Report of a comprehensive review of the age-appropriateness of formulations listed on the WHO EMLc

Identification of potential changes and formulations gaps

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Contents

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Abbreviations

EMA	European Medicines Agency
EML	Essential Medicines List
EMLc	Essential Medicines List for children
GAP-f	Global Accelerator for Paediatric Formulations Network
IM	Intramuscular (injection)
IV	Intravenous (injection)
LMICs	Low- and Middle-Income Countries
MHRA	Medicines and Healthcare Regulatory Agency
NEML	National Essential Medicines List
NTDs	Neglected Tropical Diseases
PL	Product Label
pQTPP	paediatric Quality Target Product Profile
QTPP	Quality Target Product Profile
SC	Subcutaneous (injection)
SmPC	Summary of Product Characteristics
SRA	Stringent Regulatory Authority
TB	tuberculosis
TGA	Therapeutic Goods Administration
USA	United States of America
USFDA	United States Food and Drug Administration
USP	United States Pharmacopoeia
WFI	Water for Injection
WHO	World Health Organization

1. Introduction and objectives

In 2007, the World Health Organization (WHO) published its first Model List of Essential Medicines for Children (EMLc)[1] and has since then updated the list every two years, with the most recent update published in October 2021.[2] The EMLc is an evidence-based list of medicines to satisfy the priority health care needs of children up to 12 years of age. Essential medicines are intended "to be available in functioning health systems at all times, in appropriate dosage forms, of assured quality and at prices individuals and health systems can afford". The EMLc is used as a guide by many countries in the development and update of their national essential medicines lists (NEMLs) and paediatric formularies.

Under the framework of the Global Accelerator for Paediatric Formulations (GAP-f),[a] WHO carried out a comprehensive review of medicines listed on the EMLc with a view to inform the next update of the list in 2023.

The review project included the following activities:

1. Identification of formulations of essential medicines that could be proposed for potential addition to the EMLc given their therapeutic utility in children, as well as identification of formulations to be proposed for deletion from the EMLc because they are not appropriate or are not available.

2. Identification of formulation gaps in essential medicines for children to inform additional research and development activities to fill priority unmet formulation needs for the paediatric population.

3. Comparison of the EMLc with the master Model List of Essential Medicines (EML) to identify medicines that have potential therapeutic utility in children but that are not currently included on the EMLc. A systematic comparison of medicines and indications listed on the EML and EMLc was conducted, the results of which are provided in a separate report and will not be discussed in this document.

This report describes the methodology and findings of the EMLc formulations review (i.e., activities 1 and 2, above).

Some general notes should be considered, which apply throughout the report:

- Unless otherwise stated, all medicines and formulations included in the EMLc sections listed below have been reviewed using the pQTPP.
- The report includes only medicines for which recommendations for changes or other gaps were identified as part of this project; no information is provided for medicines for which no changes to the EMLc are proposed as a result of the assessments.
- Considerations around minimizing vial/bottle size wastage according to dose for injectables and oral liquids were not carried out systematically and will require specific analysis in the future.
- Some considerations around acceptability, dose flexibility and administration depend on the dosage form and not on the specific medicine. To avoid repetition, they will not be included in the summary assessments of this report. These considerations are summarized in **Box 1**.

[a] GAP-f (https://www.who.int/initiatives/gap-f) is WHO-hosted platform to provide a sustainable mechanism dedicated to ensuring that the most-needed optimal paediatric formulations are developed and made available to children in a timely manner. GAP-f builds on and complements several initiatives that have emerged to focus efforts to deliver on this global commitment and scale-up activities to ensure that age-appropriate formulations are available for children

Box 1. General considerations around acceptability, dose flexibility and administration.

- Monolithic solid oral dosage forms (tablets and capsules) generally have poor acceptability in children aged below 6 years, due to difficulty in swallowing them. However, this depends on the dimensions of the dosage form and number of units per dose. For example, single 2 mm minitablets may be acceptable from birth whilst multiple 2 mm minitablets may be acceptable from 6 months.[3,4]
- If tablets are chewable, they are generally considered acceptable for children aged 2 years and above.
- Oral liquids are generally considered to have high dose flexibility and are easy to swallow.
- Intravenous and intramuscular injections are generally considered to have high dose flexibility and to be acceptable across the paediatric age spectrum unless pain/discomfort at the injection site is reported.
- The administration of liquid dosage forms generally requires the use of an appropriate device, which if used incorrectly can lead to dosing errors.

- "EML pathway recommendations" refer to recommendations for changes to the formulations that are listed for each medicine. These may include, for example, proposals for addition of a dosage form that may have utility in paediatric patients but that is currently not listed, proposals for addition of a dose strength that may facilitate medicine administration in younger children, removal of formulations/strengths that are not marketed.
- "GAP-f pathway recommendations" refer to gaps identified in terms of lack of age-appropriate formulations that are not currently available and should be promoted for development to fill urgent unmet needs for the paediatric population.
- The complete assessments for each medicine are available upon request. Each excel spreadsheet may include several tabs corresponding to the assessment of a specific dosage form reviewed (e.g., injectables, solid oral dosage forms, oral liquids). A summary tab includes considerations across all dosage forms.
- When possible, assessments were shared and discussed with relevant WHO technical departments for their input and feedback.
- Throughout the report, "Additional findings" refer to comments and feedback received during the expert consultation meeting held on 28-29 November 2022 (refer to Section 3).
- Unless otherwise stated, where a medicine was listed in more than one section, one assessment was performed and reported in one excel file, for all dosage forms and indications listed.
- Sections of the EMLc that were not covered by this project, will be reviewed in 2023-2024, the results of which will feed into the 2025 update of the EMLc.

2. Methodology

Full details of the review methodology were published by Walsh *et al* in February 2022.[5] An extract from this publication is reported below.

To facilitate the review of the paediatric age-appropriateness of formulations on the EMLc, WHO designed and applied an assessment tool. According to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Q8 (R2), "all medicinal products should be designed to meet patients' needs and the intended product performance".[6]

The development and application of a Quality Target Product Profile (QTPP) is a well-recognized tool within pharmaceutical development. The QTPP forms the basis of the design of a drug product and considers various product attributes including for example route of administration, dosage form, dose strength, and container closure, as well as product attributes that impact pharmacokinetic properties and the quality of the drug product.[7] The use of a paediatric-focused QTPP whereby additional attributes of key relevance to paediatric patients are included has been recommended to facilitate the development of new age-appropriate formulations.[8] Although QTPPs are usually used prospectively in the design of new pharmaceutical products, the development and utilization of a new tool, based on a paediatric-specific QTPP (pQTPP), which also included attributes focusing on the needs of low- and middle-income countries (LMICs), was conceptualized by WHO in 2020 to retrospectively evaluate existing formulations on the EMLc. Below, we describe the development of the pQTPP tool, including the design of a scoring system that allows the user to identify gaps in terms of product attributes or specific needs of the paediatric population.

2.1 Development of the pQTPP tool: identifying attributes

The first step in the process for designing the tool was to identify paediatric-centric attributes to be included in the pQTPP. An initial list was collated based upon recommendations and considerations for developing paediatric formulations discussed in regulatory agency paediatric development guidelines and literature sources.[9–14] In addition, the specific needs of, and challenges associated with medicine supply in LMICs were considered, including, for example, high humidity and temperatures, along with rudimentary and fragmented storage and transportation facilities which often lack temperature control.[15] Hence, medicine stability in non-temperate climates is an important attribute as well as the primary packaging, which should ideally be compact with a small bulk footprint, light in weight, and sufficiently robust to withstand transportation in rural areas.[12]

Targets for each of the proposed attributes were then defined based on regulatory guidance documents, taking into consideration the needs of paediatric patients as well as LMICs (**Table 1**).[16]

Table 1. Paediatric Quality Target Product Profile attributes and targets

Attribute	Target	Comments
Target population (age)	Entire age range 0 to ≤ 12 years	• Target population is for WHO EMLc. • Ideally the product should be suitable from birth although patient population age will depend upon the medicine and indication. • The drug product may be restricted to a paediatric age sub-set. • If no age or weight limits are listed, it is assumed the product is intended for 0 - ≤ 12 years.
Dose and dose flexibility	Defined paediatric dose range and dose increments	• Product concentration/strength and format should allow correct and flexible dosing, according to patient age, weight, or body surface area. • Dose banding may be possible.
Patient acceptability	Acceptable for the proposed patient population	• Dosage form must be suitable for use in the proposed paediatric population. • Different dosage forms may be required for different age groups. • Depends on many factors including route of administration, dosage form and patient/caregiver characteristics (including age, disease, ability).
Excipient safety	Excipients with acceptable safety profile for the proposed patient population.	• Excipient benefit versus risk should be considered if product excipients are listed (e.g., on label). • Where excipient details are unavailable, potential excipient risks associated with dosage form should be considered (e.g., preservatives, sweeteners, surfactants, co-solvents in liquids).
Administration considerations	Required doses can be easily and accurately administered, with minimal preparation	• Evaluate according to setting (e.g., domiciliary versus healthcare facility) and characteristics of individual administering the product. • Administration device (if required) should be readily available and appropriate for the intended use. • Multiple dilutions should be avoided. • Guidance on compatible administration vehicle(s)/ diluents and storage time (if required) should be available. • Proposed dosing vehicles should be readily available. • Accuracy of splitting scored tablets (if relevant) to be considered.
Stability, storage conditions and primary packaging material	Stable for 2 years minimum under long term storage conditions (ICH). Packaging suitable for hospital and/or home use, easy to use and unambiguous.	• Global climatic conditions should be considered, including for in-use stability if applicable. • Refrigerated (2-8 °C) and freezer storage is less favourable. • Primary packaging should ideally light-weight, portable and with child-resistant closure. • If specific information on pack and shelf life is unavailable, potential pack options and stability according to dosage form/formulation type should be considered.
Registration status	Positive opinion or approved by a Stringent Regulatory Authority	• Regulatory status and potential registration strategy (if required) to be considered. • Prior approval can facilitate further/subsequent license approvals and WHO pre-qualification.

2.2 Development of the pQTPP tool: qualitative scoring system

Next, in order to evaluate the paediatric-age appropriateness of the EMLc formulations, a scoring method was required. A qualitative scoring system was proposed to assess each medicine dosage form against the target for each predefined attribute.[17] Several scoring and risk assessment approaches were considered, for example, the application of quality risk management tools (ICH Q9)[18] and the use of an evidence to decision framework,[19] the applicability and utility of which were tested using an example EMLc formulation (i.e., amoxicillin powder for oral liquid).
During the testing of potential scoring approaches, it became clear that a simple, qualitative scoring system would meet the needs of the project and enable the identification of potentially unsuitable formulations on the EMLc, as well as paediatric formulation gaps.

A simple, qualitative scoring system (**Table 2**) was devised to minimize complexity and facilitate consistency in evaluations whereby the result of each attribute for each formulation was compared to the target and rated as follows:

- Low risk/no issues; meets target
- Moderate risk/issues; partially meets target.
- High risk/issues; does not meet target.

Each rating was allocated a score and colour, based on a "traffic-light" system, to enable a heat map of each formulation to be visualised. Low risk attributes were scored 3 (green); moderate risk attributes were scored 2 (yellow); and high-risk attributes were scored 1 (red). A score of 0 (grey) was allocated for attributes where there was no or insufficient information to conduct an evaluation.

The weighting or prioritisation of some attributes over others can be applied and was considered for the pQTPP tool but not progressed since such a weighting system would need to be developed and applied on a case-by-case basis. Hence a more generic qualitative approach was deemed to be most appropriate for the aims of the project.

Feedback from WHO disease area focal point and GAP-f partners acquired during demonstrations of the tool supported the use of this scoring system.

Table 2. Paediatric Quality Target Product Profile tool scoring criteria

Attribute	**Considerations for Scoring**		
	High risk/issues; does not meet target Score = 1	**Moderate risk/issues; partially meets target Score = 2**	**Low risk/no issues; meets target Score = 3**
Target population (age) (0-≤12 years)[1]	• Not suitable for all or the majority of patients aged less than 12 years.	• Suitable for most of the API indicated paediatric population.	• Suitable from birth. • Suitable for the API indicated age range.
Dose and dose flexibility[2]	• Lack of, or poor dose flexibility. • Not able to administer the required doses without manipulation.	• Some limited dose flexibility, (e.g., limited dose strengths available). • Not able to administer the required doses to some patients.	• High dose flexibility. • Able to easily measure and administer the required doses to all patients.

Patient acceptability[3] **0-5 years**	• Unacceptable for this age range, e.g., conventional tablets/capsules. • Anticipated to have strongly aversive taste, painful injection etc.	• Some concerns re. acceptability in this age range, e.g., poor palatability, frequent dosing, formulation unsuitable for some patients.	• Acceptable for this age range.
Patient acceptability[3] **6-12 years**	• Unacceptable for this age range, e.g., high volumes of oral liquids, large quantities of multiparticulates/ (mini) tablets per dose. • Anticipated to have strongly aversive taste, painful injection etc.	• Some concerns re. acceptability in this age range, e.g., poor palatability, frequent dosing, formulation unsuitable for some patients.	• Acceptable for this age range.
Excipient safety[4]	• Contains several excipients of potential or known concerns.	• Contains 1 or 2 excipients of potential concern.	• Contains excipients which generally have an acceptable safety profile.
Administration considerations[5]	• Complex manipulation required, e.g., reconstitution with fixed volume of vehicle (domiciliary use), multiple dilutions (HCP and domiciliary use). • Complex administration device/procedure (HCP and domiciliary use).	• Some manipulation required (e.g., food mixing), or measurement of dose required (domiciliary use). • Some manipulation required (e.g., food mixing, reconstitution with fixed volume of vehicle), or measurement of dose required (HCP use).	• No manipulation or measurement required (domiciliary use). • No manipulation required, easy to measure and administer required doses (HCP use).
Stability, storage conditions, primary packaging material[6]	• Requires freezer or refrigerated storage. • Less than 18 months shelf life. • Bulky/heavy packaging. • Complex packaging design.	• May be stored under room temperature conditions[7], but constituted product requires refrigerated storage. • Requires protection from moisture. • Less than 2 years shelf life.	• May be stored under room temperature[7] conditions. • Minimum 2-year shelf life. • Light packaging with low bulk footprint. • Simple packaging design.
Registration status	• Not approved by any Regulatory Authorities and no approvals anticipated.	• Approved by a Regulatory Authority with maturity level 3 and above[8]. • Approval by stringent Regulatory Authority anticipated.	• Approved by at least one Stringent Regulatory Authority.

[1] The lowest indicated or recommended age should be considered. Minimum age may be older than from birth. For example, if the condition is only prevalent or possible to diagnose from 3 years, minimum target age = 3 years.

[2] Strength or concentration should allow the required doses to be accurately and easily administered. Tablet splitting may be permitted if supported by the product licence. Dose banding may be possible.

[3] Score according to age group. Numerous factors involved – an overall score should be applied. Excipient considerations should be excluded and scored separately. Frequent dosing is mitigated by short-term use.
[4] Excipient safety will depend on the route of administration. Neonates and infants are more vulnerable to excipient "adverse effects" compared to older children.
[5] Need to consider setting, availability of device (if required), complexity of process, potential for mis-dosing or dosing errors.
[6] If shelf life is not listed in label, consider dosage form/formulation type, handling, required storage conditions and packaging type.
[7] Defined here as 20–25 °C (USP <659> Packaging and Storage Requirements defines controlled room temperature as 20–25 °C).
[8] Maturity level 3 is defined as "stable, well-functioning and integrated regulatory systems"; maturity level 4 is defined as "regulatory systems operating at advanced level of performance and continuous improvement".

2.3 Application of the pQTPP tool: formulation evaluation process

Finally for the formulation evaluation process, regulatory agency approved SmPCs or labelling was used as the primary source of information for medicines, from which details such as indicated age range, posology, dose administration instructions, excipients, primary packaging, shelf life, and storage conditions could be extracted. The results of these searches were recorded in the tool according to each attribute and compared against the target, and then scored as discussed above (**Table 2**). For formulations where more than one product licence is available, an overview of the results for each attribute were recorded. The dose flexibility of the formulation was evaluated considering the required posology and concentration or dose strength of the medicine. Where dose information was provided on a mg/kg basis, required doses according to age were estimated using 50th percentile figures recorded on WHO weight-for-age charts.[20] Acceptability was evaluated using literature sources of information.[21] The potential risk of the inclusion of an excipient within a formulation depends on various factors including its dose, route of administration, the age of the patient, duration of treatment, and indication. Since precise information on the full quantitative composition of formulations is not available in the public domain, this attribute was evaluated by considering the presence of potential excipients of concern within the formulations, as well as their quantity if reported and their potential function. For example, the inclusion of ethanol or propylene glycol as a solvent within a liquid formulation would be considered a much higher risk compared to their inclusion at a very low concentration within a flavouring. Where quantitative information on an excipient was provided, the total daily intake on a mg per kg body weight basis was estimated and compared with available safety information, for example, WHO and European Food Safety Authority (EFSA) derived acceptable daily intakes (ADIs).

For the administration of liquids, the ability to measure doses accurately is required to reduce the risk of dosing errors. This is especially important in young patients where low dose volumes may be required; volumes less than 0.1 mL were considered to be unacceptable.[22] However, appropriately sized syringes should be used, and it is recognised that in a domiciliary setting, untrained or inexperienced caregivers may have greater difficulty in identifying and measuring correct doses compared to trained healthcare professionals.

3. Additional findings and consultation

The findings of this report were presented during a consultation meeting with international paediatric experts and other stakeholders held virtually on 28 and 29 November 2022, alongside findings from additional work conducted by collaborators from the PENTA Foundation and St George's University of London (SGUL) that formed part of an overarching project which sought to evaluate access and availability of age-appropriate formulations of essential medicines for children. Relevant findings from this additional work, as well as input and feedback from experts during the consultation are presented within the report as "Additional findings".

3.1 PENTA Foundation – health care professionals surveys

Two online surveys were carried out to garner the views and experiences of front-line health care professionals (doctors, pharmacists, nurses) with respect to various aspects of availability and use of paediatric medicines e.g. acceptability from a child's perspective, ease of use by caregivers, need for extemporaneous preparation, off-label use, concerns regarding pharmacokinetics (PK),dose selection and safety, need for accelerated paediatric development, lack of child-appropriate formulations and obstacles to access.

The summary report of findings is available at Annex A.

3.2 St George's University of London – market landscape assessments

Data from global wholesale pharmacy sales, procurement databases, and household and health facility surveys were collected and analysed to identify child-appropriate formulations likely to be prescribed to children and assess usage patterns these formulations for EMLc-listed medicines. Descriptive analyses were performed, including frequencies and percentage for each therapeutic class. The initial analyses were carried out to assess the overall prescribing patterns of EMLc medicines. Following the initial analyses, the percentages of child-appropriate formulation use by formulation types were calculated, of which the percentage of dispersible tablets (DTs) and non-DTs (e.g. syrup, powder) were analysed. Analyses were presented by country and WHO region.

The summary report of findings is available at Annex B.

4. Assessments

General considerations that the authors of this report recommend adding to the EMLc as overarching principles and comments include:

- When both sugar-free formulations and sugar-including formulations are available, the preference should be given to the former.
- Enteric-coated tablets should not be broken nor crushed, as this may have implications for bioavailability.
- Tablets that can be administered whole or dispersed in water or other media (after crushing them) and were not developed and registered as dispersible tablets, are not identified as “dispersible” in the EMLc.
- When tablets are available both as unscored and as functionally scored tablets, preference should be generally given to the procurement of functionally scored tablets, as they allow for a higher dose flexibility which is particularly important for younger children.

Section 2.1 Non opioids and non-steroidal anti-inflammatory medicines

Ibuprofen

Current listing in section 2.1	Proposed listing in section 2.1
Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg	Oral liquid: **100 mg/5 mL**; 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg

Assessment findings

- Numerous formulations of ibuprofen oral liquid are available; sugar-containing and sugar free. The oral liquid did not meet the target for excipient safety since it generally contains several excipients of concern, e.g., sucrose, sorbitol (syrup-based variants), maltitol (sugar-free variants), preservatives, sweeteners, colorant. It should be noted sugar-free colour-free formulations had the most acceptable excipient safety profile.
- The shelf of the oral liquid may be limited (1-2 years) with an in-use shelf-life of 3-6 months.
- A 100 mg/5mL oral liquid is available in some markets and may facilitate dosing in young patients (e.g., 3-4x day dosing 3-12 months 50 mg, 1-4 years 100 mg, 4-7 years 150 mg).
- The tablet was not acceptable for patients unable to swallow them and those requiring a lower dose than 200 mg (< 6/7 years).
- Other age-appropriate ibuprofen oral dosage forms are available in some markets, e.g., oro-dispersible tablets, but may be more costly than the dosage forms currently listed.

