; 8.3; 17.2; 29.2
H02AB04	methylprednisolone	8.3
H02AB06	prednisolone	3; 8.3
H02AB09	hydrocortisone	3; 8.3
H03	**Thyroid therapy**	
H03A	Thyroid preparations	
H03AA	*Thyroid hormones*	
H03AA01	levothyroxine sodium*	18.8
H03B	Antithyroid preparations	
H03BA	*Thiouracils*	
H03BA02	propylthiouracil	18.8
H03C	Iodine therapy	
H03CA	*Iodine therapy**	18.8
H04	**Pancreatic hormones**	
H04A	Glycogenolytic hormones	
H04AA	*Glycogenolytic hormones*	
H04AA01	glucagon	18.5
J	**ANTIINFECTIVES FOR SYSTEMIC USE**	
J01	**Antibacterials for systemic use**	
J01A	Tetracyclines	
J01AA	*Tetracyclines*	
J01AA02	doxycycline	6.2.2; 6.5.3.1; 6.5.3.2

ATC code	ATC group/medicine or item	Section
J01B	Amphenicols	
J01BA	*Amphenicols*	
J01BA01	chloramphenicol	6.2.2
J01C	Beta-lactam antibacterials, penicillins	
J01CA	*Penicillins with extended spectrum*	
J01CA01	ampicillin	6.2.1
J01CA04	amoxicillin	6.2.1
J01CE	*Beta-lactamase sensitive penicillins*	
J01CE01	benzylpenicillin	6.2.1
J01CE02	phenoxymethylpenicillin	6.2.1
J01CE08	benzathine benzylpenicillin	6.2.1
J01CE09	procaine benzylpenicillin	6.2.1
J01CF	*Beta-lactamase resistant penicillins*	
J01CF02	cloxacillin	6.2.1
J01CR	*Combinations of penicillins, incl. beta-lactamase inhibitors*	
J01CR02	amoxicillin and enzyme inhibitor*	6.2.1
J01D	Other beta-lactam antibacterials	
J01DB	*First-generation cephalosporins*	
J01DB01	cefalexin	6.2.1
J01DB04	cefazolin	6.2.1
J01DD	*Third-generation cephalosporins*	
J01DD01	cefotaxime	6.2.1
J01DD02	ceftazidime	6.2.1
J01DD04	ceftriaxone	6.2.1
J01DD08	cefixime	6.2.1
J01DH	*Carbapenems*	
J01DH51	imipenem and enzyme inhibitor*	6.2.1
J01E	Sulfonamides and trimethoprim	
J01EA	*Trimethoprim and derivatives*	
J01EA01	trimethoprim	6.2.2
J01EC	*Intermediate-acting sulfonamides*	
J01EC02	sulfadiazine	6.5.4
J01EE	*Combinations of sulfonamides and trimethoprim, incl. derivatives*	
J01EE01	sulfamethoxazole + trimethoprim	6.2.2; 6.5.4

ATC code	ATC group/medicine or item	Section
J01F	Macrolides, lincosamides and streptogramins	
J01FA	*Macrolides*	
J01FA01	erythromycin	6.2.2
J01FA09	clarithromycin	6.2.2
J01FA10	azithromycin	6.2.2; 21.1
J01FF	*Lincosamides*	
J01FF01	clindamycin	6.2.2
J01G	Aminoglycoside antibacterials	
J01GA	*Streptomycins*	
J01GA01	streptomycin	6.2.4
J01GB	*Other aminoglycosides*	
J01GB03	gentamicin	6.2.2
J01GB04	kanamycin	6.2.4
J01GB06	amikacin	6.2.4
J01M	Quinolone antibacterials	
J01MA	*Fluoroquinolones*	
J01MA01	ofloxacin	6.2.4; 21.1
J01MA02	ciprofloxacin	6.2.2
J01MA12	levofloxacin	6.2.4
J01X	Other antibacterials	
J01XA	*Glycopeptide antibacterials*	
J01XA01	vancomycin	6.2.2
J01XD	*Imidazole derivatives*	
J01XD01	metronidazole	6.2.2; 6.5.1
J01XE	*Nitrofuran derivatives*	
J01XE01	nitrofurantoin	6.2.2
J01XX	*Other antibacterials*	
J01XX04	spectinomycin	6.2.2
J01XX08	linezolid	6.2.4
J02	**Antimycotics for systemic use**	
J02A	Antimycotics for systemic use	
J02AA	*Antibiotics*	
J02AA01	amphotericin B	6.3; 6.5.2

ATC code	ATC group/medicine or item	Section
J02AC	*Triazole derivatives*	
J02AC01	fluconazole	6.3
J02AX	*Other antimycotics for systemic use*	
J02AX01	flucytosine	6.3
J04	**Antimycobacterials**	
J04A	Drugs for treatment of tuberculosis	
J04AA	*Aminosalicylic acid and derivatives*	
J04AA01	p-aminosalicylic acid*	6.2.4
J04AB	*Antibiotics*	
J04AB01	cycloserine	6.2.4
J04AB02	rifampicin	6.2.3; 6.2.4
J04AB04	rifabutin	6.2.4
J04AB05	rifapentine	6.2.4
J04AB30	capreomycin	6.2.4
J04AC	*Hydrazides*	
J04AC01	isoniazid	6.2.4
J04AD	*Thiocarbamide derivatives*	
J04AD03	ethionamide	6.2.4
J04AD01	protionamide	6.2.4
J04AK	*Other drugs for treatment of tuberculosis*	
J04AK01	pyrazinamide	6.2.4
J04AK02	ethambutol	6.2.4
J04AK03	terizidone	6.2.4
J04AK05	bedaquiline	6.2.4
J04AK06	delamanid	6.2.4
J04AM	*Combinations of drugs for treatment of tuberculosis**	6.2.4
J04AM02	rifampicin and isoniazid*	6.2.4
J04AM03	ethambutol and isoniazid*	6.2.4
J04AM05	rifampicin, pyrazinamide and isoniazid*	6.2.4
J04AM06	rifampicin, pyrazinamide, ethambutol and isoniazid*	6.2.4
J04B	Drugs for treatment of lepra	
J04BA	*Drugs for treatment of lepra*	
J04BA01	clofazimine	6.2.3
J04BA02	dapsone	6.2.3