Additional findings

- Market availability of a 100 mg/5mL oral liquid formulation was reported in sales/procurement datasets evaluated by SGUL.
- From the PENTA surveys of health professionals, the 200 mg/5 mL oral liquid formulation was reported by some health professionals as being associated with dosing errors due to its high concentration. A lower concentration presentation was considered desirable.

Recommendation for the EMLc pathway

- It is recommended that the 100 mg/5mL concentration of ibuprofen oral liquid be considered for addition to the EMLc to facilitate dosing in young patients. However, it is acknowledged that this product may have similar excipient and stability/pack attributes as the 200 mg/5mL strength product, and clear differentiation from the lower concentration oral liquid is required to avoid dosing errors.
- Ibuprofen is also listed in Section 7.1 of the EMLc (Treatment of acute migraine attack). It is recommended the oral liquid formulations be considered for addition to this section of the EMLc for patients who may have difficulty in swallowing tablets.
- It is recommended the global availability of oro-dispersible tablets is evaluated and the feasibility of their addition to the EMLc is considered, due to their acceptability in young patients, lower bulk footprint and likely superior excipients safety compared to the oral liquid.

Paracetamol (acetaminophen)

Current listing in section 2.1	Proposed listing in section 2.1
Oral liquid: 120 mg/5 mL; 125 mg/5 mL Suppository: 100 mg Tablet: 100 mg to 500 mg	Oral liquid: 120 mg/5 mL **OR** 125 mg/5 mL*; **250mg/5mL** Suppository: 100 mg; **250 mg** Tablet: ~~**100 mg to 500 mg**~~ **250 mg; 325 mg; 500mg** **Tablet (dispersible) 100 mg; 250 mg** ***The presence of both 120 mg/5 mL and 125 mg/5mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided.**

Assessment findings

- Numerous formulations of paracetamol oral liquid are available; sugar-containing and sugar free. The oral liquid did not meet the target for excipient safety since it generally contains several excipients of concern, e.g., sucrose or sorbitol, preservatives, sweeteners, and may contain colorant.
- Older children may require large dose volumes of the current dose strengths. E.g., 5/6 years 10 mL, 8/10 years 15 mL. Other concentrations of paracetamol oral liquid are available in some markets, e.g., 160 mg/5 mL and 250 mg/5 mL, which may mitigate this.
- The suppositories were considered acceptable from approximately 1 year of age (depending on product licence). However, they only partially met the dose flexibility attribute and acceptability attribute for older children due to the latter requiring several suppositories per dose.
- Other dose strengths of paracetamol suppository are available, depending on the market, e.g., 60, 80, 120, 125, 250, 325, 500 mg, some of which may be more appropriate for older children.
- The tablet was not acceptable for patients unable to swallow them. Various dose strengths appear to be available, depending on market, e.g., 250, 325, 500 mg, although a 100 mg dose strength conventional tablet was not identified in any of the SRA markets interrogated.
- Dispersible paracetamol tablets are available in some markets and may have superior excipient safety and bulk footprint compared to the oral liquid.
- Other age-appropriate paracetamol oral dosage forms are available in some markets, e.g., chewable tablets, oro-dispersible tablets, but may be more costly than the dosage forms currently listed.

Additional findings

- While paracetamol is the international non-proprietary name (INN), it is also commonly known by the United States Adopted Name (USAN) “acetaminophen”. Including acetaminophen as an alternative name in the listing for paracetamol is suggested.
- The availability of two similar strengths of paracetamol oral liquid (120 mg/5 mL and 125 mg/5 mL) in the same market could contribute to confusion in prescribing/dispensing and dosing errors, as well as market fragmentation. This should be avoided wherever possible. The addition of a cautionary note to this effect in the EMLc is suggested.
- The inclusion of a higher strength oral liquid formulation (250 mg/5 mL) is supported as it would allow lower volumes to be administered. It is a stock item in the UNICEF supply catalogue.
- Shortages have been reported of rectal formulations of paracetamol. Paracetamol 250 mg suppository is a stock item in the UNICEF supply catalogue.

- Dispersible tablet formulations of paracetamol (100 mg and 250 mg) are stock items in the UNICEF supply catalogue.
- Intravenous paracetamol has an important role in some clinical settings (eg. post-operative, opioid-sparing) and should be evaluated for inclusion in the EMLc in the future.

Recommendation for the EMLc pathway

- It is recommended that the 250 mg/5mL concentration of paracetamol oral liquid be considered for addition to the EMLc to facilitate dosing older patients, by reducing required dose volumes. However, it is acknowledged that this product may have similar excipient attributes as the lower strength products, and clear differentiation between products is required to avoid dosing errors.
- It is recommended that 250 mg strength paracetamol suppositories be considered for addition to the EMLc, to reduce the number of suppositories required per dose for older children.
- It is recommended that the strengths of paracetamol tablets on the EMLc be specified, rather than be presented as a range; it is proposed to remove the 100 mg strength and amend the entry to 250 mg, 325 mg and 500 mg strengths.
- It is recommended that paracetamol dispersible tablets 100 mg and 250 mg be considered for addition to the EMLc, due to their acceptability in young patients, lower bulk footprint and likely superior excipients safety compared to the oral liquid.

Section 5 Anticonvulsants / antiepileptic

Carbamazepine

Current listing in section 5	Proposed listing in section 5
Oral liquid: 100 mg/5 mL. Tablet (chewable): 100 mg; 200 mg. Tablet (scored): 100 mg; 200 mg.	Oral liquid: 100 mg/5 mL. Tablet (chewable): 100 mg; 200 mg. Tablet (scored): 100 mg; 200 mg; **400 mg**

Assessment findings

- The availability of three dosage forms in the EMLc covers the need of the entire paediatric population, with chewable tablets and oral liquids being more acceptable to younger children (or older children who cannot swallow tablets whole). Tablets can be used to deliver appropriate dose in older/heavier children.
- At the WHO recommended dose of 5 mg/kg daily in 2-3 divided doses, followed by 5 mg/kg daily increases each week (max 40 mg/kg daily OR 1400 mg daily), tablet burden for older/heavier children becomes high at some stages of the treatment. Therefore, the availability of a higher strength tablet would increase acceptability by reducing tablet burden.
- A 400 mg tablet of carbamazepine was identified in some markets.

Additional findings

- From the PENTA surveys of health professionals, it was reported that children experience a significant pill burden with carbamazepine and the availability of a higher strength formulation would be beneficial to address this.

Recommendation for the EMLc pathway

- Considering the WHO recommended dosage for carbamazepine, the addition of the 400 mg tablet strength should be considered, to reduce pill burden in older/heavier children.
- This recommendation applies to the WHO EML as well.

Diazepam

Current listing in section 5	Proposed listing in section 5
Gel or rectal solution: 5 mg/mL in 0.5 mL; 2 mL; 4 mL tubes.	**Rectal solution: 2 mg/mL in 1.25 mL and 2.5 mL; 4 mg/mL in 2.5 mL rectal tubes** **Rectal gel: 5 mg/mL in 0.5 mL, 2 mL and 4 mL rectal delivery systems**

Assessment findings

- Gels and rectal solutions are two different formulations, and thus they were assessed separately.

  Rectal solutions
  - The currently listed rectal solutions correspond to 2.5 mg, 10 mg and 20 mg of diazepam API included in the solution. However, marketed formulations of diazepam rectal solutions identified in the context of this project correspond to 2.5 mg, 5 mg and 10 mg.
  - Diazepam rectal solution is also listed in section 2.3 (medicines for other symptoms common in palliative care) of the EMLc as "rectal solution: 2.5 mg, 5 mg, 10 mg", which is in line with the identified marketed formulations.
  - No additional rectal solution strength was identified as part of this review or flagged by WHO technical experts as available in some countries.

  Rectal gels
  - Rectal gels are available in standard rectal delivery systems
  - Available strengths found in some markets as part of this project correspond to 2.5 mg, 10 mg and 20 mg, in line with what already listed in the EMLc.

Recommendation for the EMLc pathway

- Gels and rectal solutions are two different formulations and, as such, it is recommended they be listed separately in the EMLc.
- It is also recommended that the listing aligns with how these formulations are indicated in the product packages/labels, ie: "rectal solutions in rectal tubes" and "rectal gels in rectal delivery systems".
- **Rectal solutions**
  - It is recommended that currently listed strengths (2.5 mg, 10 mg and 20 mg) are replaced with the marketed strengths identified in the context of this review (2.5 mg, 5 mg and 10 mg). In fact, this is in line with what already listed for diazepam in section 2.3 of the EMLc.
  - It is also recommended that the listing is updated to convey all information that is relevant for procurement purposes in terms of mg, volume and concentration.
  - This recommendation applies also to diazepam as listed in section 2.3 (medicines for other symptoms common in palliative care), where the medicine is currently listed as "Rectal solution: 2.5 mg; 5 mg; 10 mg".
- **Rectal gels**
  - No additional modification proposed to the way rectal gels are currently listed, as the listing already conveys all the relevant information in terms of mg, volume and concentration and it corresponds to strengths and formulations that were found in some markets as part of this project. This is also in line with the proposed new listing for rectal solutions.

Midazolam

Current listing in section 5	Proposed listing in section 5
Solution for oromucosal administration: 5 mg/mL; 10 mg/mL Ampoule*: 1 mg/mL; 10 mg/mL	**Solution for oromucosal administration**: 5 mg/mL **(in 0.5 ml, 1 ml, 1.5 ml, 2 ml pre-filled oral syringes);** 10 mg/mL **(in 0.25 ml, 0.5 ml, 0.75 ml and 1 ml pre-filled oral syringes).** ~~**Ampoule**~~**Solution for injection*:** 1 mg/mL **in 5 mL vial; 5 mg/mL in 1 mL or 3 mL vial;** ~~10 mg/mL~~
*For buccal administration when solution for oromucosal administration is not available	*For buccal administration when solution for oromucosal administration is not available

Assessment findings

- Current listing of midazolam solution for oromucosal administration only indicates the solution concentration, without any information on the volume of the solution or the amount of API included in the solution. This could correspond to a variety of different products in terms of the actual volume of the solution and mg of the API, causing procurement issues or favoring access to midazolam solutions that are not quality assured.
- By reviewing SRA databases, we identified several available strengths of midazolam solution for oromucosal administration corresponding to the two concentrations (5 mg/mL and 10 mg/mL) listed in the EMLc.
- It should also be noted that midazolam solution for oromucosal administration is supplied in pre-filled oral syringes.
- A similar issue was noted for midazolam ampoules (for buccal administration), where only the solution concentration is listed, without any information on the volume or the amount of API included.
- By reviewing SRA databases, we identified only one strength of midazolam ampoules 1 mg/mL listed in the EMLc, corresponding to 5 mg (1 mg/mL in 5 mL)
- Moreover, no ampoule at 10 mg/mL concentration was found. Instead, 5 mg/mL solutions were found in some markets, in particular 1 mL and 3 mL vials.

Additional findings

- The current description in the EMLc of the ampoule formulation for buccal administration was considered to be unclear and may give rise to confusion. It is intended to represent the solution for injection formulation, to be administered via the buccal route. Improved clarity in the listing is suggested.

Recommendation for the EMLc pathway

- Considering that several strengths of solution for oromucosal administration were identified in the markets reviewed, we recommend listing these formulations by conveying all relevant information in the EMLc listing, ie concentration and volume of the vial.
- We also recommend that the listing reflects that solutions for oromucosal administration are supplied as pre-filled oral syringes.
- Considering that several strengths of midazolam solution for injection were identified in the markets reviewed, we recommend listing these formulations by conveying all relevant information in the EMLc listing, ie concentration and volume of the vial.

- Considering that 10 mg/mL solution for injection was not found marketed, we recommend removing this concentration from the EMLc listing and rather list the identified 5 mg/mL concentration and vial sizes.

Phenobarbital

Current listing in section 5	Proposed listing in section 5
Injection: 200 mg/mL (sodium). Oral liquid: 15 mg/5 mL. Tablet: 15 mg to 100 mg.	Injection: **30 mg/mL or 60 mg/mL;** 200 mg/mL (sodium). Oral liquid: 15 mg/5 mL. Tablet: 15 mg to 100 mg.

Assessment findings

- The recommended dose for parenteral phenobarbital varies depending on the product label. As an anticonvulsant it may be given at an initial loading dose of 10-20 mg/kg, followed by a maintenance dose of 1-6 mg/kg daily. It can be administered as an IM injection or, after 1:10 dilution, by IV injection.
- The WHO recommended dose for management of status epilepticus is 15-20 mg/kg IV or IM, up to a maximum dose of 1 g.[23]
- The 200 mg/mL solution for injection is a high strength formulation which, depending on the dose, type of administration (IM or IV) and indication, may result in a high-volume wastage. For example, when given as an anticonvulsant by IM injection, the dose for a 20 kg child would be 20-120 mg/kg and, if targeting the lower end of the dose range, only 10% of the solution for injection would be used, while the rest should be discarded.
- Phenobarbital as a solution for injection at lower concentrations was found in some markets. Available strengths found included: 30 mg/mL and 60 mg/mL. Phenobarbital (as a powder for injection to be reconstituted prior to administration) was also found in some markets as 20 mg/mL and 50 mg/mL. However, powders for injection require reconstitution which is not ideal especially for LMICs settings.

Additional findings

- Phenobarbital oral liquid is known to have a high alcohol content, resulting in high blood alcohol levels following administration. Phenobarbital oral liquid is often compounded extemporaneously from other dosage forms in the hospital setting. There is a need for a phenobarbital sodium oral liquid formulation or other alcohol-free formulation.
- Global shortages of phenobarbital formulations are commonly reported.

Recommendation for the EMLc pathway

- Given that the currently listed solution for injection is a high-strength formulation that may result in a lot of wastage depending on the indication, dose and type of administration, we recommend considering the inclusion of a lower strength formulation that would facilitate administration of lower doses while avoiding volume wastage. Among the lower-strength formulations of ready-made solutions for injections found on some markets, we recommend selecting one among the 30 mg/mL and the 60 mg/mL after assessing which one is more broadly used/available in the countries that are still using this medicine.

Phenytoin

Current listing in section 5	Proposed listing in section 5
Injection: 50 mg/mL (sodium) in 5 mL vial. Oral liquid: 25 mg to 30 mg/5 mL.* Solid oral dosage form: 25 mg; 50 mg; 100 mg (sodium). 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.	Injection: 50 mg/mL (phenytoin sodium) ~~in 5 mL vial.~~ Oral liquid: ~~25 mg to~~ **30 mg/5 mL (phenytoin).**~~*~~ Solid oral dosage form: 25 mg; 50 mg; 100 mg (phenytoin sodium). Tablet (chewable): 50 mg **(phenytoin).** ~~*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.~~

Assessment findings

- Phenytoin injection was found in some markets at the concentration listed in the EMLc (50 mg/mL) in several vial sizes, including 5 mL (listed in the EMLc) and 2 mL. Lower volume ampoules may be the only ones available in some markets and would also potentially help to reduce volume wastage when dosing younger children.
- Phenytoin oral liquid 25 mg/5 mL was not found available in any of the markets reviewed.
- A higher strength oral liquid formulation (ie, 125 mg/5 mL) was found available in some markets. This higher strength formulation could be used to dose older/heavier children who would be given a lower volume of the oral liquid solution, which would potentially increase acceptability. However, the availability of solid oral dosage forms of several strengths and 50 mg chewable tablets (both listed on the EMLc) already covers the dosing needs for this specific subgroup. Therefore, a proposal for inclusion of the 125 mg/5 mL oral liquid formulation is not put forward.

Additional findings

- Phenytoin containing preparations may contain phenytoin sodium or phenytoin (free acid form). This should be made more explicit in the listings. The two forms are not bioequivalent. Formulations using the free acid form have approximately 8% greater phenytoin drug content, which may have clinical implications when switching between formulations.

Recommendation for the EMLc pathway

- Considering the availability of more vial sizes for phenytoin injection found in some markets – including lower-volume ones that could potentially reduce volume wastage – we recommend removing the reference to the 5 mL vial size and only list phenytoin injection with the relevant concentration (50 mg/mL), not to limit access to phenytoin formulations that may be available in some countries.
- Considering that a 25 mg/5 mL oral liquid formulation of phenytoin could not be found marketed, we recommend listing the oral liquid formulation only as 30 mg/5 mL and remove the footnote indicating that the presence of both the 25 mg/5 mL and 30 mg/5 mL strengths on the same market should be avoided.

Valproic acid (sodium valproate)*

Current listing in section 5	Proposed listing in section 5
Oral liquid: 200 mg/5 mL. Tablet (crushable): 100 mg. Tablet (enteric-coated): 200 mg; 500 mg.	*No modification proposed. Some considerations for the expert group listed below.*
**avoid use in pregnancy and in women and girls of child-bearing potential, unless alternative treatments are ineffective or not tolerated because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb*	

Assessment findings

- In addition to the oral liquid formulation listed in the EMLc (200 mg/5 mL), several other oral liquid solutions, at different concentrations, were found in some markets. However, considering that the identified strengths have similar concentrations to the strength already listed (eg, 300 mg/5 mL, 50 mg/mL) and do not bring any remarkable added value from a dosing perspective, and also acknowledging safety concerns around the use of valproic acid in women and girls of child-bearing potential (as indicated in the EMLc footnote), no recommendation is put forward to include additional oral liquid strengths.

Valproic acid (sodium valproate)* (complementary list)

Current listing in section 5 (Complementary list)	Proposed listing in section 5 (Complementary list)
Injection: 100 mg/mL in 4 mL ampoule; 100 mg/mL in 10 mL ampoule.	Injection: 100 mg/mL in **3 mL**, 4 mL, 10 mL ampoules.
**avoid use in pregnancy and in women and girls of child-bearing potential, unless alternative treatments are ineffective or not tolerated because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb*	**avoid use in pregnancy and in women and girls of child-bearing potential, unless alternative treatments are ineffective or not tolerated because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb*

Assessment findings

- An additional ampoule of 3 mL volume (at the same concentration listed in the EMLc, ie, 100 mg/mL) was found in some markets.
- The use of a lower-volume ampoule has also the potential to minimize liquid wastage, especially when dosing younger children.

Recommendation for the EMLc pathway

- Considering the availability of a 3 mL volume ampoule in some markets, which has also the potential to minimize volume wastage, it should be considered for addition to the EMLc.

Section 6.1.1 Intestinal anthelminthics

Ivermectin

Current listing in section 6.1.1	Proposed listing in section 6.1.1
Tablet (scored): 3 mg.	Tablet ~~(scored)~~: 3 mg

Assessment findings

- Ivermectin is indicated for use in children weighing 15 kg and above. The 3 mg tablet of ivermectin is not scored and not dispersible. Even though the tablet is small (approximately 5 mm diameter), there may be acceptability issues for children below 6 years of age who cannot swallow tablets whole.

Additional findings

- From the PENTA surveys of health professionals, acceptability issues with the swallowability and taste of oral ivermectin tablets were reported.

Recommendation for the EMLc pathway

- Considering that ivermectin 3 mg tablets are not scored, we recommend removing that specification from the EMLc listing. We recommend this change to apply to all sections where ivermectin 3 mg tablets are listed (ie, 6.1.2 antifilarials and 6.6 medicines for ectoparasitic infections).

Recommendation for the GAP-f pathway

- Despite the relatively small size of the tablet, there may be acceptability issues for young children who are given ivermectin, as the tablet should be taken whole. We recommend looking into the potential development of an age-appropriate formulation of ivermectin (ie, dispersible tablets) which can ease administration in younger children for whom the medicine is indicated.

Levamisole

Current listing in section 6.1.1	Proposed listing in section 6.1.1
Tablet: 50 mg; 150 mg (as hydrochloride)	Tablet: 50 mg; ~~150 mg~~ (as hydrochloride)

Assessment findings

- Unlike other medicines for NTDs, levamisole is not supplied to countries through a donation programme. Levamisole is used especially in case of resistance to other anthelminthics.
- Considering the WHO recommended dose of 2.5 mg/kg for adults and children for both individual treatment and community-based campaigns,[24] the 150 mg tablet of levamisole has no utility to dose children aged 0-12 years.