ATC code	ATC group/medicine or item	Section
J05	**Antivirals for systemic use**	
J05A	Direct acting antivirals	
J05AB	*Nucleosides and nucleotides excl. reverse transcriptase inhibitors*	
J05AB01	aciclovir	6.4.1
J05AB04	ribavirin	6.4.3; 6.4.4.2.5
J05AB14	valganciclovir	6.4.3
J05AE	*Protease inhibitors*	
J05AE01	saquinavir (SQV)	6.4.2.3
J05AE03	ritonavir (r)	6.4.2.3
J05AE08	atazanavir	6.4.2.3
J05AE10	darunavir	6.4.2.3
J05AE14	simeprevir	6.4.4.2.2
J05AE30	lopinavir + ritonavir (LPV/r)*	6.4.2.3
J05AF	*Nucleoside and nucleotide reverse transcriptase inhibitors*	
J05AF01	zidovudine (ZDV or AZT)	6.4.2.1
J05AF04	stavudine (d4T)	6.4.2.1
J05AF05	lamivudine (3TC)	6.4.2.1
J05AF06	abacavir (ABC)	6.4.2.1
J05AF07	tenofovir disoproxil fumarate	6.4.2.1
J05AF10	entecavir	6.4.4.1.1
J05AG	*Non-nucleoside reverse transcriptase inhibitors*	
J05AG01	nevirapine (NVP)	6.4.2.2
J05AG03	efavirenz (EFV or EFZ)	6.4.2.2
J05AH	*Neuraminidase inhibitors*	
J05AH02	oseltamivir	6.4.3
J05AR	*Antivirals for treatment of HIV infections, combinations*	
J05AR01	lamivudine + zidovudine (ZDV or AZT)	6.4.2
J05AR02	abacavir + lamivudine	6.4.2
J05AR03	emtricitabine + tenofovir	6.4.2
J05AR05	lamivudine + nevirapine + zidovudine	6.4.2
J05AR06	efavirenz + emtricitabine + tenofovir	6.4.2
J05AR07	lamivudine + nevirapine + stavudine	6.4.2
J05AX	*Other antivirals*	
J05AX14	daclatasvir	6.4.4.2.3
J05AX15	sofosbuvir	6.4.4.2.1

ATC code	ATC group/medicine or item	Section
J05AX16	dasabuvir	6.4.4.2.4
J05AX65	ledipasvir + sofosbuvir	6.4.4.2
J05AX66	ombitasvir + paritaprevir + ritonavir	6.4.4.2
J06	**Immune sera and immunoglobulins**	
J06A	Immune sera	
J06AA	*Immune sera*	
J06AA01	diphtheria antitoxin	19.2
J06AA03	snake venom antiserum*	19.2
J06B	Immunoglobulins	
J06BA	*Immunoglobulins, normal human*	
J06BA01	immunoglobulins, normal human, for extravascular admin*	11.2.1
J06BA02	immunoglobulins, normal human, for intravascular admin*	11.2.1
J06BB	*Specific immunoglobulins*	
J06BB01	anti-D immunoglobulin	11.2.1
J06BB02	tetanus immunoglobulin*	11.2.1
J06BB05	rabies immunoglobulin*	11.2.1
J07	**Vaccines**	
J07A	Bacterial vaccines	
J07AE	*Cholera vaccines**	19.3
J07AF	*Diphtheria vaccines*	
J07AF01	diphtheria toxoid*	19.3
J07AG	*Hemophilus influenzae B vaccines*	
J07AG01	hemophilus influenzae B, purified antigen conjugated*	19.3
J07AH	*Meningococcal vaccines**	19.3
J07AJ	*Pertussis vaccines*	
J07AJ01	pertussis vaccine	19.3
J07AL	*Pneumococcal vaccines*	
J07AL01	pneumococcus, purified polysaccharides antigen*	19.3
J07AM	*Tetanus vaccines*	
J07AM01	tetanus toxoid*	19.3
J07AN	*Tuberculosis vaccines*	
J07AN01	tuberculosis, live attenuated*	19.3
J07AP	*Typhoid vaccines**	19.3

ATC code	ATC group/medicine or item	Section
J07B	Viral vaccines	
J07BA	*Encephalitis vaccines*	
J07BA01	encephalitis, tick-borne, inactivated, whole virus	19.3
J07BA02	encephalitis, Japanese, inactivated, whole virus	19.3
J07BB	*Influenza vaccines**	19.3
J07BC	*Hepatitis vaccines*	
J07BC01	hepatitis B vaccine	19.3
J07BC02	hepatitis A vaccine	19.3
J07BD	*Measles vaccine**	
J07BD01	measles vaccine, live attenuated*	19.3
J07BE	*Mumps vaccines*	
J07BE01	mumps vaccine, live attenuated*	19.3
J07BF	*Poliomyelitis vaccine*	19.3
J07BG	*Rabies vaccine*	19.3
J07BH	*Rota virus diarrhea vaccines**	19.3
J07BJ	*Rubella vaccines*	19.3
J07BK	*Varicella zoster vaccines**	19.3
J07BL	*Yellow fever vaccines*	19.3
J07BM	*Papillomavirus vaccines*	
J07BM01	papillomavirus (human types 6, 11, 16, 18)*	19.3
J07BM02	papillomavirus (human types 16, 18)*	19.3
J07C	Bacterial and viral vaccines, combined	
J07CA	*Bacterial and viral vaccines, combined**	19.3
L	**ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS**	
L01	**Antineoplastic agents**	
L01A	Alkylating agents	
L01AA	*Nitrogen mustard analogues*	
L01AA01	cyclophosphamide	8.2
L01AA02	chlorambucil	8.2
L01AA09	bendamustine	8.2
L01AA06	ifosfamide	8.2
L01AX	*Other alkylating agents*	
L01AX04	dacarbazine	8.2

ATC code	ATC group/medicine or item	Section
L01B	Antimetabolites	
L01BA	*Folic acid analogues*	
L01BA01	methotrexate	8.2; 30.2
L01BB	*Purine analogues*	
L01BB02	mercaptopurine	8.2
L01BB03	tioguanine	8.2
L01BB05	fludarabine	8.2
L01BC	*Pyrimidine analogues*	
L01BC01	cytarabine	8.2
L01BC02	fluorouracil	8.2; 13.4
L01BC05	gemcitabine	8.2
L01BC06	capecitabine	8.2
L01C	Plant alkaloids and other natural products	
L01CA	*Vinca alkaloids and analogues*	
L01CA01	vinblastine	8.2
L01CA02	vincristine	8.2
L01CA04	vinorelbine	8.2
L01CB	*Podophyllotoxin derivatives*	
L01CB01	etoposide	8.2
L01CD	*Taxanes*	
L01CD01	paclitaxel	8.2
L01CD02	docetaxel	8.2
L01D	Cytotoxic antibiotics and related substances	
L01DA	*Actinomycines*	
L01DA01	dactinomycin	8.2
L01DB	*Anthracyclines and related substances*	
L01DB01	doxorubicin	8.2
L01DB02	daunorubicin	8.2
L01DC	*Other cytotoxic antibiotics*	
L01DC01	bleomycin	8.2
L01X	Other antineoplastic agents	
L01XA	*Platinum compounds*	
L01XA01	cisplatin	8.2
L01XA02	carboplatin	8.2
L01XA03	oxaliplatin	8.2