Recommendation for the EMLc pathway

- Given the lack of utility of the 150 mg tablet of levamisole to deliver the recommended dose to children aged 0-12, we recommend removing this specific strength from the EMLc. Levamisole 150 mg tablets will remain listed on the EML.

Praziquantel

Current listing in section 6.1.1	Proposed listing in section 6.1.1
Tablet: 150 mg; 600 mg	Tablet: 150 mg; **500 mg** Tablet **(scored):** 600 mg

Assessment findings

- The dose of praziquantel as an anthelminthic varies depending on the parasite, eg: 5-10 mg/kg for intestinal taeniasis (single dose); 15-25 mg/kg for hymenolepiasis (single dose). 600 mg tablets allow for a good dose flexibility allowing for x300 mg, x200 mg or x150 mg dose increments depending on the number of functional scoring lines included (depending on the manufacturer, 600 mg tablets may have 1-3 scoring lines). Irrespective of the dose, acceptability of praziquantel 150 mg and 600 mg tablets in young children and older children who are not able to swallow tablets whole, is very low.
- Praziquantel orodispersible tablets (150 mg) are currently being developed, and market availability is expected in Q4 2022/Q1 2023, upon EMA approval.
- Praziquantel tablets 150 mg (non-dispersible) are still being manufactured in China and supplied to and used in some countries.
- A 500 mg tablet formulation is also available and already listed in other sections of the EMLc.
- Availability of either the 500 mg or the 600 mg formulation vary depending on the country.

Recommendation for the EMLc pathway

- Considering the upcoming availability of praziquantel 150 mg orodispersible tablets, which would enable better dosing of younger children, we recommend an application be sought for inclusion of this tablet strength in the EMLc, for consideration by the EML expert committee.
- Given that non-dispersible 150 mg tablets are still produced and supplied to some countries, we recommend retaining this formulation on the EMLc.
- Given that 600 mg tablets have functional scoring lines that allow for high dose flexibility, we recommend specifying this information in the EMLc listing without going into the details of the number of scoring lines, as that depends on the manufacturer.
- Considering that 500 mg praziquantel tablets may also be available in some countries and that this tablet strength is already listed in the EMLc, we recommend its inclusion in section 6.1.1.
- These recommendations apply also to sections 6.1.3 and 6.1.4.

Pyrantel

Current listing in section 6.1.1	Proposed listing in section 6.1.1
Oral liquid: 50 mg (as embonate or pamoate)/mL Tablet (chewable): 250 mg (as embonate or pamoate)	~~Oral liquid: 50 mg (as embonate or pamoate)/mL~~ Tablet (chewable): 250 mg (as embonate or pamoate)

Assessment findings

- Pyrantel, like levamisole, is not widely used in control programmes. Its use is limited to those cases where resistance to other more widely used anthelminthics is detected. In mass treatment control programmes, it is given as a single dose of 2.5 mg/kg, three to four times a year to reduce the prevalence of ascariasis.
- To eliminate cases of hookworm infections, ascariasis, enterobiasis and trichostrongyliasis, it is given at a single dose of 10 mg/kg. Patients with enterobiasis should receive a second dose after 2-4 weeks.
- 250 mg chewable tablets have a scoring line, but it is unclear whether this allows for administration of two equal doses (ie, functional scoring line). The presence of a functional scoring line would increase dose flexibility.
- A 125 mg formulation of pyrantel was also found in some markets, but no additional information about the presence of a functional scoring line or the possibility to chew them could be found.
- The oral liquid formulation allows for a high dose flexibility, and it is acceptable from birth. However, issues with API precipitation were noted by WHO focal points, especially when the oral liquid formulation is kept for a long time, with the consequence of potential underdosing over time.

Recommendation for the EMLc pathway

- We recommend collecting additional information on pyrantel tablets, including the presence of a functional scoring line in both the 250 mg and the 125 mg tablet formulations and the chewability of the 125 mg tablet formulation, to evaluate whether the proposal for adding of a 125 mg tablet strength should be put forward.
- Given issues with API precipitation in the oral liquid formulation, and potential risk of underdosing if the oral liquid is stored for a long time, while also considering the limited use of pyrantel, we recommend removing the oral liquid formulation from the EMLc.

Section 6.1.2 Antifilarials

Diethylcarbamazine

Current listing in section 6.1.2	Proposed listing in section 6.1.2
Tablet: 50 mg; 100 mg (dihydrogen citrate)	*No modifications proposed*

Assessment findings

- Diethylcarbamazine could not be found registered at any of the SRAs reviewed as part of this project. The medicine was discontinued at the USFDA. 100 mg functionally scored tablets from two manufacturers are prequalified by WHO.
- The recommended dose for adults and children above 2 years of age for large scale preventative chemotherapy interventions for the control of lymphatic filariasis is 6 mg/kg (single, annual dose over 4-6 years), given with albendazole 400 mg in areas where onchocerciasis is not co-endemic. Children below 2 years of age, as well as pregnant women and lactating mothers, elderly and those with chronic or debilitating illnesses, are not included in mass drug administration programmes.

Recommendation for the EMLc pathway

- We recommend exploring the market availability of 50 mg diethylcarbamazine tablets and, depending on the result of this assessment consider removing this tablet strength from the EMLc, also noting that the 100 mg tablets which are prequalified by WHO have a functional scoring line that allows for 50 mg dose increments.

Recommendation for the GAP-f pathway

- Acknowledging that children below 2 years of age are not included in mass administration programmes, there are acceptability issues for children aged 2-6 years, who are not able to swallow tablets whole. Considering this, we recommend looking into the relevance of potentially developing an age-appropriate formulation of diethylcarbamazine that is acceptable also for younger children.

Ivermectin

See the assessment findings and recommendations in section 6.1.1 Intestinal anthelminthics

Section 6.1.3 Antischistosomals and other antitrematode medicines

Praziquantel

Current listing in section 6.1.3	Proposed listing in section 6.1.3
Tablet: 600 mg	Tablet: 150 mg; **500 mg** Tablet **(scored):** 600 mg

Assessment findings

- The dose of praziquantel as an antischistosomal is 40 mg/kg as a single dose. For mass drug administration as preventive chemotherapy, recommended by WHO for children aged 2 years and above, the dose corresponds to 40-60 mg/kg as a single dose given annually (or biannually, if there is a demonstrated lack of appropriate response to annual preventive chemotherapy, despite adequate treatment coverage).[25]
- All findings and considerations in section 6.1.1 apply.

Recommendations for the EMLc pathway

See section 6.1.1

Triclabendazole

Current listing in section 6.1.3	Proposed listing in section 6.1.3
Tablet: 250 mg	Tablet **(scored)**: 250 mg

Assessment findings

- Triclabendazole 250 mg tablets have a functional scoring line, which allows for 125 mg dose increments. This is particularly relevant considering the recommended dose of 10 mg/kg every 12 years for people aged 6 years and above.

Recommendation for the EMLc pathway

- We recommend specifying that triclabendazole 250 mg tablets are scored.

Oxamniquine*

Current listing in section 6.1.3 (complementary list)	Proposed listing in section 6.1.3 (complementary list)
Capsule: 250 mg Oral liquid: 250 mg/5 mL	*No modifications proposed*
**For use when praziquantel treatment fails*	

Assessment findings

- The formulations of oxamniquine listed in the EMLc could not be found registered at the SRAs reviewed as part of this project. 250 mg capsules were discontinued at the USFDA.
- Considering the WHO recommended doses – which vary depending on the geographical region, eg, 30 mg/kg in two divided doses in East and Central Africa and the Arabian Peninsula; 60 mg/kg over 2-3 days in Egypt and Southern Africa –, capsules allow for a very limited dose flexibility and acceptability is limited in younger children and children who cannot swallow them whole. The availability of the oral liquid formulation allows to administer the required dose across the paediatric population, with increased acceptability.

Recommendation for the EMLc pathway

- We recommend looking into the global availability and use of the 250 mg capsules and the 250 mg/5 mL oral liquid formulation and potentially consider removing capsules if not used/not available, also considering the limited utility to dose young children, the limited dose flexibility that they offer, as well as noting that the use of oxamniquine is limited to cases when treatment with praziquantel fails.

Section 6.1.4 Cysticidal medicines

Albendazole

Current listing in section 6.1.4 (complementary list)	Proposed listing in section 6.1.4 (complementary list)
Tablet (chewable): 400 mg	**Tablet (chewable): 200 mg** Tablet (chewable, **scored**): 400 mg

Assessment findings

- The dose of albendazole for echinococcosis and cysticercosis in adults and children is 10-15 mg/kg/day, divided in two doses.
- A lower strength chewable tablet (ie, 200 mg) was found in some markets. These tablets (like the listed 400 mg ones) may be crushed, chewed, or swallowed whole. This tablets strength would ease administration of the required doses, if 400 mg functionally scored tablets are not available.
- The procurement of functionally scored 400 mg tablets should be prioritized over unscored/non-functionally scored ones to avoid the risk of disintegration and thus underdosing if tablets with non-functional scoring lines are broken.
- Albendazole syrups (400 mg in 10 mL suspension) is available in many countries outside the EU and the US. However, it was noted by WHO technical experts that these formulations have stability issues, as the API precipitates over time, with the risk of underdosing. Therefore, the addition of syrups in the EMLc is not recommended.

Additional findings

- From the PENTA surveys of health professionals, albendazole was frequently reported as a problematic medicine for children with issues of safety of dosing, acceptability, tablet size, usability, lack of pharmacokinetic evidence for paediatric dosing regimens, and complicated dose regimens reported.
- The limited ability of young children to properly/safely chew tablets was noted as an important issue with the use of albendazole.

Recommendations for the EMLc pathway

- Considering the availability of 200 mg chewable tablets of albendazole in some markets, which can facilitate the administration of the required doses, we recommend including the 200 mg tablet strength in the EMLc for section 6.1.4. The addition of this tablet strength of albendazole is not recommended in sections 6.1.1 and 6.1.2 given that for the corresponding indications, albendazole dose is 400 mg daily given as single dose.
- We also recommend specifying “scored” for the 400 mg chewable tablets, to indicate that the procurement of functionally scored tablets should be prioritized over non-functionally scored or unscored tablets, the manipulation of which could lead to tablet shattering and thus to underdosing.
- We also recommend changing the title of section 6.1.4 to “Echinococcosis and cysticercosis medicines” to clarify the indication of the medicines listed in this section.

Mebendazole

Current listing in section 6.1.4 (complementary list)	Proposed listing in section 6.1.4 (complementary list)
Tablet (chewable): 500 mg	Tablet (chewable): **100 mg,** 500 mg

Assessment findings

- A 100 mg chewable tablet was found in some markets, which can be chewed, swallowed whole or crushed to facilitate administration (the same applies to the 500 mg chewable tablets). Considering that the dose of mebendazole the treatment of echinococcosis and cysticercosis is 40-50 mg/kg daily given in three divided doses (for a minimum duration of 3 months), the availability of a lower strength tablet would allow for a higher dose flexibility.
- Mebendazole oral suspensions (100 mg/5 mL in 30 mL) used to be available and used in some countries. However, it was noted by WHO technical experts that these formulations have stability issues, as the API precipitates over time, with the risk of underdosing. Therefore, the addition of oral suspensions in the EMLc is not recommended.

Recommendations for the EMLc pathway

- Considering that mebendazole is given in three divided doses for echinococcosis and cysticercosis, we recommend the addition of 100 mg chewable tablets to increase dose flexibility especially in younger children.
- The addition of a lower tablet strength is not recommended for section 6.1.1, as the dose is higher and given once daily.

Praziquantel

Current listing in section 6.1.4 (complementary list)	Proposed listing in section 6.1.4 (complementary list)
Tablet: 500 mg; 600 mg	Tablet: 150 mg; **500 mg** Tablet **(scored):** 600 mg

Assessment findings

- The dose of praziquantel for cysticercosis is 50 mg/kg/day in three divided doses, with a treatment duration of 10-14 days.
- All findings and considerations in section 6.1.1 apply.

Recommendations for the EMLc pathway

See section 6.1.1

Section 6.2.1 Access group antibiotics

Amikacin

Current listing in section 6.2.1	Proposed listing in section 6.2.1
Injection: 250 mg/mL (as sulfate) in 2 mL vial	Injection: 250 mg/mL (as sulfate) in 2 mL vial; **50 mg/mL (as sulfate) in 2 mL vial**

Assessment findings

- The injection is generally acceptable for the whole paediatric population although it contains an excipient of concern; sodium metabisulfite, which may cause allergic reactions.
- Once diluted (for infusion), the solution should be used immediately, but may be stored for hours at 2-8°C.
- A 100 mg/2 mL vial injection solution was identified in some markets and is also listed in Section 6.2.5 (Antituberculosis medicines), as 50 mg/mL (as sulfate) in 2 mL vial.

Additional findings

- Paediatric vial sizes of amikacin have been reported to be associated with more accurate dosing in neonates in a study by Allegaert and colleagues (Paediatric and Perinatal Drug Therapy, 2006; 7(2): 59-63).
- Higher prices for paediatric formulations compared with adult formulations exist and will be an important consideration for selection at the national level in many countries. However, inclusion of paediatric formulations on the EMLc can be a strong advocacy message that such formulations must be available and affordable.

Recommendation for the EMLc pathway

- Considering the WHO recommended dosage of 15mg/kg/dose once daily, the addition of the 50mg/mL strength formulation of amikacin injection to Section 6.2.1 of the EMLc should be considered, to facilitate dosing to infants and young children.

Amoxicillin

Current listing in section 6.2.1	Proposed listing in section 6.2.1
Powder for injection: 250 mg; 500 mg; 1 g (as sodium) in vial Powder for oral liquid: 125 mg/5 mL; 250mg/5mL; (as trihydrate) Solid oral dosage form: 250 mg; 500 mg (as trihydrate)	Powder for injection: 250 mg; 500 mg; 1 g (as sodium) in vial Powder for oral liquid: 125 mg/5 mL; 250mg/5mL; (as trihydrate) Solid oral dosage form: 250 mg; 500 mg (as trihydrate) **Tablet (dispersible, scored): 250 mg; 500 mg (as trihydrate)**

Assessment findings

- The injection is generally acceptable for the whole paediatric population, but patients might experience pain when it is administered via the IM route.
- The reconstituted powder for injection solution should be used immediately, but may be stored for short periods at 2-8°C.
- The powder for oral liquid did not meet the target for excipient safety since it generally contains several excipients of concern, e.g., sucrose or sorbitol, preservatives, flavouring and colours.
- Although the powder for oral liquid has acceptable stability, once reconstituted, it requires storage at 2-8°C and has a short in-use shelf life (7-14 days).
- Both hard gelatin capsules and unscored tablets are available; they are not acceptable for patients requiring a lower dose than 250 mg (< 6kg) and/or unable to swallow them.
- The capsules may have inferior stability compared to the tablets due to the need for protection from moisture.

Additional findings

- From the PENTA surveys of health professionals, amoxicillin solid oral dosage forms were reported as one of the three most problematic formulations (acceptability, size).
- Amoxicillin 250 mg and 500 mg dispersible tablets are available in the market, according to sales/procurement datasets evaluated by SGUL and are included in the UNICEF supply catalogue. However, it was reported that they are not included in formularies / national EMLs in some settings and may be more expensive than conventional tablets.
- The volume of water required for amoxicillin dispersible tablets is 5-10 mL per tablet.
- There have been reported requests for a 125 mg dispersible tablet in some settings, however WHO recommended weight-band dosing of amoxicillin (40-50 mg/kg twice daily) indicates that a 125 mg strength would not be required, and that 250 mg and 500 mg strength formulations will meet dosing requirements for the full paediatric age range.
- Higher prices for dispersible tablet formulations compared with conventional tablet formulations exist and will be an important consideration for selection at the national level in many countries. However, inclusion of dispersible tablet formulations on the EMLc can be a strong advocacy message that such formulations must be available and affordable

Recommendation for the EMLc pathway

- Scored dispersible amoxicillin tablets, 250 mg and 500 mg are available in some markets and should be considered for addition to the EMLc; they have been listed on UNICEF supply catalogue since 2011 (amoxicillin-dispersible-tablets-market-and-supply-update.pdf (unicef.org)), and are included in an Expression of Interest for product evaluation for WHO prequalification

(https://extranet.who.int/pqweb/sites/default/files/documents/EOI-MC_V01.pdf). Once dispersed in water they would be acceptable for the whole paediatric population and the administration of half a scored 250 mg dispersible tablet would enable the correct dosing of children < 6kg. Although not formally assessed, dispersible tablets are likely to have fewer excipients of concern (e.g., no preservatives) and have a lower bulk footprint compared to powders for oral liquid. In addition, a measuring device would not be required for administration.

Amoxicillin + Clavulanic acid

Current listing in section 6.2.1	Proposed listing in section 6.2.1
Powder for injection: 500 mg (as sodium) + 100mg (as potassium salt); 1000 mg (as sodium) + 200 mg (as potassium salt) in vial Powder for oral liquid: 125 mg (as trihydrate) + 31.25 mg (as potassium salt)/5 mL; 250 mg (as trihydrate) + 62.5 mg (as potassium salt)/5mL; (as trihydrate) Tablet: 500 mg (as trihydrate) + 125 mg (as potassium salt)	Powder for injection: 500 mg (as sodium) + 100mg (as potassium salt); 1000 mg (as sodium) + 200 mg (as potassium salt) in vial Powder for oral liquid: 125 mg (as trihydrate) + 31.25 mg (as potassium salt)/5 mL; 250 mg (as trihydrate) + 62.5 mg (as potassium salt)/5mL; (as trihydrate) Tablet: 500 mg (as trihydrate) + 125 mg (as potassium salt) **Tablet (dispersible): 250 mg (as trihydrate) + 62.5 mg (as potassium salt)**

Assessment findings

- The injection is generally acceptable for the whole paediatric population, although once constituted, it should be used immediately. Diluted solutions for infusion may be stored for several hours at 2-8°C.
- The powder for oral liquid partially met the target for excipient safety since it contains one or two excipients of concern, e.g., aspartame, flavouring.
- The powder for oral liquid has acceptable stability, but once reconstituted, it requires storage at 2-8°C and has a short in-use shelf life (7-14 days).
- Although WHO guidelines propose a dose of 500 + 125 mg every 12 hours in patients 10-15 kg (from approx. 1 year),[26] several SRA labels state the tablets should not be used in patients <40 kg (12 years). In addition to poor acceptability in patients unable to swallow them (they are large; approximately 10 x 21 mm), the tablets did not meet the target for dose flexibility.

Additional findings

- There is a growing move to use amoxicillin + clavulanic acid in a higher ratio of amoxicillin to clavulanic acid than the 4:1 ratio currently included on the EMLc. Trials are ongoing.
- UNICEF report that many countries cannot accept the powder for oral liquid due to poor stability once reconstituted.

Recommendation for the EMLc pathway

- Based on the assessment findings above, the need for and suitability of the 500 mg + 125 mg tablets for inclusion in the EMLc should be reviewed.
- Amoxicillin/clavulanic acid 250 mg + 62.5 mg dispersible tablets are available in some markets (SRA and non-SRA markets) and are listed in the UNICEF supply catalogue (https://supply.unicef.org/all-materials.html). It is recommended their availability should be confirmed, and their addition to the EMLc considered. They have not been formally assessed but once dispersed, they are easy to swallow and have a lower bulk footprint compared to powders for oral liquid. In addition, a measuring device would not be required for administration.

Recommendation for the GAP-f pathway

- Investigate the development of low bulk footprint and stable age-appropriate amoxicillin/clavulanic acid 125 mg + 31.25 mg formulations, e.g., dispersible tablets. The value of developing 250 mg + 62.5mg conventional tablets (and/or dispersible tablets if currently available products are unsuitable) may also be explored.

Cefalexin

Current listing in section 6.2.1	Proposed listing in section 6.2.1
Powder for oral liquid: 125 mg/5 mL; 250 mg /5mL (anhydrous) Solid oral dosage form: 250 mg (as monohydrate)	Powder for oral liquid: 125 mg/5 mL; 250 mg /5mL (anhydrous) Solid oral dosage form: 250 mg (as monohydrate) **Tablet (dispersible): 125 mg; 250 mg**

Assessment findings

- The powder for oral liquid did not meet the target for excipient safety since it generally contains several excipients of concern, e.g., sucrose, other sweeteners, preservative, flavouring and colorants.
- The powder for oral liquid has acceptable stability, but once reconstituted, it requires storage at 2-8°C and has a short in-use shelf life (up to 14 days).
- Both tablets and capsules are available, although they scored poorly for acceptability in young patients and for dose flexibility.
- Some tablet variants contain an excipient of concern e.g., (saccharin sweetener).
- Tablets and capsules require protection from moisture.