ATC code	ATC group/medicine or item	Section
L01XB	*Methylhydrazines*	
L01XB01	procarbazine	8.2
L01X	Other antineoplastic agents	
L01XC	*Monoclonal antibodies*	
L01XC02	rituximab	8.2
L01XC03	trastuzumab	8.2
L01XC07	bevacizumab	21.6
L01XE	*Protein kinase inhibitors*	
L01XE01	imatinib	8.2
L01XX	*Other antineoplastic agents*	
L01XX02	asparaginase	8.2
L01XX05	hydroxycarbamide	8.2; 10.3
L01XX09	miltefosine	6.5.2
L01XX14	tretinoin*	8.2
L01XX19	irinotecan	8.2
L02	**Endocrine therapy**	
L02A	Hormones and related agents	
L02AE	*Gonadotrophin releasing hormone analogues*	
L02AE02	leuprorelin	8.3
L02B	Hormone antagonists and related agents	
L02BA	*Anti-estrogens*	
L02BA01	tamoxifen	8.3
L02BB	*Anti-androgens*	
L02BB03	bicalutamide	8.3
L02BG	*Aromatase inhibitors*	
L02BG03	anastrozole	8.3
L03	**Immunostimulants**	
L03A	Immunostimulants	
L03AA	*Colony stimulating factors*	
L03AA02	filgrastim	8.2
L03AB	*Interferons*	
L03AB10	peginterferon alfa-2b*	6.4.4.2.5
L03AB11	peginterferon alfa-2a*	6.4.4.2.5

ATC code	ATC group/medicine or item	Section
L04	**Immunosuppressants**	
L04A	Immunosuppressants	
L04AD	*Calcineurin inhibitors*	
L04AD01	ciclosporin	8.1
L04AX	*Other immunosuppressants*	
L04AX01	azathioprine	8.1; 30.2
M	**MUSCULO-SKELETAL SYSTEM**	
M01	**Antiinflammatory and antirheumatic products**	
M01A	Antiinflammatory and antirheumatic products, non-steroids	
M01AE	*Propionic acid derivatives*	
M01AE01	ibuprofen	2.1; 29
M01C	Specific antirheumatic agents	
M01CC	*Penicillamine and similar agents*	
M01CC01	penicillamine	4.2; 30.2
M03	**Muscle relaxants**	
M03A	Muscle relaxants, peripherally acting agents	
M03AB	*Choline derivatives*	
M03AB01	suxamethonium	20
M03AC	*Other quaternary ammonium compounds*	
M03AC03	vecuronium	20
M03AC04	atracurium	20
M04	**Antigout preparations**	
M04A	Antigout preparations	
M04AA	*Preparations inhibiting uric acid production*	
M04AA01	allopurinol	8.2; 30.1
N	**NERVOUS SYSTEM**	
N01	**Anesthetics**	
N01A	Anesthetics, general	
N01AB	*Halogenated hydrocarbons*	
N01AB01	halothane	1.1.1
N01AB06	isoflurane	1.1.1
N01AX	*Other general anesthetics*	
N01AX03	ketamine	1.1.2

ATC code	ATC group/medicine or item	Section
N01AX10	propofol	1.1.2
N01AX13	nitrous oxide	1.1.1
N01B	Anesthetics, local	
N01BB	*Amides*	
N01BB01	bupivacaine	1.2
N01BB02	lidocaine	1.2
N01BB52	lidocaine, combinations*	1.2
N02	**Analgesics**	
N02A	Opioids	
N02AA	*Natural opium alkaloids*	
N02AA01	morphine	1.3; 2.2
N02AA03	hydromorphone	2.2
N02AA05	oxycodone	2.2
N02B	Other analgesics and antipyretics	
N02BA	*Salicylic acid and derivatives*	
N02BA01	acetylsalicylic acid	2.1; 7.1
N02BE	*Anilides*	
N02BE01	paracetamol	2.1; 7.1
N03	**Antiepileptics**	
N03A	Antiepileptics	
N03AA	*Barbiturates and derivatives*	
N03AA02	phenobarbital	5
N03AB	*Hydantoin derivatives*	
N03AB02	phenytoin	5
N03AD	*Succinimide derivatives*	
N03AD01	ethosuximide	5
N03AF	*Carboxamide derivatives*	
N03AF01	carbamazepine	5; 24.2.2
N03AG	*Fatty acid derivatives*	
N03AG01	valproic acid	5; 24.2.2
N04	**Anti-parkinson drugs**	
N04A	Anticholinergic agents	
N04AA	*Tertiary amines*	
N04AA02	biperiden	9

ATC code	ATC group/medicine or item	Section
N04B	Dopaminergic agents	
N04BA	*Dopa and dopa derivatives*	
N04BA02	levodopa and decarboxylase inhibitor*	9
N05	**Psycholeptics**	
N05A	Antipsychotics	
N05AA	*Phenothiazines with aliphatic side-chain*	
N05AA01	chlorpromazine	24.1
N05AB	*Phenothiazines with piperazine structure*	
N05AB02	fluphenazine	24.1
N05AH	*Diazepines, oxazepines, thiazepines and oxepines*	
N05AH02	clozapine	24.1
N05AD	*Butyrophenone derivatives*	
N05AD01	haloperidol	2.3; 24.1
N05AN	*Lithium*	
N05AN01	lithium*	24.2.2
N05AX	*Other antipsychotics*	
N05AX08	risperidone	24.1
N05B	Anxiolytics	
N05BA	*Benzodiazepine derivatives*	
N05BA01	diazepam	2.3; 5; 24.3
N05BA06	lorazepam	5
N05C	Hypnotics and sedatives	
N05CD	*Benzodiazepine derivatives*	
N05CD08	midazolam	1.3; 5
N06	**Psychoanaleptics**	
N06A	Antidepressants	
N06AA	*Non-selective monoamine reuptake inhibitors*	
N06AA04	clomipramine	24.4
N06AA09	amitriptyline	2.3; 24.2.1
N06AB	*Selective serotonin reuptake inhibitors*	
N06AB03	fluoxetine	24.2.1
N06B	Psychostimulants, agents used for ADHD and nootropics	
N06BC	*Xanthine derivatives*	
N06BC01	caffeine citrate	29