Additional findings

- Cefalexin dispersible tablets were reported to be available and affordable in Sri Lanka. They are easy to store and do not require refrigeration.
- Market availability of cefalexin dispersible tablets was reported in sales/procurement datasets evaluated by SGUL.

Recommendation for the EMLc pathway

- Cefalexin 125 mg and 250 mg dispersible tablets are available in some markets (not SRA markets), and it is recommended their availability should be confirmed and their addition to the EMLc considered. Although not formally assessed, dispersible tablets are easy to swallow once dispersed, and have a lower bulk footprint compared to powders for oral liquid. In addition, a measuring device would not be required for administration.

Chloramphenicol

Current listing in section 6.2.1	Proposed listing in section 6.2.1
Capsule: 250 mg Oily suspension for injection: 0.5 g/mL (as sodium succinate) in 2 mL ampoule Oral liquid: 150 mg/5 mL (as palmitate) Powder for injection: 1 g (sodium succinate) in vial.	~~**Capsule: 250 mg**~~ Oily suspension for injection: 0.5 g/mL (as sodium succinate) in 2 mL ampoule ~~**Oral liquid: 150 mg/5 mL (as palmitate)**~~ Powder for injection: 1 g (sodium succinate) in vial.

Assessment findings

- The capsules were found to have limited dose flexibility and poor acceptability in young patients.
- Limited information was available for the oily suspension for injection, and it was therefore not possible to perform a full assessment. It is not authorized for human use in the SRA markets interrogated, although listed on the Médecins Sans Frontières Drugs list. It was noted that it may cause pain/discomfort on injection.
- Limited information was available for the oral liquid, and it was therefore not possible to perform a full assessment. It does not appear to be authorized for human use in the SRA markets interrogated, although a 125 mg/5 mL product may be available in India.
- The powder for injection was found to be acceptable for paediatric patients, although the reconstituted injection solution should be used immediately, but may be stored for up to 24 hours at 2-8°C.

Additional findings

- Safety concerns with chloramphenicol (eg. bone marrow depression) limit its use.

Recommendation for the EMLc pathway

- Since the only indication listed for chloramphenicol on the EMLc is acute bacterial meningitis which requires parenteral treatment, it is recommended that both oral formulations (capsule and oral liquid) are removed from the EMLc.
- Given the inclusion of the power for injection on the EMLc, it is recommended the availability and clinical need for the oily suspension for injection is clarified.

Clindamycin

Current listing in section 6.2.1	Proposed listing in section 6.2.1
Capsule: 150 mg (as hydrochloride) Injection: 150 mg/mL (as phosphate) Oral liquid: 75 mg/5 mL (as palmitate)	Capsule: 150 mg (as hydrochloride) Injection: 150 mg/mL (as phosphate) ~~**Oral liquid: 75 mg/5 mL (as palmitate)**~~ **Powder for oral liquid: 75 mg/5 mL (as palmitate hydrochloride)**

Assessment findings

- The capsules were found to be unacceptable for young children, and partially met the target for excipients (they contain lactose) and stability (they require moisture, light and heat protection).
- The injection is generally acceptable but may cause pain or irritation when given IM. Various formulations appear to be available, some of which contain benzyl alcohol which is contra-indicated in neonates. In addition, required storage conditions and shelf life of the product varied, with some formulations requiring storage at 2-8°C.
- A ready to use oral liquid of clindamycin did not appear to be available, only powder (granules) for oral liquid, which was assessed instead.
- The powder for oral liquid did not meet the target for excipient safety since it generally contains several excipients of concern, e.g., sucrose, preservative, flavouring. In addition, once reconstituted, it is stable for up to 2 weeks only, although it is stored at 20-25°C, and not 2-8°C.

Additional findings

- Market availability of clindamycin dispersible tablets manufactured by one Chinese company was reported in sales/procurement datasets evaluated by SGUL, with 60% of global clindamycin sales of child-appropriate formulations reported to be this formulation. However, clindamycin dispersible tablets were not identified in the pQTPP assessments from the regulatory authorities interrogated.

Recommendation for the EMLc pathway

- It is recommended the entry for the oral liquid is changed to powder for oral liquid 75mg/5 mL (as palmitate hydrochloride) to reflect the formulation currently available.

Recommendation for the GAP-f pathway

- Investigate the development of an alternative oral age-appropriate formulation of clindamycin with a more favourable excipient safety profile and lower bulk footprint (e.g., not bottles).
- A Chinese patent for clindamycin dispersible tablets is available, CN100356925C) and the global availability of this formulation should be determined.

Cloxacillin (and therapeutic alternatives)

Current listing in section 6.2.1	Proposed listing in section 6.2.1
Capsule: 500 mg; 1 g (sodium) Powder for injection: 500 mg (as sodium) in vial Powder for oral liquid: 125 mg/5 mL (as sodium)	Capsule: **250 mg**; 500 mg; 1 g (sodium) Powder for injection: **250 mg**; 500 mg (as sodium) in vial Powder for oral liquid: 125 mg/5 mL; **250 mg/ 5mL** (as sodium)

Assessment findings

- Cloxacillin appears to have limited availability in the SRA markets interrogated (e.g., UK and Australia), although it is recognized therapeutic equivalents are permitted to ensure broad global availability of this group of antibiotics.
- The capsules were found to have low acceptability in young patients unable to swallow them and those requiring less than 500 mg dose. In addition, they require moisture protection.
- The powder for injection is generally acceptable, although once reconstituted should be used immediately, but may be stored for up to 24 hours at 2-8°C.
- Excipient and stability information for cloxacillin powder for oral liquid were not available, but the alternative flucloxacillin powder for oral liquid did not meet the target for excipient safety since it generally contains several excipients of concern, e.g., sucrose, preservative, colour, flavouring. In addition, once reconstituted, it requires storage at 2-8°C with a shelf life of up to 7 days.

Additional findings

- Market availability and procurement challenges were reported by stakeholders. Having more options in EMLc listed formulations/strengths was welcomed.

Recommendation for the EMLc pathway

- Although limited information on cloxacillin was available, it was noted that 250 mg flucloxacillin capsules, 250 mg powder for injection in vial and 250 mg/5 mL powder for oral liquid are available.
- It is recommended the 250 mg capsule strength is considered for addition to the EMLc to facilitate flexibility of dosing in 250 mg increments.
- It is recommended the 250 mg power for injection vial size is considered for addition to the EMLc to facilitate dosing in neonates and infants and to reduce waste.
- It is recommended the 250 mg/5 mL powder for oral liquid is considered for addition to the EMLc to facilitate dosing to children unable to swallow capsules and avoid the need to administer large dose volumes of the 125 mg/5 mL product (recommended dose 6-< 15 kg 250 mg every 6 hours, 15-< 20kg 500 mg every 6 hours).[26]

Recommendation for the GAP-f pathway

- Investigate the development of an alternative oral age-appropriate formulation of cloxacillin/flucloxacillin (or other therapeutic alternative) with a more favourable excipient safety profile and lower bulk footprint (e.g., not bottles), for example dispersible tablets.

Doxycycline

Current listing in section 6.2.1	Proposed listing in section 6.2.1
Oral liquid: 25 mg/5 mL; 50 mg/5 mL (anhydrous) Powder for injection: 100 mg in vial Solid oral dosage form: 50 mg; 100 mg (as hyclate)	**Powder for oral liquid: 25 mg/5 mL (monohydrate)** **Oral liquid: ~~25 mg/5 mL;~~ 50 mg/5 mL (calcium)** Powder for injection: 100 mg in vial Solid oral dosage form: 50 mg; 100 mg (as hyclate) **Tablet (dispersible): 100 mg (as monohydrate)**

Assessment findings

- Doxycycline oral liquid appears to be available as a ready to use syrup (oral suspension) as doxycycline calcium equivalent to 50 mg/ 5 mL and as a powder for oral suspension as doxycycline monohydrate equivalent to 25 mg/5 mL.
- Neither oral liquid formulation met the target for excipient safety since they contained several excipients of concern, e.g., sucrose, sorbitol, sodium metabisulfite, propylene glycol, preservatives, colours, flavourings. After reconstitution, the powder for oral suspension has a short shelf life of up to 2 weeks.
- The powder for injection is generally acceptable, although it requires reconstitution and dilution for use. Both the powder and reconstituted solution require protection from light. Once reconstituted/diluted, the product may be stored for short periods at 2-8°C.
- Capsules appear to be more commonly available than tablets. Capsules and tablets were found to have low acceptability in young patients unable to swallow them. However, the product is recommended for use in patients from 8 years and hence this is not considered to be a key concern. In addition, the capsules require moisture protection.
- A dispersible tablet 100 mg is also available and is listed in Section 6.5.3.1 of the EMLc (Antimalarial medicines, for curative treatment).

Recommendation for the EMLc pathway

- It is recommended the availability and description of the oral liquid is reviewed and updated to reflect the different doxycycline forms and types of formulation available.
- Since the dispersible tablet 100 mg is already listed in the EMLc, it is recommended it is considered for addition to Section 6.2.1, to facilitate dosing and harmonize the EMLc listings for doxycycline solid oral dosage forms.

Metronidazole

Current listing in section 6.2.1	Proposed listing in section 6.2.1
Injection: 500 mg in 100 mL vial Oral liquid: 200 mg/5 mL (as benzoate) Tablet: 200 mg to 500 mg	Injection: 500 mg in 100 mL vial Oral liquid: 200 mg/5 mL (as benzoate) **Tablet: 200 mg; 250 mg; 400 mg; 500 mg**

Assessment findings

- The injection is generally acceptable. It requires protection from light and must be used immediately after opening, although diluted solutions for infusion may be stored for up to 24 hours at 2-8°C.
- A powder for injection product is also available but did not meet the target for administration considerations due to its complex handling method (reconstitution, dilution, and neutralization). It achieved the same scores as the solution for other pQTPP attributes and so overall there does not appear to be a benefit for its addition to the EMLc.
- The oral liquid did not meet the target for excipient safety since it generally contains several excipients of concern, e.g., sorbitol, glucose, fructose, sucrose, preservatives, propylene glycol, ethanol. It has acceptable stability but must be protected from light.
- The tablets were found to have low acceptability in young patients unable to swallow them and those requiring a lower dose than 200 mg (< 20 kg). They also require light protection.
- Metronidazole capsules (375 mg) are also available in some markets (e.g., USA).

Additional findings

- A metronidazole injection in a 100 mg/20 mL formulation was reported to be available and may be beneficial to avoid/reduce overdosing of younger children. Global availability should be investigated.

Recommendation for the EMLc pathway

- The dose strength for tablets is listed as a range; 200 mg to 500 mg, and it is recommended that specific dose strengths are listed for greater clarity. The following dose strengths appear to be currently available: 200 mg, 250 mg, 400 mg, 500 mg. (The suitability of these should be confirmed).
- Note, metronidazole is also listed in Section 6.5.1 (Antiamoebic and antigiardiasis medicines) and both sections of the EMLc should be harmonized.

Nitrofurantoin

Current listing in section 6.2.1	Proposed listing in section 6.2.1
Oral liquid: 25 mg/5 mL Tablet: 100 mg	Oral liquid: 25 mg/5 mL **Solid oral dosage form: 50mg; 100 mg**

Assessment findings

- The oral liquid did not meet the target for excipient safety since it generally contains several excipients of concern, e.g., sorbitol, sodium saccharin, preservatives, flavourings.
- In addition, it only partially met the administration and stability/packaging attributes due to the need to shake the product vigorously before dose withdrawal, the need to protect it from light and moisture (packed in amber glass bottles), and a limited shelf life of 30-90 days after opening.
- The 100 mg tablet did not meet the target for acceptability in patients aged below 8-12 years due to the inability to administer the required dose (2-4 mg/kg every 12 hours),[26] as well as the difficulty these patients may have in swallowing it.
- Capsules are also available in some markets. Although not defined as modified release, they are reported to contain a larger crystal form of nitrofurantoin that has similar clinical effectiveness but delayed and decreased absorption with fewer GI effects. According to the PLs of SRA interrogated, both immediate release (standard) tablets and capsules are to be dosed four times a day (e.g., 3-7 mg/kg in 4 divided doses), whilst WHO guidance states twice daily dosing (2-4 mg/kg every 12 hours).[26]
- Some capsule products are specifically defined as prolonged release and their PLs stipulate twice daily dosing.
- 50 mg tablets and capsules are available in some markets.

Additional findings

- The general principle applied on the Model Lists is that the term ‘solid oral dosage form’ is not intended to represent any type of modified-release formulation. The listing on the EMLc for nitrofurantoin solid oral dosage forms relates only to immediate-release formulations.

Recommendation for the EMLc pathway

- Due to the availability of nitrofurantoin capsules as well as tablets, it is recommended to change the EMLc listing entry to solid oral dosage form.
- It is also recommended to consider the addition of the 50 mg dose strength to facilitate dosing to younger patients.

Recommendation for the GAP-f pathway

- Investigate the development of an alternative oral age-appropriate formulation of nitrofurantoin with a more favourable excipient safety profile and lower bulk footprint (e.g., not bottles), for example dispersible tablets.

Phenoxymethylpenicillin

Current listing in section 6.2.1	Proposed listing in section 6.2.1
Powder for oral liquid: 250 mg/5 mL (as potassium) Tablet: 250 mg (as potassium)	Oral liquid: 25 mg/5 mL **Solid oral dosage form: 250 mg (as potassium)**

Assessment findings

- The powder for oral liquid did not meet the target for excipient safety since it generally contains several excipients of concern, e.g., sorbitol, sucrose, sodium saccharin, preservatives, flavourings, colour.
- Although the stability of the powder is acceptable, once reconstituted, the product must be stored at 2-8°C and has a shelf-life of 7-10 days.
- A 125 mg/5 mL dose strength product is available in some markets. However, considering WHO dosing guidelines (15 mg/kg every 6 hours),[26] and the limited indications for use, the current 250mg/5mL product will meet the dose administration needs of young paediatric patients including neonates (e.g., 1 mL volume required), although care is required to ensure accurate dosing.
- The tablet did not meet the target for acceptability in young patients unable to swallow it.
- Phenoxymethylpenicillin capsules are also available in some markets.

Recommendation for the EMLc pathway

- Due to the availability of phenoxymethylpenicillin capsules as well as tablets, it is recommended to change the EMLc listing entry to solid oral dosage form.

Procaine benzylpenicillin

Current listing in section 6.2.1	Proposed listing in section 6.2.1
Powder for injection 1 g (=1 million IU); 3 g (=3 million IU)	No changes proposed

Assessment findings

- The powder for injection does not appear to be available in the SRA markets interrogated but is listed in the International Pharmacopoeia; a suspension injection is listed as marketed in the USA (600 000IU/mL available in 1 mL and 2 mL syringe) and Australia (1.5 g injection syringe).
- Limited information was available for some pQTTP attributes, although overall the product is considered acceptable for paediatric patients.
- Once reconstituted, the powder for injection requires immediate use.
- The injection suspension is viscous, requires storage at 2-8°C and may contain 1 or 2 excipients of concern.

Additional findings

- Reported shortages and procurement difficulties of procaine benzylpenicillin are commonplace. Having additional formulation options listed on the EMLc was considered desirable.
- Procaine benzylpenicillin is included on the EMLc only for the treatment of congenital syphilis in infants for which the recommended dose is 50 000 IU/kg once daily IM. The availability of a lower strength formulation is therefore considered valuable.
- MSF's Essential drugs guidelines report powder for injection formulations of 0.6 million IU/vial and 1.2 million IU/vial.

Recommendation for the EMLc pathway

- It is recommended that the global availability of procaine benzylpenicillin powder for injection and injection suspension, including strengths, should be determined, and the EMLc updated accordingly.

Sulfamethoxazole + Trimethoprim

Current listing in section 6.2.1	Proposed listing in section 6.2.1
Injection: 80 mg + 16 mg/mL in 5 mL ampoule; 80mg + 16 mg in 10 mL ampoule Oral liquid: 200 mg + 40 mg/5 mL Tablet: 100 mg + 20 mg; 400 mg + 80 mg	Injection: 80 mg + 16 mg/mL in 5 mL ampoule; 80mg + 16 mg in 10 mL ampoule Oral liquid: 200 mg + 40 mg/5 mL Tablet: 100 mg + 20 mg; 400 mg + 80 mg **Tablet (dispersible) 100 mg + 20 mg**

Assessment findings

- Although the injection allows the flexible dosing of the entire paediatric population, it did not meet the target for excipient safety since it may contain several excipients of concern, e.g., propylene glycol, sodium metabisulfite, ethanol, benzyl alcohol.
- It has an acceptable shelf life but must be diluted for use and immediate use is recommended.
- The oral liquid also did not meet the target for excipient safety since it generally contains several excipients of concern, e.g., sorbitol, sucrose, sodium saccharin, propylene glycol, preservatives, ethanol, colorants. In addition, older children may require high dose volumes.
- It was not possible to identify any 100 mg + 20 mg tablets authorized by the SRAs interrogated. The 400 mg + 80 mg strength tablet did not meet the target for acceptability in young patients unable to swallow it (and requiring a lower dose; < 10 kg). In addition, it may contain an excipient of concern (preservative).
- It has been noted that dispersible 100 mg + 20 mg tablets are available in some markets and used for prophylaxis of HIV-related infections. This strength formulation is also listed in Section 6.5.4 (Antipneumocystosis and antitoxoplasmosis medicines), although dispersible tablets are not specified.

Additional findings

- Market availability of sulfamethoxazole + trimethoprim dispersible tablets was reported in sales/procurement datasets evaluated by SGUL.

Recommendation for the EMLc pathway

- It is recommended that the availability of 100 mg + 20 mg conventional and dispersible tablets is clarified. Dispersible tablets are suitable from birth and would provide an alternative age-appropriate formulation to the oral liquid containing excipients with a superior safety profile.
- If dispersible tablets are available, the EMLc should be updated accordingly.
- If conventional 100 + 20 mg tablets are not available, they should be considered for removal.

Recommendation for the GAP-f pathway

- If dispersible 100 mg + 20 mg sulfamethoxazole + trimethoprim tablets of appropriate quality are not readily available, investigate the development of a new dispersible tablet formulation.

Trimethoprim

Current listing in section 6.2.1	Proposed listing in section 6.2.1
Tablet: 100 mg; 200 mg Oral liquid: 50 mg/5 mL	Tablet: 100 mg; 200 mg Oral liquid: 50 mg/5 mL ***No changes proposed***

Assessment findings

- The tablet was not acceptable for young children unable to swallow it, or those requiring a lower dose. In addition, it requires protection from moisture.
- The oral liquid appeared to have limited availability but did not meet the target for excipient safety since it contains several excipients of concern, e.g., sorbitol, sodium saccharin, preservatives.
- No alternative age-appropriate formulations appear to be available.

Recommendation for the EMLc pathway

- No changes are proposed.

Recommendation for the GAP-f pathway

- Investigate the development of an alternative age-appropriate formulation of trimethoprim, with improved excipient safety profile and low bulk footprint.

Section 6.2.2 Watch group antibiotics

Azithromycin

Current listing in section 6.2.2	Proposed listing in section 6.2.2
Capsule: 250 mg; 500 mg (anhydrous) Oral liquid: 200 mg/5 mL	**Solid oral dosage form:** 250 mg; 500 mg (anhydrous) **Powder for** oral liquid: 200 mg/5 mL **(anhydrous)**

Assessment findings

- Azithromycin tablets were found registered in some markets. Capsules were found to be less widely registered than tablets and the 500 mg capsule did not appear to be registered by any of the SRAs reviewed.
- Considering the dose recommended in the EML antibiotic handbook (lower: 10 mg/kg once daily; higher: 20 mg/kg every 12 hours), the 500 mg capsules and tablets have limited utility in people aged up to 12 years, but they are worth keeping reducing pill burden in young adolescents.
- The 200 mg/5 mL oral liquid dosage is registered at SRAs as a powder for oral liquid, which requires reconstitution with water rather than a ready-made solution.

Recommendation for the EMLc pathway

- To acknowledge the availability of azithromycin tablets, it is recommended to list capsules and tablets as “solid oral dosage form: 250 mg; 500 mg”.
- To reflect the fact that the oral liquid formulation is marketed as a powder that requires reconstitution prior to use, it is recommended to list the oral liquid dosage form as “powder for oral liquid: 200 mg/5 mL (anhydrous)”.

Recommendation for the GAP-f pathway

- Even if the oral liquid solution already listed in the EMLc allows for enough dose flexibility to deliver recommended dose across the paediatric population, it requires some manipulation (ie, reconstitution) before administration, which is not ideal especially in low-resource settings.
- Thus, we recommend exploring the potential development of an age-appropriate, flexible formulation of azithromycin to dose younger children, eg dispersible tablets.

Cefixime

Current listing in section 6.2.2	Proposed listing in section 6.2.2
Powder for oral liquid: 100 mg/5 mL Solid oral dosage form: 200 mg; 400 mg (as trihydrate)	Powder for oral liquid: 100 mg/5 mL ~~Solid oral dosage form: 200 mg; 400 mg (as trihydrate)~~ **Tablet: 200 mg (as trihydrate)**

Assessment findings

- 200 mg solid oral dosage forms have limited flexibility, as they can be used in children and young adolescents aged 6-12 years who can swallow tablets whole. 400 mg solid oral dosage forms have no utility to deliver the dose of 10 mg/kg given once daily for 5 days as indicated in the WHO AWaRe antibiotic book in children and young adolescents aged below 12 years.[26]
- Acceptability of tablets for children below 6 years of age scored as very low given their challenges swallowing solid oral dosage forms whole. Oral liquid formulations are more suitable to deliver appropriate dose in this subgroup.
- Most solid oral dosage forms found registered at SRAs were tablets. Capsules (only 400 mg) were found registered only at USFDA from one manufacturer. 200 mg capsules were not found registered at any SRAs.
- Chewable tablets of several strengths (100 mg, 150 mg, 200 mg) were found in some markets. Alongside the oral liquid formulation, they can help to deliver the appropriate dose in younger children. Indeed, chewable tablets are considered as acceptable for children aged 2 years and above. No product label could be found, so no additional information on the other attributes assessed with the pQTPP tool is available (e.g., storage, excipients).

Additional findings

- Market availability of cefixime dispersible tablets was reported in sales/procurement datasets evaluated by SGUL, with 44% of cefixime sales reported to be this dosage form.

Recommendation for the EMLc pathway

- Considering that 400 mg solid oral dosage forms have no utility in delivering the recommended dose in children below 12 years of age, and that the only strength found for capsules corresponds to 400 mg, which has no utility in delivering the recommended dose, we recommend replacing “Solid oral dosage form: 200 mg; 400 mg (as trihydrate)” with “Tablets: 200 mg (as trihydrate)
- Considering the availability of chewable tablets, which were found in some markets at several strengths, and which could be used to deliver the indicated dose in children down to 2 years of age, we recommend an application be sought for inclusion of chewable tablets (100 mg, 150 mg, 200 mg) in the EMLc.

Cefotaxime

Current listing in section 6.2.2	Proposed listing in section 6.2.2
Powder for injection: 250 mg (as sodium) in vial	Powder for injection: 250 mg, **500 mg, 1 g, 2 g** (as sodium) in vial

Assessment findings

- A 250 mg powder for injection could not be found registered at the SRAs databases reviewed as part of this project. Considering the recommended dose of 50 mg/kg given every 8 hours[26] (with duration of treatment depending on the condition), this strength would also have limited utility in the EMLc population, with the need to use more than one vial to dose most children.
- 500 mg, 1g and 2g strengths were found in some markets. Considering the recommended dose mentioned above, all three strengths may be used to dose children and young adolescents.
- It should be noted that reconstituted cefotaxime powder has a shelf/life of up to 24h when stored at 2-8C and up to 3h when stored at 25C.

Additional findings

- Supply issues for cefotaxime have been reported. The availability of additional strengths on the EMLc was considered a potential means to improve supply by making more options available.

Recommendation for the EMLc pathway

- We recommend assessing the market availability of the 250 mg strength, including in LMICs with a view to removing this strength from the EMLc if availability is limited.
- We recommend the addition of the following strengths: 500 mg, 1 g and 2 g. Considerations around the number of vials needed to deliver the recommended dose in children aged 0-12, alongside considerations around reducing undesired volume wastage should be done to take a final decision on which vial strengths to include.

Ceftriaxone

Current listing in section 6.2.2	Proposed listing in section 6.2.2
Powder for injection: 250 mg, 1 g (as sodium) in vial	Powder for injection: 250 mg, **500 mg**, 1 g (as sodium) in vial

Assessment findings

- A 500 mg powder for injection was also found registered at several SRAs.
- Considering the recommended dose of 50-80 mg/kg (single dose), the availability of the 250 mg strength allows for more precise dosing in children and may contribute to reducing volume wastage. However, for some children, it may result in a high number of vials to be used. In these cases, availability of a 500 mg strength formulation would be beneficial.

Recommendation for the EMLc pathway

- Considering the availability of a 500 mg powder for injection found in some markets, and its potential to reduce the number of vials used for some children, we recommend considering its inclusion alongside those already listed.

Ciprofloxacin

Current listing in section 6.2.2	Proposed listing in section 6.2.2
Oral liquid: 250 mg/5 mL (anhydrous) Solution for IV infusion: 2 mg/mL (as hyclate) Solid oral dosage form: 250 mg (as hydrochloride)	Oral liquid: 250 mg/5 mL (anhydrous) Solution for IV infusion: 2 mg/mL (as hyclate) Solid oral dosage form: **100 mg;** 250 mg (as hydrochloride)

Assessment findings

- The recommended dose of ciprofloxacin includes dose increments of 50-100 mg for children weighing 3 to <30 kg. (eg, 3 to <6 kg: 50 mg q12h; 6 to <10 kg: 100 mg q12h; 10 to <15 kg: 150 mg q12h; 15 to <20 kg: 200 mg q12h; 20 to <30 kg: 300 mg q12h).

- For children aged below 6 years (weighing <20 kg), a 250 mg solid oral dosage form does not provide the necessary dose flexibility to deliver the recommended dose, and acceptability is also low given that young children cannot swallow tablets whole. Other dosage forms, including oral liquid solutions, are more suitable for this subgroup.
- For children aged 6-12 years (weighing 20-35 kg), whole tablets may be given, even if some may have challenges swallowing. However, 250 mg tablets have limited flexibility to administer the recommended dose in this group.
- Dose increments of 100-125 mg would allow for a higher dose flexibility.
- 250 mg tablets may have a scoring line and may allow dose increments of 125 mg (if scoring is functional). However, not all quality-assured, generic versions of ciprofloxacin may have a functional scoring line.
- 100 mg strength tablets were found in some markets, which may be used to more accurately dose children who are able to swallow tablets whole.

Additional findings

- Market availability of ciprofloxacin dispersible tablets was not reported in sales/procurement datasets evaluated by SGUL.

Recommendation for the EMLc pathway

- Given the limited flexibility of 250 mg tablets to deliver the recommended dose of ciprofloxacin across the paediatric population, we recommend to also include 100 mg tablets to increase dose flexibility and precision.

Recommendation for the GAP-f pathway

- Explore the potential utility of developing dispersible tablet formulations of ciprofloxacin, which could be used to dose younger children and older children with challenges swallowing tablets whole.

Clarithromycin

Current listing in section 6.2.2	Proposed listing in section 6.2.2
Powder for oral liquid: 125 mg/5 mL; 250 mg/5 mL Powder for injection: 500 mg in vial Solid oral dosage form: 500 mg	Powder for oral liquid: 125 mg/5 mL; 250 mg/5 mL Powder for injection: 500 mg in vial Solid oral dosage form: **250 mg** ~~**500 mg**~~

Assessment findings

- None of the 500 mg clarithromycin formulations found registered at the SRAs reviewed as part of this project has a functional scoring line.
- Clarithromycin should be given at a dose of 7.5 mg/kg (twice daily), therefore a 500 mg solid oral dosage form cannot deliver the indicated dose to children aged 0-12y (weighing approximately <35 kg).
- A 250 mg strength tablet was found in some markets, which could be used to dose older children who can swallow tablets whole.

Additional findings

- Market availability of clarithromycin dispersible tablets was reported in sales/procurement datasets evaluated by SGUL, however the majority of sales (80%) of child-appropriate formulations of clarithromycin sales were reported to be powder for oral liquid formulations.

Recommendation for the EMLc pathway

- Given that 500 mg solid oral dosage form cannot deliver the recommended dose to children aged 0-12 years, we recommend replacing this strength with a lower-strength solid oral dosage form, ie, 250 mg, which was found in some markets.

Recommendation for the GAP-f pathway

- Powders for oral liquid are available and already listed in the EMLc, which have a high dose flexibility to deliver appropriate dose across the paediatric population. They do not have issues in terms of stability or storage conditions. However, they contain a few excipients of concern (eg, castor oil, which may cause stomach upset and diarrhoea) and they require reconstitution, which is not ideal for low-resourced settings.
- Considering the above, we recommend exploring the potential development of a flexible, age-appropriate formulation of clarithromycin, which would be particularly useful to deliver the recommended dose in younger children.

Vancomycin - oral

Current listing in section 6.2.2	Proposed listing in section 6.2.2
Capsule: 125 mg; 250 mg (as hydrochloride)	Capsule: 125 mg; 250 mg (as hydrochloride) ***NOTE: Vancomycin powder for injection may also be used for oral administration.***

Assessment findings

- The 125 mg capsules allow for limited dose flexibility in children aged 0-12 years. Moreover, acceptability for children below 6 years of age is very low, given issues with swallowing capsules whole, and there may be acceptability issues also for older children.
- Children weighing below 10 kg require doses corresponding to ≤ 50-100 mg, which cannot be administered with listed capsules.
- Powder for oral solutions were found in some markets, which would allow for a higher dose flexibility and are acceptable across the paediatric age spectrum.
- Vancomycin powder for injection, currently listed in the Complementary List of section 6.2.2 (see below) can also be used for oral administration after appropriate compounding and potential addition of common flavouring syrups to improve palatability.

Additional findings

- Use of vancomycin in LMICs was reported to be primarily the injection formulation. The availability and affordability of vancomycin capsules outside HICs was reported to be limited.
- Oral vancomycin is indicated on the EMLc as a second choice treatment for Clostridioides difficile infection and there is likely only a small paediatric population to be treated.
- The value of including a powder for oral liquid formulation of vancomycin on the EMLc was considered limited.

Recommendation for the EMLc pathway

- Given that capsules have limited dose flexibility and acceptability, especially in younger children, we recommend including a note in the current listing to indicate that vancomycin powder for injection may be used for oral administration after appropriate reconstitution.

Recommendation for the GAP-f pathway

- Explore whether an age-appropriate formulation of vancomycin (eg, dispersible tablets) should be considered for development.

Vancomycin - IV

Current listing in section 6.2.2 (Complementary list)	Proposed listing in section 6.2.2 (Complementary list)
Powder for injection: 250 mg (as hydrochloride) in vial	Powder for injection: 250 mg, **500 mg, 1g** (as hydrochloride) in vial

Assessment findings

- Vancomycin powder for injection 250 mg could not be found registered at the SRAs reviewed in the context of this project.
- Other strengths could be found in some markets, including: 500 mg, 750 mg, 1g. The recommended dose for vancomycin IV is 15 mg/kg (given every 12 hours) for neonates and 15 mg/kg (given every 8 hours) for children. These strengths will meet the dosing needs of neonates and children. Use of the higher strength formulations (750 mg, 1g) may minimize the number of vials required for dosing older/heavier children. After reconstitution, vancomycin solutions of 50 mg/mL in water for injection can be stored at 2-5C for 24-96h. When further diluted (e.g., 10 mg/mL or 1 mg/mL) with NaCl 0.9% or glucose IV infusion 5%, solutions are chemically stable for up to 28 days at 2-8C.
- Readymade solutions for injections were also found registered at USFDA, which do not require reconstitution but information on product stability and storage conditions could not be found.

Additional findings

- The more commonly available strengths of vancomycin powder for injection were reported to be 250 mg, 500 mg and 1 g.

Recommendation for the EMLc pathway

- We recommend assessing the market availability of the 250 mg powder for injection, including in LMICs with a view to removing this strength from the EMLc if availability is limited.
- We also recommend including 500 mg and 1g powder for injections. Considerations around which strengths to include should take into account the recommended dose and dose frequency, as well as the stability of the reconstituted solution.
- We also advise looking into the potential addition of ready-made solutions for injections, after assessing their global availability, stability and excipient profile to evaluate potential benefits of adding them to/replacing the powder for injection formulation.

Section 6.2.3 Reserve group antibiotics

Colistin

Current listing in section 6.2.3	Proposed listing in section 6.2.3
Powder for injection: 1 million IU (as colistimethate sodium) in vial	Powder for injection: 1 million IU (as colistimethate sodium) **(equivalent to 34 mg colistin base activity)** in vial

Assessment findings

- Overall, the injection is acceptable for the whole paediatric population, although once reconstituted the solution should be used immediately, but may be kept for up to 24 hours at 2-8°C.
- The 1 million IU size vial was only available in one SRA interrogated (UK). Other vial sizes, for example 4.5 million IU, are available in other SRA markets (Australia and USA). Care is required for calculating the dose of colistin due to differences in the way the dose is prescribed and expressed in different countries. For example, in Europe the dose of colistimethate sodium (CMS) is prescribed as IU, in USA and elsewhere the dose is expressed in mg of colistin base activity (CBA). 1 million IU ~ 34 mg CBA ~ 80mg CMS.

Recommendation for the EMLc pathway

- It is recommended to review the global availability of colistin powder for injection including vial sizes and consider describing vial sizes expressed in mg CBA as well as IU CMS on the EMLc.

Linezolid

Current listing in section 6.2.3	Proposed listing in section 6.2.3
Injection for intravenous administration: 2mg/mL in 300 mL bag Powder for oral liquid: 100 mg/5 mL Tablet: 400 mg; 600 mg	Injection for intravenous administration: 2mg/mL in 300 mL bag Powder for oral liquid: 100 mg/5 mL ~~**Tablet: 400 mg; 600 mg**~~ **Tablet (dispersible): 150 mg**

Assessment findings

- The injection for IV administration is acceptable for paediatric patients although it should be used with caution in patients with conditions associated with glucose intolerance or a low sodium diet due to its glucose and sodium content. Each pack is for single use only and as a result of the large bag size, there is potential for wastage when treating young children. (Dose 10 mg/kg every 12 or 8 hours).[26]
- The powder for oral liquid did not meet the target for excipient safety as it contained several excipients of concern, e.g., sucrose, mannitol, aspartame, preservatives, flavourings. Older children may require high dose volumes, e.g., 10 mL for a 6-year-old/20 kg child.
- After reconstitution, the powder for oral suspension has a short shelf life of up to 3 weeks.
- It was not possible to identify 400 mg dose strength linezolid tablets authorized by the SRAs interrogated, although the 600 mg tablet appears to be widely available.
- The 600 mg tablets had low acceptability in young children due to swallowing difficulties. In addition, this dose strength appears to be unsuitable for patients less than 12 years old.
- A 150 mg dispersible tablet is listed in Section 6.2.5 (Antituberculosis medicines Complementary list).

Recommendation for the EMLc pathway

- It is recommended the 400 mg tablet is removed due to its lack of availability (this dose strength was removed from Section 6.2.5 in 2021 as it was determined to be not available).
- It is recommended the 600 mg tablet is removed since this strength is unsuitable for dosing children less than 12 years old.
- Since the dispersible tablet 150 mg is already listed in the EMLc, it is recommended it is considered for addition to Section 6.2.3, to facilitate dosing to young patients. The formulation is likely to have better stability, lower bulk footprint and fewer excipients of concern compared to the powder for oral liquid.

Recommendation for the GAP-f pathway

- Investigate the feasibility and development of a lower volume bag (container) for linezolid injection for intravenous administration.
- Investigate the feasibility and development of an oral liquid formulation with an improved excipient profile.

Polymyxin B

Current listing in section 6.2.3	Proposed listing in section 6.2.3
Powder for injection: 500,000 IU in vial	Powder for injection: 500,000 IU **(equivalent to 50 mg polymyxin B base)** in vial

Assessment findings

- Overall, the injection is acceptable for the whole paediatric population, although it can be very painful if given IM. In the interests of safety, once reconstituted, the solution should only be kept for up to 72 hours at 2-8°C.
- The product was only available in one SRA interrogated (USA). Care is required to ensure correct dosing in the prescribed units of measure (each mg of pure polymyxin B base is equivalent to 10,000 units of polymyxin B).

Recommendation for the EMLc pathway

- Since doses may be expressed in mg or IU, (e.g., maintenance dose from 2 years 1.5mg/kg (15,000 IU/kg) every 12 hours),[26] it is recommended to review the way in which polymyxin is expressed on the EMLc, with consideration given to the addition of mg equivalents.

Section 6.2.4 Antileprosy medicines

Clofazimine

Current listing in section 6.2.4	Proposed listing in section 6.2.4
Capsule: 50 mg; 100 mg	**Solid oral dosage form:** 50 mg; 100 mg

Assessment findings

- Clofazimine soft-gel capsules (50 mg, 100 mg) allow for limited dose flexibility. They are not acceptable for children who have difficulty swallowing them whole, and unlike hard capsules, soft-gel capsules cannot be opened, and the contents administered by dispersing them in water. As a result of clofazimine's long half-life, it is possible to dose on alternate days without affecting drug exposure; WHO recommends a dose of 150 mg once a month, and 50 mg on alternate days for children and young adolescents aged 10-14 years (for 6-12 months depending on the presence of paucibacillary or multibacillary disease). For children aged below 10 years or below 40 kg, WHO recommends a dose of 100 mg once a month, and 50 mg twice weekly.
- Issues with dosing clofazimine in young children have also been highlighted by clinicians working in high-resource settings if only soft-gel capsules are available (irrespective of whether they aim for daily or less frequent dosing), given the difficulty to manipulate the contents of the capsules.[b]
- Soft-gel capsules do not meet the pQTPP target attribute for stability since they are sensitive to humidity and high temperatures. The WHO-supplied multi-drug treatment (MTD) blister packs[c] include clofazimine capsules and are provided in humidity-resistant containers, which protect capsules from moisture. In addition, the capsules contain some excipients of potential concern for paediatric patients including, for example, propylene glycol and parabens.
- Clofazimine tablets (50 mg, 100 mg) have recently become available, and their availability is reflected in the way clofazimine is listed in section 6.2.5 Antituberculosis medicines, ie "solid oral dosage form: 50 mg; 100 mg". Tablets have a better stability profile than capsules (i.e., they are not sensitive to humidity and thus are preferred for LMICs) and they can be administered after being dispersed in water.[d]
- Acknowledging that antileprosy medicines are provided free of charge to countries and national leprosy programmes through WHO as part of MTD blister packs that include clofazimine capsules, the addition of clofazimine tablets to the EMLc would enable countries and programmes to also procure a formulation that can support the administration of indicated dose to younger children.
- Indeed, WHO guidelines indicate that the treatment for children with body weight below 40 kg requires single formulation medications since no MDT combination blister packs are available.[27]

[b] UK Neonatal and Paediatric Pharmacists Group, Online Discussion. Available online: http://nppg.org.uk/ (accessed on 25 October 2021).

[c] The standard WHO-recommended treatment regimen for leprosy includes a three-drug regimen of rifampicin, dapsone, and clofazimine for all leprosy patients, with a duration of treatment of 6 and 12 months for paucibacillary and multibacillary leprosy, respectively. For leprosy, clofazimine (as 50 mg or 100 mg soft-gel capsules) is provided free of charge to countries and national leprosy programmes through WHO, as part of multidrug regimens together with rifampicin and dapsone in standard blister packs. Access to clofazimine (capsules and tablets) outside the WHO donation programme might be hindered by the lack of clofazimine registration (for either the leprosy or the tuberculosis indication) by any SRA (https://apps.who.int/iris/bitstream/handle/10665/274127/9789290226383-eng.pdf)

[d] http://sentinel-project.org/wp-content/uploads/2021/07/Drug-Sheets_Dispersibles-April_2021-1.pdf

Recommendation for the EMLc pathway

- Considering the availability of clofazimine tablets, which can be administered after being dispersed in water and have a better stability profile than capsules, we recommend to list clofazimine as “solid oral dosage form: 50 mg; 100 mg” in line with how clofazimine is already listed in section 6.2.5.