ATC code	ATC group/medicine or item	Section
N07	**Other nervous system drugs**	
N07A	Parasympathomimetics	
N07AA	*Anticholinesterases*	
N07AA01	neostigmine	20
N07AA02	pyridostigmine	20
N07B	Drugs used in addictive disorders	
N07BA	*Drugs used in nicotine dependence*	
N07BA01	nicotine*	24.5
N07BC	*Drugs used in opioid dependence*	
N07BC02	methadone	24.5
P	**ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS**	
P01	**Antiprotozoals**	
P01A	Agents against amoebiasis and other protozoal diseases	
P01AB	*Nitroimidazole derivatives*	
P01AB01	metronidazole	6.5.1
P01AC	*Dichloroacetamide derivatives*	
P01AC01	diloxanide	6.5.1
P01B	Antimalarials	
P01BA	*Aminoquinolines*	
P01BA01	chloroquine	2.4; 6.5.3.1; 6.5.3.2
P01BA02	hydroxychloroquine	30.2
P01BA03	primaquine	6.5.3.1
P01BA06	amodiaquine	6.5.3.1
P01BB	*Biguanides*	
P01BB01	proguanil	6.5.3.2
P01BC	*Methanolquinolines*	
P01BC01	quinine	6.5.3.1
P01BC02	mefloquine	6.5.3.1; 6.5.3.2
P01BD	*Diaminopyrimidines*	
P01BD01	pyrimethamine	6.5.4
P01BD51	pyrimethamine, combinations*	6.5.3.1

ATC code	ATC group/medicine or item	Section
P01BE	*Artemisinin and derivatives*	
P01BE02	artemether	6.5.3.1
P01BE03	artesunate	6.5.3.1
P01BF01	artemether and lumefantrine	6.5.3.1
P01BF02	artesunate and mefloquine	6.5.3.1
P01BF03	artesunate and amodiaquine	6.5.3.1
P01C	Agents against leishmaniasis and trypanosomiasis	
P01CA	*Nitroimidazole derivatives*	
P01CA02	benznidazole	6.5.5.2
P01CB	*Antimony compounds*	
P01CB01	meglumine antimoniate	6.5.2
P01CB02	sodium stibogluconate	6.5.2
P01CC	*Nitrofuran derivatives*	
P01CC01	nifurtimox	6.5.5.1; 6.5.5.2
P01CD	*Arsenic compounds*	
P01CD01	melarsoprol	6.5.5.1
P01CX	*Other agents against leishmaniasis and trypanosomiasis*	
P01CX01	pentamidine isethionate*	6.5.4; 6.5.5.1
P01CX02	suramin sodium	6.5.5.1
P01CX03	eflornithine	6.5.5.1
P02	**Anthelmintics**	
P02B	Antitrematodals	
P02BA	*Quinoline derivatives and related substances*	
P02BA01	praziquantel	6.1.1; 6.1.3
P02BA02	oxamniquine	6.1.3
P02BX	*Other antitrematodal agents*	
P02BX04	triclabendazole	6.1.3
P02C	Antinematodal agents	
P02CA	*Benzimidazole derivatives*	
P02CA01	mebendazole	6.1.1
P02CA03	albendazole	6.1.1; 6.1.2
P02CB	*Piperazine and derivatives*	
P02CB02	diethylcarbamazine	6.1.2

ATC code	ATC group/medicine or item	Section
P02CC	*Tetrahydropyrimidine derivatives*	
P02CC01	pyrantel	6.1.1
P02CE	*Imidazothiazole derivatives*	
P02CE01	levamisole	6.1.1
P02CF	*Avermectines*	
P02CF01	ivermectin	6.1.2
P02D	Anticestodals	
P02DA	*Salicylic acid derivatives*	
P02DA01	niclosamide	6.1.1
P03	**Ectoparasiticides, incl. scabicides, insecticides and repellents**	
P03A	Ectoparasiticides, incl. scabicides	
P03AC	*Pyrethrines, incl. synthetic compounds*	
P03AC04	permethrin	13.5
P03AX	*Other ectoparasiticides, incl. scabicides*	
P03AX01	benzyl benzoate	13.5
R	**RESPIRATORY SYSTEM**	
R01	**Nasal preparations**	
R01A	Decongestants and other nasal preparations for topical use	
R01AA	*Sympathomimetics, plain*	
R01AA07	xylometazoline	28
R01AD	*Corticosteroids*	
R01AD05	budesonide	28
R03	**Drugs for obstructive airway diseases**	
R03A	Adrenergics, inhalants	
R03AC	*Selective beta-2-adrenoreceptor agonists*	
R03AC02	salbutamol	25.1
R03B	Other drugs for obstructive airway diseases, inhalants	
R03BA	*Glucocorticoids*	
R03BA01	beclometasone	25.1
R03BB	*Anticholinergics*	
R03BB01	ipratropium bromide	25.1

ATC code	ATC group/medicine or item	Section
R03C	Adrenergics for systemic use	
R03CC	*Selective beta-2-adrenoreceptor agonists*	
R03CC02	salbutamol	25.1
R05	**Cough and cold preparations**	
R05D	Cough suppressants, excl. combinations with expectorants	
R05DA	*Opium alkaloids and derivatives*	
R05DA04	codeine	2.2
R06	**Antihistamines for systemic use**	
R06A	Antihistamines for systemic use	
R06AE	*Piperazine derivatives*	
R06AE3	cyclizine	2.3
R06AX	*Other antihistamines for systemic use*	
R06AX13	loratadine	3
R07	**Other respiratory system products**	
R07A	Other respiratory system products	
R07AA	*Lung surfactants*	29.1
S	**SENSORY ORGANS**	
S01	**Ophthalmologicals**	
S01A	Antiinfectives	
S01AA	*Antibiotics*	
S01AA09	tetracycline	21.1
S01AA11	gentamicin	21.1
S01AD	*Antivirals*	
S01AD03	aciclovir	21.1
S01B	Antiinflammatory agents	
S01BA	*Corticosteroids, plain*	
S01BA04	prednisolone	21.2
S01E	Antiglaucoma preparations and miotics	
S01EA	*Sympathomimetics in glaucoma therapy*	
S01EA01	epinephrine	21.5
S01EB	*Parasympathomimetics*	
S01EB01	pilocarpine	21.4