Rifampicin

Current listing in section 6.2.4	Proposed listing in section 6.2.4
Solid oral dosage form: 150 mg; 300 mg	Solid oral dosage form: 150 mg; 300 mg **Oral liquid: 20 mg/mL**

Assessment findings

- 150 mg capsules provide very limited dose flexibility for young children, considering the WHO recommendation to administer 10-15 mg/kg once a month (for 6-12 months depending on paucibacillary or multibacillary disease) to children <10 years of age (or below 40 kg). Also, young children may have severe difficulties swallowing capsules whole. The same gap was noted for dosing young children with rifampicin for the prevention of leprosy.
- Rifampicin capsules are provided free of charge to countries and national leprosy programmes through WHO, as part of MTD blister packs together with clofazimine and dapsone.
- However, WHO guidelines indicate that the treatment for children with body weight below 40 kg requires single formulation medications since no MDT combination blister packs are available.[27]
- Rifampicin oral liquid (20 mg/mL) was found in some markets, and it is already listed in the EMLc in section 6.2.5 (antituberculosis medicines).

Recommendation for the EMLc pathway

- Considering the limited dose flexibility and the low acceptability of rifampicin capsules in children and acknowledging that some clinicians may be already using rifampicin syrup in very young children with leprosy, we recommend the addition of rifampicin oral liquid: 20 mg/mL to section 6.2.4. This would also align the way rifampicin is listed in sections 6.2.4 and 6.2.5

Recommendation for the GAP-f pathway

- Even though rifampicin oral liquid can enable the administration of the indicated dose to younger children with leprosy, thanks to higher dose flexibility and acceptability, this dosage form is not ideal. In fact, it requires protection from moisture, it is supplied in glass bottles and it contains several excipients of concerns including benzoates and bisulphites.
- Therefore, while acknowledging that few children below 10 years of age are affected by leprosy, we recommend looking into the potential development of age-appropriate formulations of rifampicin (eg, dispersible tablets), that can be used to dose younger children with leprosy. The potential utility of such formulation for children with tuberculosis or at risk of tuberculosis should also be explored.

Dapsone

Current listing in section 6.2.4	Proposed listing in section 6.2.4
Tablet: 25 mg; 50 mg; 100 mg	*No modification proposed*

Assessment findings

- WHO recommendations indicate that for children younger than 10 years, the dose must be adjusted according to body weight, ie, 2 mg/kg daily. Dapsone tablets are scored and allow for relatively small dose increments (ie, x12.5 mg). Also, they are supposed to be taken whole, limiting acceptability for younger children and older children who cannot swallow tablets whole.

Recommendation for the GAP-f pathway

- Considering the low acceptability of dapsone tablets for younger children, as well as the limited dose flexibility, while at the same time acknowledging that few children below 10 years of age are affected by leprosy, we recommend looking into the potential development of suitable paediatric formulations of dapsone.

Section 6.3 Antifungal medicines

The considerations listed in this section are based on information found in product labels and on the assessment done with the pQTPP and take into account comments shared by members of a WHO advisory group on antifungal medicines, consulted in the context of this project. A total of nine experts from both high-income and low-income countries provided their feedback.

Amphotericin B

Current listing in section 6.3	Proposed listing in section 6.3
Powder for injection: 50 mg in vial (as sodium deoxycholate or liposomal complex)	**Powder for injection: 50 mg in vial (liposomal complex)*** **Powder for injection: 50 mg in vial (as sodium deoxycholate)** ***Liposomal amphotericin B has a better safety profile than the deoxycholate formulation and should be prioritized for selection and use depending on local availability and cost.**

Assessment findings

- The two currently listed formulations of amphotericin B have different safety and efficacy profiles. The liposomal complex has a better safety profile, and it has become the standard of care, while deoxycholate is used only as a rescue medicine for very severe patients, such as those with comorbidities and frequent relapses.
- Members of the antifungal advisory group as well as WHO focal points for leishmaniasis indicated that other lipid-based formulations (not-liposomal) of amphotericin B are being used in some countries. Some experts indicated the use of a not-liposomal amphotericin B lipid complex in paediatrics. In Australia, it is (seldomly) used when liposomal amphotericin is not available. In EU, it is no longer available, while it is registered at the USFDA. Experts from Mali and China indicated that it is not available in their countries.

Additional findings

- There is a large cost difference between liposomal amphotericin B and the sodium deoxycholate formulation, with the former being significantly more expensive, limiting its availability in many countries due to unaffordability.
- Liposomal amphotericin B is preferred for use due to its better safety profile compared to the deoxycholate formulation, particularly in children. Selection and use of liposomal amphotericin B should be encouraged, and efforts made to improve affordability and access.

Recommendation for the EMLc pathway

- Given that the liposomal complex of amphotericin B is the standard of care for antifungal infections (and treatment of leishmaniasis, see 6.5.2), we recommend listing the liposomal and deoxycholate formulations separately, and including a note with the listing to indicate that liposomal amphotericin B is the preferred formulation because of its better safety profile.
- Based on evidence collected on the availability of non-liposomal amphotericin B lipid complex formulations in some countries, we recommend looking into the potential inclusion of this formulation upon having assessed the availability and use of such formulation in more countries.

- We recommend these changes to also apply to amphotericin B as listed in section 6.5.2 (see below)

Fluconazole

Current listing in section 6.3	Proposed listing in section 6.3
Capsule: 50 mg. Injection: 2 mg/mL in vial. Oral liquid: 50 mg/5 mL	Capsule: 50 mg. Injection: 2 mg/mL in vial. Oral liquid **or powder for oral liquid:** 50 mg/5 mL.

Assessment findings

- Fluconazole oral liquid was found in some markets both as a powder that requires reconstitution before administration, as well as a ready-made syrup. Some of the members of the antifungal expert advisory group indicated that both formulations are used in their country, while others indicated that only the powder or the syrup is available and used.

Recommendation for the EMLc pathway

- To acknowledge that the specific oral liquid formulation (ie, a powder for oral liquid or a ready-made syrup) found in countries may vary, we recommend rephrasing the listing to account for both products.

Griseofulvin

Current listing in section 6.3	Proposed listing in section 6.3
Oral liquid: 125 mg/5 mL Solid oral dosage form: 125 mg; 250 mg	*No modification proposed*

Assessment findings

- Griseofulvin is an old medicine and no longer the standard recommended treatment in most settings, but most antifungal experts recommended not to remove it from the EMLc given that it is still used in some LMICs, especially in tinea capitis endemic areas, especially because of its lower cost compared to newer alternatives. Therefore, removing it from the list would hinder access.

Recommendation for the EMLc pathway

- Considering that griseofulvin is still widely used in LMICs, we do not recommend removing it from the EMLc, even if better alternatives in terms of safety and efficacy are available.

Nystatin

Current listing in section 6.3	Proposed listing in section 6.3
Lozenge: 100 000 IU. Oral liquid: 50 mg/5 mL; 100 000 IU/mL. Tablet: 100 000 IU; 500 000 IU.	Lozenge: 100 000 IU. Oral liquid: ~~50 mg/5 mL;~~ 100 000 IU/mL. **Solid oral dosage form:** ~~100 000 IU~~; 500 000 IU

Assessment findings

- Nystatin lozenges are not widely available, but they may still be used in some countries. One of the experts consulted noted that in Mali, lozenges are still available and used in some areas because of ease of conservation compared to the oral liquid.
- Nystatin oral liquid allows for a high dose flexibility, and it is acceptable across the paediatric population, also given the presence of flavouring agents. A few excipients of concern were identified, including benzoates, which may cause allergic reactions. Based on the feedback received from members of the antifungal expert group, the oral liquid formulation of nystatin is the most widely used. A 50 mg/5 mL oral liquid formulation of nystatin could not be found.
- 100 000 IU tablets could not be found registered at the SRAs reviewed as part of this project. Based on the feedback received from experts of the antifungal expert group, this tablet strength is not available in any of the countries where experts are based.
- 500 000 IU tablets and capsules could be found in some markets. Nystatin dose for adults and adolescents indicated in product labels ranges from 500 0000 to 1 000 000 IU three or four times daily, corresponding to 3 to 6 tablets or capsules of the 500 000 IU formulation. However, most product labels reviewed, indicate that tablets are not recommended for use in infants and children up to 5 years of age. Indeed, as mentioned above, there is evidence that the oral liquid formulation (given at a dose of 1 mL four times daily, corresponding to 400 000 IU daily) is used in practice for younger children. The little utility of a 500 000 IU tablet strength in dosing young children was also highlighted by one of the experts consulted. However, this formulation may be used in young adolescents, depending on weight.

Recommendation for the EMLc pathway

- A preliminary assessment of the availability and use of nystatin lozenges globally suggest that lozenges are not widely available, but they may still be used in some countries. Therefore, we advise to retain this formulation in the EMLc. However, we recommend expanding this assessment by inquiring about the availability and use of lozenges in more countries, especially LMICs and potentially reconsider listing lozenges in the EMLc depending on the findings of this broader assessment.
- Given that only a 100 000 IU/mL formulation of nystatin oral liquid could be found, we recommend removing the 50 mg/5 mL oral liquid formulation from the EMLc.
- Given that 100 000 IU tablets could not be found in any of the markets reviewed as part of this project, we recommend removing them from the EMLc listing.
- Given that 500 000 IU capsules could be found in some markets, we recommend changing the listing to “solid oral dosage form”, to account for the availability of both tablets and capsules.

Section 6.5.2 Antileishmaniasis medicines

Amphotericin B

See section 6.3 Antifungal medicines

Miltefosine

Current listing in section 6.5.2	Proposed listing in section 6.5.2
Solid oral dosage form: 10 mg; 50 mg	*No modification proposed*

Assessment findings

- Miltefosine is dosed at 2.5 mg/kg per day for 28 days in children aged 2-11 years.[28] Despite the availability of a low-strength formulation (10 mg capsules, alongside 50 mg capsules), dose flexibility is limited. Moreover, capsules have low acceptability especially for younger children and older children who cannot swallow them whole.
- Miltefosine capsules need to be protected from moisture, which is not ideal for their use in LMICs.

Recommendation for the GAP-f pathway

- Considering the limited dose flexibility of miltefosine capsules, and especially the low acceptability of capsules in young children, we recommend to further explore the development of a flexible age-appropriate formulation, with improved characteristics in terms of stability and storage conditions.

Sodium stibogluconate or meglumine antimoniate

Current listing in section 6.5.2	Proposed listing in section 6.5.2
Injection: 100 mg/mL, 1 vial = 30 mL **or** 30%, equivalent to approximately 8.1% antimony (pentavalent) in 5 mL ampoule.	**Sodium stibogluconate** **Injection: 100 mg/mL in 30 mL vial** **Meglumine antimoniate** **Injection: 1.5 g/5 mL in 5 mL ampoule**

Assessment findings

- Sodium stibogluconate (SSG) and meglumine antimoniate (MA) are both pentavalent antimonials with similar chemical structures. However, given the different antimonial content, they have different efficacy and safety profiles.[28] SSG is more toxic, but it is still widely used by national programmes, especially in East Africa, also because of its lower price.

Recommendation for the EMLc pathway

- Considering the very different safety profile of SSG and MA, while also acknowledging that SSG is still widely used especially in East Africa and has a lower price than MA, we recommend retaining both formulations on the list, but listing them separately. Alternatively, a square box listing could also be considered.
- We also recommend that the listing should only specify the concentration and vial/ampoule size. Thus, we recommend removing the information on the percentage of antimonial content included.

Section 6.5.5.1 African trypanosomiasis

Fexinidazole*

Current listing in section 6.5.5.1	Proposed listing in section 6.5.5.1
Tablet: 600 mg *For the treatment of 1st and 2nd stage of human African trypanosomiasis due to *Trypanosoma brucei gambiense* infection	No changes proposed

Assessment findings

- Fexinidazole is currently recommended for children aged 6 years and above. It should be taken once daily for 10 days, with a loading dose over the first four days and a maintenance dose over the last six days. For people weighing 20-34 kg, the loading dose is 1200 mg, and the maintenance dose is 600 mg.[29]
- Fexinidazole tablets should be swallowed whole and should not be broken or crushed, as this affects bioavailability (increased bioavailability, with related toxicity effects).
- Fexinidazole tablets have extremely limited acceptability especially in younger children for whom fexinidazole is indicated, as they may have challenges swallowing tablets whole.
- Fexinidazole is currently listed in the EMLc for the treatment of 1st and 2nd stage of human African trypanosomiasis due to *Trypanosoma brucei gambiense* infection. Studies are ongoing in children ≥ 6 years (≥ 20 kg) to expand the indication for use of fexinidazole also for African trypanosomiasis due to *Trypanosoma brucei rhodeniense* infection.[30] The study has completed recruitment and follow-up for efficacy is ongoing and expected to be completed by November 2022. Data are being submitted to the EMA for a label update, and the EMA scientific opinion is expected in Q2 2023.

Recommendation for the EMLc pathway

- Given the expected upcoming expansion of indication for fexinidazole for use in *Trypanosoma brucei rhodesiense* infection, an application to similarly expand the EML/EMLc listing of fexinidazole should be sought.

Recommendation for the GAP-f pathway

- Given issues in administering the recommended dose of fexinidazole in younger children for whom the medicine is indicated, who cannot swallow tablets whole and considering that fexinidazole tablets cannot be broken or crushed without affecting the bioavailability, we recommend looking into the development of an age-appropriate formulation of fexinidazole (e.g., dispersible tablets). Indeed, EMA has already recommended the development of a child-friendly formulation of fexinidazole.[31]

Pentamidine

Current listing in section 6.5.5.1	Proposed listing in section 6.5.5.1
Powder for injection: 200 mg (as isethionate) in vial	Powder for injection: ~~200 mg;~~ **300 mg (as isethionate) in vial**
*To be used for the treatment of *Trypanosoma brucei gambiens*e infection	*To be used for the treatment of *Trypanosoma brucei gambiens*e infection

Assessment findings

- Pentamidine powder for injection 200 mg has been discontinued. The currently available formulation corresponds to a 300 mg powder for injection.
- Indeed, WHO guidelines for the treatment of gambiense human African trypanosomiasis indicate that pentamidine is supplied in vials with 300 mg of pentamidine isethionate powder.[29]
- All medicines for African trypanosomiasis are supplied through donation programmes via WHO.

Recommendation for the EMLc pathway

- Considering that the 200 mg strength of pentamidine powder for injection has been discontinued and that a 300 mg strength formulation is available, we recommend updating the listing in the EMLc accordingly.

Eflornithine*

Current listing in section 6.5.5.1	Proposed listing in section 6.5.5.1
Injection: 200 mg/mL (hydrochloride) in 100 mL bottle	Injection: 200 mg/mL (hydrochloride) in ~~100 mL~~ **50 mL bottle**
*To be used for the treatment of *Trypanosoma brucei gambiens*e infection	*To be used for the treatment of *Trypanosoma brucei gambiens*e infection

Assessment findings

- Eflornithine is donated by the manufacturers and distributed by WHO free of charge to countries. Eflornithine is supplied as part of the nifurtimox-eflornithine combination therapy (NECT) for second stage African trypanosomiasis caused by *Trypanosoma brucei gambiense* infection. The NECT kit comprises medicines and materials such as catheters, needles, syringes and others.
- From June 2022 onwards, the manufacturers will supply eflornithine in 50 mL bottles rather than 100 mL bottles and the NECT kit donated to countries will be modified accordingly.

Recommendation for the EMLc pathway

- Considering the recent change in the packaging of eflornithine solution for injection that will be donated by the manufacturers and distributed free of charge by WHO as part of the NECT kit, we recommend changing the bottle size to 50 mL.

Nifurtimox*

Current listing in section 6.5.5.1	Proposed listing in section 6.5.5.1
Tablet: 120 mg	Tablet **(scored): 30 mg**, 120 mg
*Only to be used in combination with eflornithine, for the treatment of *Trypanosoma brucei gambiens*e infection	*Only to be used in combination with eflornithine, for the treatment of *Trypanosoma brucei gambiens*e infection

Assessment findings

- Nifurtimox is dosed at 15 mg/kg daily in three divided doses (given every 8 hours) for 10 days.[29] 120 mg tablet are functionally scored and may be broken to obtain the corrected dose or, if needed, cut, crushed and diluted into food or water with sugar to facilitate their intake. The dosing table included in the WHO guidelines is complex and requires administration of 1/2, 3/4 or 1/4 fractions of the 120 mg tablets, which involves manipulation with risk of dosing errors. Indeed, while administering half tablet may be easily given the presence of a functional scoring line, administration of 3/4 or 1/4 tablets requires a pill cutter.
- Nifurtimox is donated by the manufacturers and distributed by WHO free of charge to countries for the treatment of gambiense human African trypanosomiasis. Nifurtimox (120 mg) is supplied as part of the nifurtimox-eflornithine combination therapy (NECT). The NECT kit comprises medicines and materials such as catheters, needles, syringes and others.
- 30 mg functionally scored tablets were found in some markets. This lower-dose formulation is more flexible than the 120 mg tablets and would avoid excessive tablet manipulation.

Recommendation for the EMLc pathway

- Given that 30 mg functionally scored tablets were found in some market, which would enable easier administration of the recommended dose across the paediatric age spectrum by also minimizing tablet manipulation, we recommend the inclusion of this tablet strength in the EMLc, considering that it is already listed in section 6.5.5.2. This would align nifurtimox listing across section 6.5.5.1 and 6.5.5.2. Acknowledging that the NECT kit distributed by WHO free of charge includes 120 mg tablets, we hope that the inclusion of 30 mg tablets into the EMLc may prompt additional discussion on the inclusion of a lower strength formulation of nifurtimox in the kit.
- We also recommend specifying that both the 30 mg and the 120 mg tablets have a functional scoring line.

Section 6.5.5.2 American trypanosomiasis

Benznidazole

Current listing in section 6.5.5.1	Proposed listing in section 6.5.5.1
Tablet: 12.5 mg; 100 mg Tablet (scored): 50 mg	Tablet: 12.5 mg Tablet **(scored)**: 50 mg; 100 mg

Assessment findings

- Benznidazole 50 mg and 100 mg tablet are functionally scored tablets which can be split into one-half or one quarter at the scored lines to provide doses less than 50 mg or 100 mg. This allows for a greater dose flexibility considering the WHO recommended dose of 10 mg/kg daily given in two divided dose (for 60 days) for children up to 12 years of age.
- The USFDA product label indicates that benznidazole tablets may be made into a slurry in a specified volume of water and provide specific instructions on how to prepare it and administer it across paediatric weigh bands (including for children <15 kg).[32] This enhances acceptability especially for younger children, or older children who cannot swallow tablets whole.

Recommendation for the EMLc pathway

- Considering that the presence of functional scoring lines on the 50 mg and 100 mg tablets enables a much greater flexibility to administer the correct dose to children, we recommend including this information in the EML listing of benznidazole.
- Depending on the outcome of ongoing discussions on registration places and location of manufacturing of benznidazole, the 50 mg tablet formulation might be discontinued in the future, and the manufacturing will focus on the 12.5 mg and 100 mg tablets. This development should be followed closely, and the 50 mg tablet formulation should be reviewed again for appropriateness in the context of the 2025 update of the EML/EMLc.

Nifurtimox

Current listing in section 6.5.5.1	Proposed listing in section 6.5.5.1
Tablet: 30 mg; 120 mg; 250 mg.	**Tablet (scored):** 30 mg; 120 mg; ~~250 mg~~

Assessment findings

- Nifurtimox is indicated for children aged 0-18 years for American trypanosomiasis (Chagas) and dosages indicated in product labels are based on body weight and they include narrow weigh bands with accurate dose to administer, which may require half tablets.
- Both the 30 mg and the 120 mg tablets are functionally scored, which allows for a high dose precision.
- A 250 mg strength of nifurtimox tablet is not available on the market. Available presentations include 30 mg and 120 mg functionally scored tablets, which can be dispersed into a slurry with water to dose patients who have difficulty swallowing them.

Recommendation for the EMLc pathway

- Considering that a 250 mg tablet is not available on the market, we recommend removing this specific strength from the EMLc listing.
- Acknowledging the relevance of the functional scoring lines for both nifurtimox tablet strengths to increase dose flexibility and precision, we recommend specifying this information for both formulations.