ATC code	ATC group/medicine or item	Section
S01EC	*Carbonic anhydrase inhibitors*	
S01EC01	acetazolamide	21.4
S01ED	*Beta blocking agents*	
S01ED01	timolol	21.4
S01EE	*Prostaglandin analogues*	
S01EE01	latanoprost	21.4
S01F	Mydriatics and cycloplegics	
S01FA	*Anticholinergics*	
S01FA01	atropine	21.5
S01FA06	tropicamide	14.1
S01H	Local anesthetics	
S01HA	*Local anesthetics*	
S01HA03	tetracaine	21.3
S01J	Diagnostic agents	
S01JA	*Colouring agents*	
S01JA01	fluorescein	14.1
S02	**Otologicals**	
S02A	Antiinfectives	
S02AA	*Antiinfectives*	
S02AA10	acetic acid	28
S02AA15	ciprofloxacin	28
V	**VARIOUS**	
V03	**All other therapeutic products**	
V03A	All other therapeutic products	
V03AB	*Antidotes*	
V03AB03	edetates*	4.2
V03AB06	thiosulfate*	4.2; 13.1
V03AB08	sodium nitrite	4.2
V03AB09	dimercaprol	4.2
V03AB14	protamine*	10.2
V03AB15	naloxone	4.2
V03AB17	methylthioninium chloride (methylene blue)	4.2
V03AB23	acetylcysteine	4.2
V03AB31	potassium ferric hexacyanoferrate (II) ·$2H_2O$ (Prussian blue)	4.2
V03AB34	fomepizole	4.2

ATC code	ATC group/medicine or item	Section
V03AC	*Iron chelating agents*	
V03AC01	deferoxamine	4.2; 10.3
V03AF	*Detoxifying agents for antineoplastic treatment*	
V03AF01	mesna	8.2
V03AF03	calcium folinate	8.2
V03AN	*Medical gases*	
V03AN01	oxygen	1.1.1
V04	**Diagnostic agents**	
V04C	Other diagnostic agents	
V04CF	*Tuberculosis diagnostics*	
V04CF01	tuberculin, purified protein derivative (PPD) - BCG*	19.1
V07	**All other non-therapeutic products**	
V07A	All other non-therapeutic products	
V07AB	*Solvents and diluting agents, incl. irrigating solutions**	26.3
V07AB	*Water for Injection*	26.3
V07AV	*Technical disinfectants**	15.2
V08	**Contrast media**	
V08A	X-ray contrast media, iodinated	
V08AA	*Watersoluble, nephrotropic, high osmolar X-ray contrast media*	
V08AA01	diatrizoic acid*	14.2
V08AB	*Watersoluble, nephrotropic, low osmolar X-ray contrast media*	
V08AB02	iohexol	14.2
V08AC	*Watersoluble, hepatotropic X-ray contrast media*	
V08AC02	iotroxic acid*	14.2
V08B	X-ray contrast media, non-iodinated	
V08BA	*Barium sulfate containing X-ray contrast media*	
V08BA01	barium sulfate with suspending agents*	14.2

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

Annex 4

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

Medicine or item as in EML	ATC code	Section
abacavir (ABC)	J05AF06	6.4.2.1
abacavir + lamivudine	J05AR01	6.4.2
acetazolamide	S01EC01	21.4
acetic acid	S02AA10	28
acetylcysteine	V03AB23	4.2
acetylsalicylic acid	B01AC06	7.1; 12.5.1; 30.3
acetylsalicylic acid	N02BA01	2.1; 7.1
aciclovir	J05AB01	6.4.1
aciclovir	S01AD03	21.1
albendazole	P02CA03	6.1.1; 6.1.2
allopurinol	M04AA01	8.2; 30.1
amikacin	J01GB06	6.2.4
amiloride	C03DB01	16
amiodarone	C01BD01	12.2
amitriptyline	N06AA09	2.3; 24.2.1
amlodipine	C08CA01	12.3
amodiaquine	P01BA06	6.5.3.1
amoxicillin	J01CA04	6.2.1
amoxicillin and enzyme inhibitor*	J01CR02	6.2.1
amphotericin B	J02AA01	6.3; 6.5.2
ampicillin	J01CA01	6.2.1
anastrozole	L02BG03	8.3
anti-D immunoglobulin	J06BB01	11.2.1
artemether	P01BE02	6.5.3.1
artemether and lumefantrine	P01BF01	6.5.3.1
artesunate	P01BE03	6.5.3.1
artesunate and amodiaquine	P01BF03	6.5.3.1
artesunate and mefloquine	P01BF02	6.5.3.1
ascorbic acid	A11GA01	27
asparaginase	L01XX02	8.2
atazanavir	J05AE08	6.4.2.3
atenolol	C07AB03	12.3
atracurium	M03AC04	20

Medicine or item as in EML	ATC code	Section
atropine	A03BA01	1.3; 4.2
atropine	S01FA01	21.5
azathioprine	L04AX01	8.1; 30.2
azithromycin	J01FA10	6.2.2; 21.1
bacterial and viral vaccines, combined*	J07CA	19.3
barium sulfate with suspending agents*	V08BA01	14.2
beclometasone	R03BA01	25.1
bedaquiline	J04AK05	6.2.4
bendamustine	L01AA09	8.2
benzathine benzylpenicillin	J01CE08	6.2.1
benznidazole	P01CA02	6.5.5.2
benzoyl peroxide	D10AE01	13.4
benzyl benzoate	P03AX01	13.5
benzylpenicillin	J01CE01	6.2.1
betamethasone	D07AC01	13.3
bevacizumab	L01XC07	21.6
bicalutamide	L02BB03	8.3
biperiden	N04AA02	9
bisoprolol	C07AB07	12.1; 12.2; 12.3; 12.4
bleomycin	L01DC01	8.2
budesonide	R01AD05	28
bupivacaine	N01BB01	1.2
caffeine citrate	N06BC01	29
calcium folinate	V03AF03	8.2
calcium gluconate	A12AA03	4.2; 27
capecitabine	L01BC06	8.2
capreomycin	J04AB30	6.2.4
carbamazepine	N03AF01	5; 24.2.2
carbamide*	D02AE01	13.4
carbohydrates*	B05BA03	26.2
carboplatin	L01XA02	8.2
carvedilol	C07AG02	12.1; 12.2; 12.3; 12.4
cefalexin	J01DB01	6.2.1
cefazolin	J01DB04	6.2.1
cefixime	J01DD08	6.2.1
cefotaxime	J01DD01	6.2.1
ceftazidime	J01DD02	6.2.1
ceftriaxone	J01DD04	6.2.1