Section 6.6 Medicines for ectoparasitic infections

See section 6.1.1 Intestinal anthelminthics for the modifications proposed to ivermectin.

Section 8.1 Immunomodulators for non-malignant disease

Adalimumab

Current listing in section 8.1	Proposed listing in section 8.1
Injection: 40 mg/0.8 mL; 40 mg/0.4 mL	Injection: 40 mg/0.8 mL; 40 mg/0.4 mL; **20mg/0.4mL; 10 mg/0.2 mL**

Assessment findings

- The injection partially met the attribute for acceptability due to injection site reactions (pain, swelling, redness, itchiness) being very common. In addition, it contained an excipient of potential concern (polysorbate 80) and requires storage at 2-8°C.
- The product is presented as a pre-filled syringe for SC administration, and it was not clear if a partial dose could be administered; depending on the PL, patients 10-< 30 kg require a 10 or 20 mg dose every other week.
- Other pre-filled dose strength/volumes are available in some markets, e.g., 20 mg/0.4 mL, 20mg/0.2mL, 10 mg/0.2mL and 10 mg/0.1 mL.

Recommendation for the EMLc pathway

- It is recommended the global availability of other syringe dose strengths/volumes is determined and they are considered for addition to the EMLc to facilitate dosing to young patients. For example, the addition of 20 mg/0.4 mL and 10 mg/0.2 mL syringes is proposed, to facilitate dosing in patients 10-< 30 kg.

Azathioprine

Current listing in section 8.1	Proposed listing in section 8.1
Powder for injection: 100 mg (as sodium salt) in vial Tablet (scored): 50 mg	Powder for injection: **50 mg**; 100 mg (as sodium salt) in vial Tablet (scored): 50 mg **Tablet: 25 mg** **Oral liquid: 10 mg/mL**

Assessment findings

- Overall, the injection is acceptable for the paediatric population, although the undiluted solution is irritant. Reconstitution and dilution should be performed immediately before use. However, the solution is stable for up to 5 days, whilst once diluted, it is stable for up to 24 hours only.
- A 50 mg vial size is available in some markets.
- The tablet had low acceptability in young children unable to swallow them and those requiring a lower dose. Although the scored tablet may be split to provide 25 mg dose increments, some PLs indicated the tablets should not be split or crushed (due to health and safety).
- A 25 mg tablet is available in some markets. In addition, a 10 mg/mL oral suspension is available in the UK/Europe (not fully reviewed, contains preservative and sweetener, and has a 12-week in-use shelf life).

Recommendation for the EMLc pathway

- It is recommended the global availability of the powder for injection 50 mg vial size is determined and considered for addition to the EMLc. A smaller vial size may facilitate dosing to young patients and reduce potential wastage of unused solution.
- It is recommended that the 25 mg tablet is considered for addition to the EMLc to avoid the need for caregivers to split the 50 mg tablet, taking into account the potential health and safety risks associated with the handling of azathioprine.
- To facilitate the dosing of young patients and those unable to swallow tablets, it is recommended to further evaluate and consider the addition of the 10 mg/mL oral liquid to the EMLc.

Ciclosporin

Current listing in section 8.1	Proposed listing in section 8.1
Capsule: 25 mg Concentrate for injection: 50 mg/mL in 1 mL ampoule	Capsule: 25 mg Concentrate for injection: 50 mg/mL in 1 mL ampoule **Oral solution: 100 mg/mL**

Assessment findings

- The capsule did not meet the target for patient acceptability for young patients due to difficulty in swallowing it and those requiring a lower dose than 25 mg (2-15 mg/kg in 2 divided doses).
- In addition, the capsule did not meet the target for excipient safety as it contains several excipients of concern, e.g., ethanol or ethyl lactate (hydrolyses to ethanol), macrogolglycerol hydroxystearate, Transcutol. Since they are soft capsules, they require moisture-protective packaging.
- An oral solution (100 mg/mL) is available in some markets but contains several excipients of concern (e.g., ethanol, propylene glycol, polyoxyl 35 castor oil), may require dilution with a beverage prior to administration and has a short in-use shelf-life.
- The concentrate injection contains two excipients of concern; polyoxyl 35 castor oil (65 %), which can cause severe anaphylactoid reactions when given IV, and ethanol (26 %). Due to the high risk associated with these excipients, the formulation did not meet the excipient safety attribute.
- Once opened, the ampoule contents should be used immediately. Diluted solutions should also be used straight away but may be stored for up to 24 hours at 2-8°C.
- A 250 mg/5mL ampoule is also available in some markets but not proposed for addition due to its larger size and likelihood of wastage.

Additional findings

- Given the high clinical importance of preventing and treating organ transplant rejection in children, inclusion of an oral solution formulation of ciclosporin on the EMLc was considered essential to provide access to a more child-appropriate formulation for children, even if the excipient profile is not optimal.

Recommendation for the EMLc pathway

- Inclusion of ciclosporin oral solution 100 mg/mL on the EMLc is recommended.

Recommendation for the GAP-f pathway

- Although an oral liquid ciclosporin oral liquid is available, it is not considered to be optimal due to its excipient profile. It is therefore recommended to investigate the development of an alternative age-appropriate formulation of ciclosporin, containing excipients with a better safety profile, to facilitate dosing to young patients and those unable to swallow capsules.
- The concentrate for injection is also sub-optimal in terms of excipient safety and the development of an alternative formulation containing excipients with a better safety profile is recommended.

Section 8.2.1 Cytotoxic medicines

It should be noted that due to the toxicity and irritancy of cytotoxic medicines, many of the injection products listed in this section require the use of personal protective equipment (PPE) including for example, gloves, goggles/face mask, and gown, for all handling. In addition, a designated area such as a laminar flow cabinet should be used, and special precautions taken for the handling of any waste materials. Where such measures are required, the formulation did not meet the target attribute for handling and administration. However, to avoid repetition, this has not been specified in the assessment findings provided below.

Arsenic trioxide

Current listing in section 8.2.1	**Proposed listing in section 8.2.1**
Concentrate for solution for infusion: 1 mg/mL	Concentrate for solution for infusion: 1 mg/mL; **2 mg/mL**

Assessment findings

- The concentrate for solution for infusion injection solution is acceptable for paediatric patients. It must be diluted immediately after withdrawal from the vial. Once diluted it should be used immediately but may be stored for up to 24 hours at 2-8°C.
- A 2 mg/mL concentrate for infusion solution appears to be available in some markets instead of the 1 mg/mL concentration (e.g., USA).

Recommendation for the EMLc pathway

- It is recommended that the global availability of the 1 mg/mL concentrate for solution for infusion is clarified and to consider the addition to the EMLc of the 2 mg/mL concentration formulation of arsenic trioxide solution for infusion.

Bleomycin

Current listing in section 8.2.1	Proposed listing in section 8.2.1
Powder for injection: 15 mg (as sulfate) in vial	Powder for injection: **15 000 IU** (as sulfate) in vial

Assessment findings

- The powder for injection is generally acceptable, although pain may be experienced on administration (IV and IM) and it may require storage at 2-8°C. The reconstituted solution should be used immediately but may be stored for up to 24 hours at 2-8°C.
- Product labels recommend bleomycin is prescribed in IU or Units and not mg. For example, in the UK and Australia bleomycin strength is listed in IU, whilst in the USA it is listed as Units. (UK/Europe: "Posology for all therapeutic indications is provided in IU and not in mg..... This product should therefore only be prescribed in international units (IU)." USA: “A Unit of Bleomycin is equal to the formerly used mg activity (latter is a misnomer and was changed to Units to be more precise.)”

Recommendation for the EMLc pathway

- It is recommended the EMLc listing is updated such that the product strength is expressed in IU and not mg, to reflect dosing protocols.

Calcium folinate (leucovorin calcium)

Current listing in section 8.2.1	Proposed listing in section 8.2.1
Injection: 3 mg/mL in 10 mL ampoule Tablet: 5 mg; 15 mg; 25 mg	Injection: 3 mg/mL in 10 mL ampoule**; 7.5 mg/mL in 2 mL ampoule; 10 mg/mL in 5 mL ampoule** Tablet: 5 mg; 15 mg; 25 mg

Assessment findings

- The injection solution is acceptable for paediatric patients although the IM route is less preferred in neonates and infants. It should be used immediately but diluted solutions may be stored for up to 24 hours at 2-8°C.
- The 3 mg/mL in 10 mL size ampoule was not found in the SRA territories interrogated, although other vial sizes and concentrations were found, e.g., UK a 3 mg/mL in 1 mL ampoule is available. In addition, 7.5mg/mL (as 15 mg/2 mL ampoule) and 10mg/mL (as 50 mg/5 mL, 100 mg/10 mL, 300 mg/30mL glass vials) are available in UK, Australia, and Europe. A powder for injection was also available in some markets (e.g., USA, some European territories).
- The 5 mg and 25 mg tablet dose strengths of calcium folinate appeared to have limited availability in some markets (e.g., UK, Australia). A 10 mg strength tablet was also available elsewhere (e.g., USA). Overall, the tablet did not meet the target for acceptability in young patients due to difficulties in swallowing. (The tablet may be scored but splitting was not described in the PLs interrogated).

Additional findings

- Calcium folinate is also commonly known by the United States Adopted Name (USAN) “leucovorin calcium”. Including leucovorin calcium as an alternative name in the listing for calcium folinate is suggested.

Recommendation for the EMLc pathway

- It is recommended the global availability of calcium folinate injection solution and powder for injection is clarified, including concentrations and vial sizes, and the EMLc listing updated accordingly. It is suggested that 7.5 mg/mL in 2 mL ampoule and 10 mg/mL in 5 mL ampoule are considered for addition.
- It is recommended the global availability of calcium folinate tablet strengths is clarified, and the EMLc listing considered to be updated if required.

Recommendation for the GAP-f pathway

- It is recommended to investigate the development of an age-appropriate oral formulation of calcium folinate.

Cyclophosphamide

Current listing in section 8.2.1	Proposed listing in section 8.2.1
Powder for injection: 500 mg; 1 g; 2 g in vial Tablet: 25 mg; 50 mg	Powder for injection: 500 mg; 1 g; 2 g in vial **Solid oral dosage form**: 25 mg; 50 mg

Assessment findings

- The powder for injection is generally acceptable for the paediatric population. Temperature fluctuations can lead to the drug power melting and so should be avoided. Once reconstituted, it is recommended the solution, or diluted solution, is used immediately, although both are reported to be stable for short periods when stored at 25°C or 2-8°C.
- The 25 mg dose strength tablet appeared to be less widely available compared to the 50 mg tablet (e.g., not available in UK or Australia). The diameter of the 25 mg tablet was reported to be 8 mm whilst that of the 50 mg strength was 11 mm. Due to the size and dose strength of the tablets, they did not meet the target for acceptability in young patients and only partially met this attribute for those aged 6-12 (may be suitable from approx. 8 years).
- Cyclophosphamide capsules 25 mg and 50 mg appear to be available in some markets.
- It was reported that an oral liquid preparation can be extemporaneously prepared by dissolving the powder for injection in Aromatic Elixir USP; this would not meet the excipient safety and stability attributes due to the inclusion of e.g., “alcohol” and syrup, and short-term shelf life with the need for storage at 2-8°C.

Recommendation for the EMLc pathway

- To reflect the availability of capsules, it is recommended the EMLc listed in modified to solid oral dosage form, to allow greater flexibility in procurement.

Recommendation for the GAP-f pathway

- It is recommended the development of an age-appropriate oral formulation is investigated, for administration to young patients unable to swallow the tablet/capsule and those requiring a lower dose. (Although dose modification to e.g., twice weekly dosing in infants is undertaken, there are still challenges in medicine administration).

Cytarabine

Current listing in section 8.2.1	Proposed listing in section 8.2.1
Powder for injection: 100 mg in vial	Powder for injection: 100 mg in vial **Solution for injection: 100 mg/mL in vial**

Assessment findings

- Limited information was available for cytarabine powder for injection, and it did not appear to be authorized in the SRA territories interrogated. It was noted that it requires reconstitution with WFI containing benzyl alcohol (not recommended for use in neonates/infants).
- Cytarabine injection solution is widely available in various concentrations and vial sizes (e.g., 20 mg/mL, 100 mg/mL (in UK), and 2 g/20 mL, 500 mg/25 mL, 1 g/10 mL, 5000 mg/50 mL, 40 mg/2 mL, 100 mg/5 mL, 500 mg/5 mL vials (in Australia). A brief review of the solution found it to be acceptable for paediatric patients. As with other injection solutions, it requires immediate use after opening, however diluted solutions may be stored for up to 24 hours at 25°C.

Additional findings

- Cytarabine 1 g powder for injection formulation was reported to be used and available in Asia.

Recommendation for the EMLc pathway

- It is recommended the global availability of cytarabine power for injection is clarified with a view to updating the EMLc to reflect available formulations and strengths in the future.
- It is recommended cytarabine injection solution 100 mg/mL is added to the EMLc.

Dacarbazine

Current listing in section 8.2.1	Proposed listing in section 8.2.1
Powder for injection: 100 mg in vial	Powder for injection: 100 mg; **200 mg** in vial

Assessment findings

- The 100 mg vial size had limited availability in the SRA territories interrogated (UK only); a 200 mg vial size appeared to be more broadly available.
- The product is acceptable for paediatric patients. It should be used immediately after reconstitution, although it may be stored for up to 24 hours at 2-8°C.

Recommendation for the EMLc pathway

- It is recommended the global availability of the 100 mg vial size is clarified, and the 200 mg strength be considered for addition to the EMLc, given its apparent broader availability. (However, it is recognized small vial sizes are preferred for paediatric patients).

Daunorubicin

Current listing in section 8.2.1	Proposed listing in section 8.2.1
Powder for injection: 50 mg in vial	Powder for injection: 50 mg; **20 mg** in vial **Injection solution: 2 mg/mL; 5 mg/mL**

Assessment findings

- The 50 mg vial size was not authorized in any of the SRA territories interrogated; a 20 mg powder for injection was available in the UK and USA, whilst a solution for injection 2 mg/mL and 5 mg/mL was available in Australia and USA respectively (both solutions require storage at 2-8°C).
- The injection is suitable for the paediatric population but may cause burning or irritation at the injection site (due to drug). The powder requires reconstitution and dilution before being added to a 0.9 % sodium chloride infusion. The reconstituted solution should be used immediately, although it may be stored for up to 24 hours at 2-8°C.

Recommendation for the EMLc pathway

- It is recommended the global availability of the powder for injection 50 mg is clarified, and the 20 mg strength considered for addition to the EMLc. In addition, the availability of the solution for injection and concentrations should be evaluated and considered for addition to the EMLc, if appropriate; 2 mg/mL and 5 mg/mL have been proposed for addition. (It is recognized the solutions require refrigerated storage, but they require less manipulation than the powder).

Doxorubicin

Current listing in section 8.2.1	Proposed listing in section 8.2.1
Powder for injection: 10 mg; 50 mg (hydrochloride) in vial	Powder for injection: 10 mg; 50 mg (hydrochloride) in vial **Injection solution 2 mg/mL (hydrochloride) in vial**

Assessment findings

- The powder for injection is not available in all SRA markets interrogated and some PLs appear to be discontinued. Doxorubicin injection solution 2 mg/mL is more widely available (UK, USA, Australia) and is available in various vial sizes, e.g., 5, 10, 25, 50 and 100 mL.
- In general, the injection is acceptable for paediatric patients, although it may cause stinging/burning at the injection site. The powder for injection only partially met the excipient safety attribute as it may contain lactose and preservative. It requires reconstitution and is administered via dilution during infusion. The reconstituted solution may be stored for up to 15 days at 2-8°C or 7 days at 15-30°C, although unused solution must be discarded.
- The injection solution does not contain any excipients of concern or require reconstitution, although it should be stored at 2-8°C.

Additional findings

- Shortages of doxorubicin 10 mg powder for injection have been reported.

Recommendation for the EMLc pathway

- It is recommended the global availability of doxorubicin power for injection is clarified with a view to updating the EMLc to reflect available formulations and strengths.
- Considering its wider availability, it is recommended doxorubicin 2mg/mL injection solution is considered for addition to the EMLc.

Etoposide

Current listing in section 8.2.1	Proposed listing in section 8.2.1
Capsule: 50 mg; 100 mg Injection: 20 mg/mL in 5 mL ampoule	Capsule: 50 mg; 100 mg Injection: 20 mg/mL in 5 mL ampoule **Powder for injection: 100 mg (as phosphate) in vial**

Assessment findings

- The capsule did not meet the target for acceptability in young patients who may not be able to swallow them, as well as those requiring a lower dose. They partially met the excipient attribute as they contain small quantities of preservatives and colorants.
- In addition, the capsules require protection from moisture and excessive heat (they are soft capsules).
- It was noted that some PLs appear to have been discontinued and therefore the availability of the capsule product was not clear.
- The injection may cause injection site reactions to occur. It did not meet the target for excipient safety as it contains several excipients of concern, e.g., ethanol (33 % volume) and polysorbate 80, and may contain benzyl alcohol. The solution must be diluted before administration and used immediately although it may be stored for up to 24 hours.
- Etoposide powder for injection is available in some markets (as etoposide phosphate); it does not contain any excipients of concern, although it must be reconstituted and requires storage at 2-8°C.

Recommendation for the EMLc pathway

- It is recommended to consider the addition of etoposide powder for injection 100 mg in vial (as phosphate) to the EMLc due to its superior excipient safety profile compared to the injection solution. (It is however recognized that its requirement for refrigerated storage may be a challenge in some markets).

Recommendation for the GAP-f pathway

- It is recommended the development of an age-appropriate oral formulation is investigated, for administration to young patients unable to swallow the capsule and those requiring a lower dose. It may also be necessary to develop an age-appropriate oral formulation for older paediatric patients if the capsules are found to be unavailable.

Fluorouracil

Current listing in section 8.2.1	Proposed listing in section 8.2.1
Injection: 50 mg/mL in 5 mL ampoule	Injection: 50 mg/mL in **~~5 mL ampoule~~ vial**

Assessment findings

- The injection is acceptable for paediatric patients. Once opened and/or diluted, it should be used immediately although it may be stored for up to 24 hours at 2-8°C.
- Other vial sizes are available, e.g., 10 mL, 20 mL, 50 mL and 100 mL. In addition, a 25 mg/mL concentration (in 10, 20, and 100 mL vials) is available in the UK.

Recommendation for the EMLc pathway

- It was noted that PLs referred to injection vials and not ampoules. In addition, various vial sizes of the injection solution are available, and it is therefore recommended to remove specified sizes to maximize flexibility.
- It is recommended the global availability of different injection concentrations is clarified and the EMLc entry updated if required.

Hydroxycarbamide (hydroxyurea)

Current listing in section 8.2.1	Proposed listing in section 8.2.1
Solid oral dosage form: 200 mg; 250 mg; 300 mg; 400 mg; 500 mg; 1 g	Solid oral dosage form: **100 mg**; 200 mg; ~~**250 mg;**~~ 300 mg; 400 mg; 500 mg; 1 g

Assessment findings

- The 500 mg dose strength solid oral dosage form (capsule and tablet) appeared to be the most widely available dose strength (e.g., 200, 250, 300 and 400 mg not available in UK or Australia but authorized in USA, although 250 mg appears to be discontinued).
- Tablets and capsules had poor acceptability in young children due to difficulty in swallowing (500 mg capsules reported to be Size 0). However, according to some PLs, the capsule contents may be mixed with water to facilitate dosing although palatability is not known, but likely to be poor due to a lack of taste masking. Also, some PLs state the tablets can be broken. It is recommended gloves are worn during any manipulation due to the toxicity of the drug.
- Tablets and capsules require protection from moisture.
- A 100 mg hydroxycarbamide tablet that can be split into two equal parts is available in some markets (e.g., UK, USA), although indicated for sickle cell disease. In addition, an oral solution 100mg/mL is available in the UK, although it requires storage at 2-8°C.
- While hydroxycarbamide is the international non-proprietary name of the medicine, it is also commonly known in many settings by the United States Adopted Name (USAN) 'hydroxyurea'.