Medicine or item as in EML	ATC code	Section
chlorambucil	L01AA02	8.2
chloramphenicol	J01BA01	6.2.2
chlorhexidine	D08AC02	15.1; 29.1
chloroquine	P01BA01	2.4; 6.5.3.1; 6.5.3.2
chloroxylenol	D08AE05	15.2
chlorpromazine	N05AA01	24.1
cholera vaccines*	J07AE	19.3
ciclosporin	L04AD01	8.1
ciprofloxacin	J01MA02	6.2.2
ciprofloxacin	S02AA15	28
cisplatin	L01XA01	8.2
clarithromycin	J01FA09	6.2.2
clindamycin	J01FF01	6.2.2
clofazimine	J04BA01	6.2.3
clomifene	G03GB02	18.6
clomipramine	N06AA04	24.4
clopidogrel	B01AC04	12.5.1
clotrimazole	G01AF02	6.3
cloxacillin	J01CF02	6.2.1
clozapine	N05AH02	24.1
coagulation factor IX, II, VII and X in combination*	B02BD01	11.2.2
coagulation factor VIII*	B02BD02	11.2.2
codeine	R05DA04	2.2
colecalciferol*	A11CC05	27
Combinations of drugs for treatment of tuberculosis*	J04AM	6.2.4
cyclizine	R06AE3	2.3
cyclophosphamide	L01AA01	8.2
cycloserine	J04AB01	6.2.4
cytarabine	L01BC01	8.2
dacarbazine	L01AX04	8.2
daclatasvir	J05AX14	6.4.4.2.3
dactinomycin	L01DA01	8.2
dalteparin	B01AB04	10.2
dapsone	J04BA02	6.2.3
darunavir	J05AE10	6.4.2.3
dasabuvir	J05AX16	6.4.4.2.4
daunorubicin	L01DB02	8.2

Medicine or item as in EML	ATC code	Section
deferoxamine	V03AC01	4.2; 10.3
delamanid	J04AK06	6.2.4
desmopressin	H01BA02	10.2
dexamethasone	H02AB02	2.3; 3; 8.3; 17.2; 29.2
dextran*	B05AA05	11.3
diatrizoic acid*	V08AA01	14.2
diazepam	N05BA01	2.3; 5; 24.3
diethylcarbamazine	P02CB02	6.1.2
digoxin	C01AA05	12.2; 12.4
diloxanide	P01AC01	6.5.1
dimercaprol	V03AB09	4.2
diphtheria antitoxin	J06AA01	19.2
diphtheria toxoid*	J07AF01	19.3
docetaxel	L01CD02	8.2
docusate sodium	A06AA02	2.3
dopamine	C01CA04	12.4
doxorubicin	L01DB01	8.2
doxycycline	J01AA02	6.2.2; 6.5.3.1; 6.5.3.2
edetates*	V03AB03	4.2
efavirenz (EFV or EFZ)	J05AG03	6.4.2.2
efavirenz + emtricitabine + tenofovir	J05AR06	6.4.2
eflornithine	P01CX03	6.5.5.1
electrolytes with carbohydrates*	B05BB02	26.2
electrolytes*	B05BB01	26.2
emtricitabine + tenofovir	J05AR03	6.4.2
enalapril	C09AA02	12.3; 12.4
encephalitis, Japanese, inactivated, whole virus*	J07BA02	19.3
encephalitis, tick-borne, inactivated, whole virus*	J07BA01	19.3
enoxaparin	B01AB05	10.2
entecavir	J05AF10	6.4.4.1.1
ephedrine	C01CA26	1.2
epinephrine	S01EA01	21.5
epinephrine (adrenaline)	C01CA24	3; 12.2; 25.1
ergocalciferol	A11CC01	27
ergometrine	G02AB03	22.1
erythromycin	J01FA01	6.2.2
ethambutol	J04AK02	6.2.4

Medicine or item as in EML	ATC code	Section
ethambutol and isoniazid*	J04AM03	6.2.4
ethanol	D08AX08	15.1; 15.2
ethionamide	J04AD03	6.2.4
ethosuximide	N03AD01	5
etonorgestrel	G03AC08	18.3.5
etoposide	L01CB01	8.2
filgrastim	L03AA02	8.2
fluconazole	J02AC01	6.3
flucytosine	J02AX01	6.3
fludarabine	L01BB05	8.2
fludrocortisone	H02AA02	18.1
fluorescein	S01JA01	14.1
fluorouracil	L01BC02	8.2; 13.4
fluoxetine	N06AB03	24.2.1
fluphenazine	N05AB02	24.1
folic acid	B03BB01	10.1
fomepizole	V03AB34	4.2
fresh frozen plasma*	B05AX03	11.1
furosemide	C03CA01	12.4; 16
gemcitabine	L01BC05	8.2
gentamicin	J01GB03	6.2.2
gentamicin	S01AA11	21.1
glibenclamide	A10BB01	18.5
gliclazide	A10BB09	18.5
glucagon	H04AA01	18.5
glucose*	B05BA03	26.2
glyceryl trinitrate	C01DA02	12.1
griseofulvin	D01BA01	6.3
haloperidol	N05AD01	2.3; 24.1
halothane	N01AB01	1.1.1
hemophilus influenzae B, purified antigen conjugated*	J07AG01	19.3
heparin*	B01AB01	10.2
hepatitis A vaccine	J07BC02	19.3
hepatitis B vaccine	J07BC01	19.3
hydrazaline	C02DB02	12.3
hydrochlorothiazide	C03AA03	12.3; 12.4; 16

Medicine or item as in EML	ATC code	Section
hydrocortisone	A07EA02	17.3
hydrocortisone	D07AA02	13.3
hydrocortisone	H02AB09	3; 8.3
hydromorphone	N02AA03	2.2
hydroxocobalamin	B03BA03	10.1
hydroxycarbamide	L01XX05	8.2; 10.3
hydroxychloroquine	P01BA02	30.2
hyoscine butylbromide*	A03BB01	2.3
hyoscine hydrobromide*	A04AD01	2.3
ibuprofen	M01AE01	2.1; 29
ifosfamide	L01AA06	8.2
imatinib	L01XE01	8.2
imipenem and enzyme inhibitor*	J01DH51	6.2.1
immunoglobulins, normal human, for extravascular admin*	J06BA01	11.2.1
immunoglobulins, normal human, for intravascular admin*	J06BA02	11.2.1
influenza vaccine	J07BB	19.3
insulin injection (soluble)*	A10AB	18.5
insulin, intermediate-acting*	A10AC	18.5
Intravaginal contraceptives*	G02BB	18.3.4; 18.3.6
Iodine therapy*	H03CA	18.8
iohexol	V08AB02	14.2
iotroxic acid*	V08AC02	14.2
ipratropium bromide	R03BB01	25.1
irinotecan	L01XX19	8.2
Iron in combination with folic acid*	B03AD	10.1
Iron preparations*	B03A	10.1
isoflurane	N01AB06	1.1.1
isoniazid	J04AC01	6.2.4
isopropanol*	D08AX05	15.2
isosorbide dinitrate	C01DA08	12.1
Isotonic solutions*	B05DA	23
ivermectin	P02CF01	6.1.2
kanamycin	J01GB04	6.2.4
ketamine	N01AX03	1.1.2
lactulose	A06AD11	2.3
lamivudine (3TC)	J05AF05	6.4.2.1

Medicine or item as in EML	ATC code	Section
lamivudine + nevirapine + stavudine	J05AR07	6.4.2
lamivudine + nevirapine + zidovudine	J05AR05	6.4.2
lamivudine + zidovudine (ZDV or AZT)	J05AR01	6.4.2
latanoprost	S01EE01	21.4
ledipasvir + sofosbuvir	J05AX65	6.4.4.2
leuprorelin	L02AE02	8.3
levamisole	P02CE01	6.1.1
levodopa and decarboxylase inhibitor*	N04BA02	9
levofloxacin	J01MA12	6.2.4
levonorgestrel	G03AC03	18.3.1; 18.3.3; 18.3.5
levonorgestrel	G03AD01	18.3.1
levonorgestrel and estrogen*	G03AB03	18.3.1
levonorgestrel and ethinylestradiol	G03AA07	18.3.1
levothyroxine sodium*	H03AA01	18.8
lidocaine	C01BB01	12.2
lidocaine	N01BB02	1.2
lidocaine, combinations*	N01BB52	1.2
linezolid	J01XX08	6.2.4
lithium*	N05AN01	24.2.2
loperamide	A07DA03	2.3
lopinavir + ritonavir (LPV/r)*	J05AE30	6.4.2.3
loratadine	R06AX13	3
lorazepam	N05BA06	5
Lung surfactants	R07AA	29.1
magnesium sulfate	B05XA05	5
mannitol	B05BC01	16
measles vaccine, live attenuated*	J07BD01	19.3
mebendazole	P02CA01	6.1.1
medicinal charcoal*	A07BA01	4.1
medroxyprogesterone and estrogen*	G03AA08	18.3.2
medroxyprogesterone*	G03AC06	18.3.2; 18.7
mefloquine	P01BC02	6.5.3.1; 6.5.3.2
meglumine antimoniate	P01CB01	6.5.2
melarsoprol	P01CD01	6.5.5.1
meningococcal vaccines*	J07AH	19.3
mercaptopurine	L01BB02	8.2
mesna	V03AF01	8.2
metformin	A10BA02	18.5
methadone	N07BC02	24.5

Medicine or item as in EML	ATC code	Section
methotrexate	L01BA01	8.2; 30.2
methyldopa (levorotatory)*	C02AB01	12.3
methylprednisolone	H02AB04	8.3
methylthioninium chloride (methylene blue)	V03AB17	4.2
metoclopramide	A03FA01	2.3; 17.2
metoprolol	C07AB02	12.1; 12.2; 12.3; 12.4
metronidazole	J01XD01	6.2.2; 6.5.1
metronidazole	P01AB01	6.5.1
miconazole	D01AC02	13.1
midazolam	N05CD08	1.3; 5
mifepristone	G03XB01	22.1
miltefosine	L01XX09	6.5.2
misoprostol	G02AD06	22.1
morphine	N02AA01	1.3; 2.2
multienzymes (lipase, protease, etc.)*	A09AA02	17
mumps vaccine, live attenuated*	J07BE01	19.3
mupirocin	D06AX09	13.2
nadroparin	B01AB06	10.2
naloxone	V03AB15	4.2
neostigmine	N07AA01	20
nevirapine (NVP)	J05AG01	6.4.2.2
niclosamide	P02DA01	6.1.1
nicotinamide	A11HA01	27
nicotine*	N07BA01	24.5
nifedipine	C08CA05	22.2
nifurtimox	P01CC01	6.5.5.1; 6.5.5.2
nitrofurantoin	J01XE01	6.2.2
nitroprusside*	C02DD01	12.3
nitrous oxide	N01AX13	1.1.1
norethisterone and ethinylestradiol	G03AA05	18.3.1
norethisterone*	G03AC01	18.3.2
nystatin	D01AA01	6.3
ofloxacin	J01MA01	6.2.4; 21.1
ombitasvir + paritaprevir + ritonavir	J05AX66	6.4.4.2
omeprazole	A02BC01	17.1
ondansetron	A04AA01	17.2
oral rehydration salt formulations*	A07CA	17.5.1; 26.1
oseltamivir	J05AH02	6.4.3

Medicine or item as in EML	ATC code	Section
other antiseptics and disinfectants*	D08AX	15.2
other mineral products*	A12CX	27
oxaliplatin	L01XA03	8.2
oxamniquine	P02BA02	6.1.3
oxycodone	N02AA05	2.2
oxygen	V03AN01	1.1.1
oxytocin	H01BB02	22.1
paclitaxel	L01CD01	8.2
p-aminosalicylic acid*	J04AA01	6.2.4
paracetamol	N02BE01	2.1; 7.1
paromomycin	A07AA06	6.5.2
peginterferon alfa-2a*	L03AB11	6.4.4.2.5
peginterferon alfa-2b*	L03AB10	6.4.4.2.5
penicillamine	M01CC01	4.2; 30.2
pentamidine isethionate*	P01CX01	6.5.4; 6.5.5.1
permethrin	P03AC04	13.6
pertussis vaccine	J07AJ01	19.3
phenobarbital	N03AA02	5
phenoxymethylpenicillin	J01CE02	6.2.1
phenytoin	N03AB02	5
phytomenadione	B02BA01	10.2
pilocarpine	S01EB01	21.4
plastic IUD with copper*	G02BA02	18.3.3
plastic IUD with progesteron*	G02BA03	18.3.3
platelet concentrates	B05A	11.1
pneumococcus, purified polysaccharides antigen*	J07AL01	19.3
podophyllotoxin*	D06BB04	13.4
poliomyelitis vaccine	J07BF	19.3
potassium chloride	B05XA01	26.1; 26.2
potassium ferric hexacyanoferrate (II) $\cdot 2H_2O$ (Prussian blue)	V03AB31	4.2
potassium permanganate	D08AX06	13.2
povidone-iodine*	D08AG02	15.1
praziquantel	P02BA01	6.1.1; 6.1.3
prednisolone	H02AB06	3; 8.3
prednisolone	S01BA04	21.2
primaquine	P01BA03	6.5.3.1
procaine benzylpenicillin	J01CE09	6.2.1

Medicine or item as in EML	ATC code	Section
procarbazine	L01XB01	8.2
progesterone	G03DA04	18.3.6
proguanil	P01BB01	6.5.3.2
propofol	N01AX10	1.1.2
propranolol	C07AA05	7.2
propylthiouracil	H03BA02	18.8
protamine*	V03AB14	10.2
protionamide	J04AD01	6.2.4
pyrantel	P02CC01	6.1.1
pyrazinamide	J04AK01	6.2.4
pyridostigmine	N07AA02	20
pyridoxine	A11HA02	27
pyrimethamine	P01BD01	6.5.4
pyrimethamine, combinations*	P01BD51	6.5.3.1
quinine	P01BC01	6.5.3.1
rabies immunoglobulin	J06BB05	11.2.1
rabies vaccine	J07BG	19.3
ranitidine	A02BA02	17.1
red blood cells*	B05AX01	11.1
retinol	A11CA01	27
ribavirin	J05AB04	6.4.3; 6.4.4.2.5
riboflavin	A11HA04	27
rifabutin	J04AB04	6.2.4
rifampicin	J04AB02	6.2.3; 6.2.4
rifampicin and isoniazid*	J04AM02	6.2.4
rifampicin, pyrazinamide and isoniazid*	J04AM05	6.2.4
rifampicin, pyrazinamide, ethambutol and isoniazid*	J04AM06	6.2.4
rifapentine	J04AB05	6.2.4
risperidone	N05AX08	24.1
ritonavir (r)	J05AE03	6.4.2.3
rituximab	L01XC02	8.2
rota virus diarrhea vaccines*	J07BH	19.3
rubella vaccines	J07BJ	19.3
salbutamol	R03AC02	25.1
salbutamol	R03CC02	25.1
salicylic acid	D01AE12	13.4

Medicine or item as in EML	ATC code	Section
saquinavir (SQV)	J05AE01	6.4.2.3
selenium sulfide	D01AE13	13.1
senna glycosides*	A06AB06	17.4
silver sulfadiazine	D06BA01	13.2
simeprevir	J05AE14	6.4.4.2.2
simvastatin	C10AA01	12.6
snake venom antiserum*	J06AA03	19.2
sodium bicarbonate*	B05XA02	26.2
sodium chloride	B05XA03	26.2
sodium fluoride	A12CD01	27
sodium nitrite	V03AB08	4.2
sodium stibogluconate	P01CB02	6.5.2
sofosbuvir	J05AX15	6.4.4.2.1
Solvents and diluting agents, incl. irrigating solutions*	V07AB	26.3
spectinomycin	J01XX04	6.2.2
spironolactone	C03DA01	12.4; 16
stavudine (d4T)	J05AF04	6.4.2.1
streptokinase	B01AD01	12.5.2
streptomycin	J01GA01	6.2.4
sulfadiazine	J01EC02	6.5.4
sulfamethoxazole + trimethoprim	J01EE01	6.2.2; 6.5.4
sulfasalazine	A07EC01	17.3; 30.2
suramin sodium	P01CX02	6.5.5.1
suxamethonium	M03AB01	20
tamoxifen	L02BA01	8.3
Technical disinfectants*	V07AV	15.2
tenofovir disoproxil fumarate	J05AF07	6.4.2.1
terbinafine	D01BA02	13.1
terizidone	J04AK03	6.2.4
testosterone	G03BA03	18.2
tetanus immunoglobulin*	J06BB02	11.2.1
tetanus toxoid*	J07AM01	19.3
tetracaine	S01HA03	21.3
tetracycline	S01AA09	21.1
thiamine	A11DA01	27
thiosulfate*	V03AB06	4.2; 13.1
timolol	S01ED01	21.4
tioguanine	L01BB03	8.2

Medicine or item as in EML	ATC code	Section
tranexamic acid	B02AA02	10.2
trastuzumab	L01XC03	8.2
tretinoin*	L01XX14	8.2
triclabendazole	P02BX04	6.1.3
trimethoprim	J01EA01	6.2.2
tropicamide	S01FA06	14.1
tuberculin, purified protein derivative (PPD) - BCG*	V04CF01	19.1
tuberculosis, live attenuated*	J07AN01	19.3
typhoid vaccine	J07AP	19.3
valganciclovir	J05AB14	6.4.3
valproic acid	N03AG01	5; 24.2.2
vancomycin	J01XA01	6.2.2
varicella zoster vaccines*	J07BK	19.3
vecuronium	M03AC03	20
verapamil	C08DA01	12.1; 12.2
vinblastine	L01CA01	8.2
vincristine	L01CA02	8.2
vinorelbine	L01CA04	8.2
warfarin	B01AA03	10.2
Water for Injection	V07AB	26.3
whole blood*	B05A	11.1
xylometazoline	R01AA07	28
yellow fever vaccines	J07BL	19.3
zidovudine (ZDV or AZT)	J05AF01	6.4.2.1
Zinc products*	D02AB	13.3
zinc sulfate	A12CB01	17.5.2

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

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This report presents the recommendations of the WHO Expert Committee responsible for updating the WHO Model Lists of Essential Medicines. It contains a summary of the Committee's considerations and justifications for additions and changes to the Model Lists, including its recommendations. Annexes to the main report include the revised version of the WHO Model List of Essential Medicines (19th edition) and the WHO Model List of Essential Medicines for Children (5th edition). In addition there is a list of all the items on the Model Lists sorted according to their Anatomical Therapeutic Chemical (ATC) classification codes.

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