Recommendation for the EMLc pathway

- The WHO Childhood Cancer team noted that only the 500 mg dose strength is available in the countries they had interviewed. In addition, the 250 mg dose strength appears to be discontinued. It is therefore recommended the 250 mg solid oral dosage form is removed from the EMLc, the global availability of the other strengths confirmed, and the EMLc entry updated accordingly.
- It is recommended the 100 mg strength tablet is considered for addition to the EMLc, to facilitate dosing to young patients.
- Including 'hydroxyurea' as an alternative name in the listing for hydroxycarbamide is recommended.

Mercaptopurine

Current listing in section 8.2.1	Proposed listing in section 8.2.1
Tablet: 50mg	Tablet: 50mg **Oral liquid: 20 mg/mL**

Assessment findings

- The tablet had poor acceptability for young patients unable to swallow it or requiring a lower dose than 50 mg; the tablet is reported to be 10 mm diameter. (One PL stated "do not administer to patients who are unable to swallow tablets"). Although some mercaptopurine tablets are scored, this does not appear to be intended for breaking.
- The tablets require protection from moisture and light.
- An oral suspension (liquid) 20 mg/mL is available in some markets (e.g., UK, Australia), but contains several excipients of concern (e.g., preservatives, aspartame, sucrose) and has a short shelf life (15 months) and an in-use shelf life of 56 days.

Additional findings

- From the PENTA surveys of health professionals, it was reported that an oral liquid formulation of mercaptopurine is not available in some settings but would be highly valuable to facilitate paediatric dosing.
- It was also reported that in settings where it is available, the cost of mercaptopurine oral liquid is high, thereby limiting access.

Recommendation for the EMLc pathway

- It is recommended the oral liquid 20mg/mL is considered for addition to the EMLc. Although it has sub-optimal excipient safety and stability, it will enable the correct and flexible dosing of young patients as well patients who have difficulty in swallowing tablets.

Recommendation for the GAP-f pathway

- It is recommended the development of an age-appropriate oral formulation is investigated, with superior excipient safety and stability compared to the 20 mg/mL oral liquid.

Methotrexate

Current listing in section 8.2.1	Proposed listing in section 8.2.1
Powder for injection: 50 mg (as sodium salt) in vial Tablet: 2.5 mg (as sodium salt)	Powder for injection: 50 mg (as sodium salt) in vial **Injection solution: 50 mg/2 mL, 1000 mg/10 mL in vial** Tablet: 2.5 mg (as sodium salt)

Assessment findings

- The powder for injection may have limited availability since it does not appear to be authorized in many SRA territories (USA only).
- The powder for injection is acceptable for paediatric patients, although local injection site reactions may occur if given IM. It requires reconstitution before use and may be further diluted for infusion. After dilution the solution should be used immediately although it may be stored for up to 24 hours at 2-8°C.
- A methotrexate solution for injection is available (e.g., UK and Australia). Various concentrations and vial sizes are available, 50 mg/2 mL vial, 250 mg/10 mL vial, 500 mg/20 mL vial, 1000 mg/10 mL vial, 1000 mg/40 mL vial. Pre-filled pen/syringe/injectors are also listed in these markets, e.g., 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 25 mg, 27.5 mg, 30 mg.
- The tablet did not meet the acceptability target in young patients unable to swallow it (size not known). It partially met the acceptability target in older children since some patients may be required to take several tablets per dose.
- Other tablet strengths are widely available, e.g., 10 mg. (Also 5, 7.5 and 15 mg may be available in some markets). However, due to risk of methotrexate mis-dosing, higher strength tablets will not be proposed for addition to the EMLc.
- A 2 mg/mL oral solution is available in the UK, although it contains several excipients of concern (preservatives, sweeteners) and has a short shelf life (18 months) and a short in-use shelf life (3 months).
- A 2.5 mg/mL oral solution is available in the USA, but contains several excipients of concern (preservatives, sweeteners), requires storage at 2-8°C and has a short in-use shelf life of 60 days.

Additional findings

- Inclusion of higher strength methotrexate injection solution was considered important to facilitate dosing in treatment protocols that involve high-dose methotrexate.
- Preservative-free formulations of methotrexate are necessary for intrathecal use.

Recommendation for the EMLc pathway

- Given its broad availability, it is recommended the injection solution is considered for addition to the EMLc. It is proposed to include 50 mg/2 mL and 1000 mg/10 mL vials.
- It is recommended the clinical need for an oral liquid to facilitate dosing in young patients is ascertained and if required, considered for addition to the EMLc. The 2 mg/mL oral liquid described above may be superior to the 2.5 mg/mL formulation due to its better stability, without the need for cold storage. However, the global availability of oral liquid formulations should be confirmed.

Recommendation for the GAP-f pathway

If there is a clinical need, it is recommended that the development of an age-appropriate oral formulation for dosing young children is investigated, with superior stability compared to currently available oral liquid formulations.

Pegaspargase

Current listing in section 8.2.1	Proposed listing in section 8.2.1
Injection: 3,750 units/5 mL in vial	Injection: 3,750 units/5 mL in vial **Powder for injection: 3,750 units in vial**

Assessment findings

- The injection is acceptable for paediatric patients although care is required when measuring low doses for young children and infants (0.1 mL required). Since unused solution should be discarded, there is potential for high wastage when treating these patients.
- The product requires storage at 2-8°C. It may be diluted for infusion, and the diluted solution may be stored for up to 24-48 hours.
- Pegaspargase is presented as a powder for injection in the UK and Australia. This requires reconstitution before use and may be diluted further for infusion. As with the solution injection, it requires storage at 2-8°C.

Recommendation for the EMLc pathway

- It is recommended the EMLc listing is updated to reflect the availability of an injection solution and powder for injection.

Procarbazine

Current listing in section 8.2.1	Proposed listing in section 8.2.1
Capsule: 50mg (as hydrochloride)	Capsule: 50mg (as hydrochloride) ***No changes proposed***

Assessment findings

- The capsule had poor acceptability for young patients unable to swallow it or requiring a lower dose than 50 mg. (The size of the capsule is not known).
- The capsules contain one excipient of concern (mannitol) and require protection from moisture and light.

Recommendation for the EMLc pathway

- No changes proposed

Recommendation for the GAP-f pathway

- It is recommended that the need for and the development of a lower dose strength and age-appropriate oral formulation is investigated.

Tioguanine

Current listing in section 8.2.1	Proposed listing in section 8.2.1
Solid oral dosage form: 40mg	Solid oral dosage form: 40mg ***No changes proposed***

Assessment findings

- Tioguanine solid oral dosage form (tablet or capsule) had poor acceptability for young patients unable to swallow it (tablets reported to be 9 mm diameter, capsule size not known). Some PLs suggest daily doses should be calculated in multiples of 20 mg, and that scored tablets may be split accordingly. However, other PLs state this is not recommended, and that splitting is to facilitate swallowing only. Gloves should be worn for handling due to the toxicity of the drug. Limited information on capsules was available (they not authorized in the SRA territories interrogated, but available in other markets, e.g., India).
- It was not possible to identify other dose strength tioguanine (thioguanine) tablets or capsules authorized by the SRAs interrogated. However, 10 mg and 20 mg tioguanine tablets appear to have received conditional marketing approval in the Netherlands for the treatment of inflammatory bowel disease (Crohn disease, ulcerative colitis) in adults (https://db.cbg-meb.nl/pars/h114681.pdf).
- The tablets require protection from moisture and light.

Additional findings

- Use of tioguanine was reported to be limited, with treatment regimens employing mercaptopurine in preference to tioguanine. Priority for paediatric formulation development would be higher for mercaptopurine than tioguanine.

Recommendation for the EMLc pathway

- It is recommended the availability of 20 mg and 10 mg tioguanine solid oral dosage forms is clarified, and considered for potential future addition to the EMLc, if appropriate.

Recommendation for the GAP-f pathway

- It is recommended the need for development of an age-appropriate oral formulation is investigated, to facilitate the dosing of young children.

Vinblastine

Current listing in section 8.2.1	Proposed listing in section 8.2.1
Injection: 10 mg/10 mL (sulfate) in vial Powder for injection: 10 mg (sulfate) in vial	***No changes proposed***

Assessment findings

- The injection is suitable for the paediatric population and does not contain any excipients of concern but may cause pain or irritation at the injection site (due to drug). It requires storage at 2-8°C and protection from light. Following dilution, it should be used immediately, although it may be stored for up to 24 hours at 2-8°C.
- Limited information was available on the 10 mg powder for injection, and it appears to have been discontinued in the SRA markets interrogated.
- The powder requires reconstitution, and the resulting solution may be further diluted for infusion. As with vinblastine injection solution, the powder must be stored at 2-8°C, protected from light. Unused solution should be discarded unless a diluent containing a preservative is used for reconstitution, in which case it may be stored for up to 28 days at 2-8°C. (It should be noted that the preservative benzyl alcohol is not recommended in children under 3 years of age).

Additional findings

- Availability and use of vinblastine powder for injection was reported in some settings.

Recommendation for the EMLc pathway

- The ongoing availability of the powder for injection should be monitored. However, it does not appear to offer any benefits over the injection solution and requires more manipulation and could therefore be considered for future removal from the EMLc, if the injection solution is available.

Vincristine

Current listing in section 8.2.1	Proposed listing in section 8.2.1
Injection: 1 mg/mL (sulfate); 2 mg/2 mL (sulfate) in vial Powder for injection: 1 mg; 5 mg (sulfate) in vial	***No changes proposed***

Assessment findings

- The injection is suitable for the paediatric population and does not contain any excipients of concern, but the drug is a vesicant and may cause a severe local reaction at the injection site. The product requires storage at 2-8°C and protection from light. Following dilution, it should be used immediately, although it may be stored for up to 24 hours at 2-8°C.
- Limited information was available on the powder for injection; the 1 mg vial size appears to be authorized in Australia, but the PL/SmPC was not provided on the TGA website. The powder does not appear to be available in other SRA markets interrogated, although 5 mg and 10 mg vials appear to be available in India.
- The powder requires reconstitution, and the resulting solution may be further diluted for infusion. No information was available on its stability or required storage conditions.

Additional findings

- Availability and use of vincristine powder for injection was reported in some settings.

Recommendation for the EMLc pathway

- The ongoing availability of vincristine powder for injection should be monitored. However, it does not appear to offer any benefits over the injection solution and requires more manipulation and could therefore be considered for future removal from the EMLc, if the injection solution is available.

Vinorelbine

Current listing in section 8.2.1	Proposed listing in section 8.2.1
Capsule: 20 mg; 30 mg; 80 mg Injection: 10 mg/mL in 1 mL vial; 50 mg/5 mL in 5 mL vial	Capsule: 20 mg; 30 mg; ~~80 mg~~ Injection: 10 mg/mL in **1 mL and 5 mL vials.**

Assessment findings

- Vinorelbine injections were found in some markets at the concentration listed on the EMLc, ie 10 mg/mL. Two vial sizes (1 mL and 5 mL) could be found, corresponding to 10 mg and 50 mg of vinorelbine.
- Vinorelbine capsules are available in three strengths, which allow for some dose flexibility at the indicated dose of 60 mg/m^2. However, they are not acceptable for children below 6 years of age who are not able to swallow capsules whole, and there may be acceptability issues also in older children.
- The recommended dose of vinorelbine is 60 mg/m^2, corresponding to 66 mg for a child with a BSA of 1.1 m^2 (30 kg) and 78 mg for a child with BSA of 1.3 m^2 (40 kg). Therefore, an 80 mg capsule has limited utility in children and young adolescents aged below 12 years.

Recommendations for the EMLc

- Given that the two formulations of vinorelbine injection listed on the EMLc correspond to the same concentration, with different amounts of the medicine included in each vial, we recommend listing the injection as “Injection: 10 mg/mL in 1 mL and 5 mL vials”.
- Given the limited utility of an 80 mg capsule to dose vinorelbine in children and young adolescents below 12 years of age, we recommend considering its removal from the EMLc.

Recommendations for the GAP-f pathway

- Noting a formulation gap for younger children, who cannot be given vinorelbine if they are not able to swallow soft-gel capsules whole, we recommend looking into the potential development of an age-appropriate formulation that can aid administration in children below 6 years, with improved stability characteristics (ideally not needing to be stored at refrigerated conditions).

Section 8.2.2 Targeted therapies

All-trans retinoid acid (ATRA)

Current listing in section 8.2.2	Proposed listing in section 8.2.2
Capsule: 10 mg.	*No modification proposed*

Assessment findings

- The paediatric dosing scheme of ATRA for acute promyelocytic leukaemia depends on the body surface area (BSA) and corresponds to 25 mg/m^2. For children with a BSA of 0.49 m^2 (10 kg), the indicated dose is 12 mg; for children with a BSA of 0.79 m^2 (20 kg), the indicated dose is 20 mg; for children with a BSA of 1.1 m^2 (30 kg), the indicated dose is 28 mg
- Even though ATRA low-strength capsules allow for a high dose flexibility, they are not acceptable for younger children and those with issues swallowing tablets whole. Indeed, they are soft-gel capsules that need to be administered whole, and they also need protection from moisture.

Recommendation for the GAP-f pathway

- Given acceptability issues in administering ATRA to younger children, and suboptimal storage conditions for the ATRA soft-gel capsules, we recommend looking into the potential development of an age-appropriate formulation of ATRA with an improved stability profile.

Dasatinib

Current listing in section 8.2.2	Proposed listing in section 8.2.2
Tablet: 20 mg; 50 mg; 70 mg; 80 mg; 100 mg; 140 mg.	Tablet: 20 mg; 50 mg; 70 mg; 80 mg; ~~100; 140 mg~~

Assessment findings

- The recommended doses of dasatinib (tablet) for treatment of chronic myeloid leukaemia in children are: 40 mg once daily (10-20 kg), 60 mg once daily (20-30 kg) and 70 mg once daily (30-45 kg). In case of lack of treatment response and if tolerated, doses may be increased to 50 mg, 70 mg and 90 mg once daily, respectively for the weight bands described.
- Dasatinib is available as tablets of six different strengths, which allow quite some dose flexibility across the paediatric age spectrum. However, they are not acceptable for younger children and those with challenges swallowing tablets whole. Considering recommended doses, 100 mg and 140 mg tablet strengths are not useful to dose children aged below 12 years.
- A powder for oral suspension (10 mg/mL) was found in some markets, which would increase dose acceptability in younger children. However, the oral suspension and tablet formulations are not bioequivalent, and recommended dosages differ. Recommended doses of dasatinib 10 mg/mL powder for oral suspension correspond to 4 mL (40 mg) for those weighing 5 to <10 kg, 6 mL (60 mg) for those weighing 10 to <20 kg, 9 mL (90 mg) for those weighing 20 to <30 kg and 10.4 mL (105 mg) for those weighing 30 to <45 kg.

Recommendation for the EMLc pathway

- Considering that 100 mg and 140 mg tablets are high-strength formulations that are not useful to deliver the recommended dose of dasatinib in children aged 0 to 12 years, we recommend removing them from the EMLc listing.
- We also recommend exploring the extent of acceptability issues affecting young children who are given dasatinib, to evaluate whether the powder for oral liquid, which was found in some markets, could be considered for addition. Additional information on the bioavailability of the oral liquid formulation, particularly in children with malnutrition, should also be collected to inform a potential proposal for its inclusion.

Imatinib

Current listing in section 8.2.2	Proposed listing in section 8.2.2
Solid oral dosage form: 100 mg; 400 mg.	*No modifications (see recommendations)*

Assessment findings

- Imatinib is available as capsules and tablets. Tablets can be administered whole or after dissolving them in water or apple juice, which is particularly helpful to increase acceptability for younger children, even though palatability of the dispersion is unknown. Tablets may have scoring lines, which increases dose flexibility considering the recommended dose of 340 mg/m^2 (with potential increase to 570 mg/m^2) for the indications listed in the EMLc.
- An oral liquid formulation (80 mg/mL) was found in some markets, with flavouring agents to improve palatability and acceptability

Recommendation for the EMLc pathway

- Even though imatinib tablets can be given after being dispersed in water or apple juice, palatability of the dispersed solution is unknown. Imatinib tablets may also not be scored, limiting dose flexibility.
- Therefore, we recommend an application be sought for the addition of the oral liquid formulation of imatinib 80 mg/mL to the EMLc to increase acceptability in younger children and increase dose flexibility, allowing for a higher dosing precision.

Nilotinib

Current listing in section 8.2.2	Proposed listing in section 8.2.2
Capsule: 150 mg; 200 mg	No changes proposed

Assessment findings

- The paediatric dosing scheme of nilotinib depends on the body surface area (BSA). For children with a BSA of 0.32 m^2 (5.5 kg), the indicated dose is 50 mg twice daily; for children with a BSA between 0.33 m^2 and 0.54 m^2 (5-12 kg), the indicated dose is 100 mg twice daily and for children with a BSA between 0.55 and 0.76 m^2 (12-18 kg) and 0.77-0.97 m^2 (18-27 kg) the indicated dose is 150 mg and 200 mg, respectively, given twice daily.
- 150 mg and 200 mg capsule enable dosing of children weighing above 12 kg, even though acceptability may be low for children who cannot swallow capsules whole. However, product labels indicate that capsules may also be administered after dispersing them in one teaspoon of apple sauce.
- A 50 mg capsule was found in some markets, which would allow to administer the indicated dose to children weighing below 12 kg (assuming that capsules are opened, as acceptability of whole capsules is very low for children below 6 years of age).

Recommendation for the EMLc pathway

- Assessment of the burden of imatinib-resistant chronic myeloid leukaemia in children weighing below 12 kg is suggested to ascertain whether inclusion of nilotinib 50 mg capsules on the EMLc should be considered a high priority.

Rituximab*

Current listing in section 8.2.2	Proposed listing in section 8.2.2
Injection (intravenous): 100 mg/10 mL in 10 mL vial; 500 mg/50 mL in 50 mL vial	*No modification proposed*

*including quality-assured biosimilars

Assessment findings

- Rituximab should be given at a dose of 375 mg/m^2 BSA to be administered as an IV infusion. This corresponds to 135 mg, 183 mg and 380 mg for children with BSA corresponding to 0.3 m^2 (5 kg), 0.49 m^2 (10 kg) and 1.1 m^2 (30 kg), respectively.
- A subcutaneous formulation of rituximab was found in some markets. In 2019, an application for inclusion of this formulation in section 8.2.2 was submitted for inclusion on the EML. However, with the availability of biosimilar versions of intravenous rituximab, the Committee was concerned that listing of the sub-cutaneous formulation, for which biosimilars are not yet available, could limit competition and therefore limit access for patients and therefore rejected the inclusion of the sub-cutaneous formulation. To help improve access, the Expert Committee recommended the current listing for intravenous rituximab on the EML should indicate that quality-assured biosimilars of rituximab should also be considered as essential medicines.

Recommendation for the GAP-f pathway

- Given the recommended dose, we recommend looking into different vial sizes that would maximize dose flexibility while minimizing the use of several vials, but also volume wastage.

Section 12.3 Antihypertensive medicines

Enalapril

(Therapeutic alternatives: 4th level ATC chemical subgroup (C09AA ACE inhibitors, plain)

Current listing in section 12.3	Proposed listing in section 12.3
Tablet: 2.5 mg; 5 mg (as hydrogen maleate)	Tablet: 2.5 mg; 5 mg; **10 mg** (as hydrogen maleate) **Oral solution: 1 mg/mL (as hydrogen maleate)**

Assessment findings

- Listed tablet strengths enable administration of recommended dose which corresponds to 2.5 mg in patients 20 to <50 kg and 5 mg in patients ≥ 50 kg based on EMA and 0.08 mg/kg/day (up to 5 mg) in 1-2 divided doses based on USFDA. However, children below 30-20 kg will require doses below 2.5 mg/day.
- Also, enalapril tablets are not dispersible, with acceptability issues in younger children who cannot swallow tablets whole.
- A paediatric investigation plan for an age-appropriate solid oral dosage form of enalapril has been agreed by the European Medicines Agency.[33]
- Enalapril oral solution (1 mg/mL) was found in some markets, which would enable administration of the recommended dose in younger children. An oral liquid formulation would also be more acceptable for younger children.
- Enalapril 10 mg tablets were also found in some markets. Considering that EMA indicates a maximum of 20 mg daily in patients 20 to < 50 kg (initial dose can be increased based on patients' response), a 10 mg tablet could minimize tablet burden for older children if the dosed is increased.

Additional findings

- Availability of dispersible tablet formulations of enalapril in some countries (Argentina, China, Greece, India, Japan, Spain) was reported in sales/procurement datasets evaluated by SGUL.
- From the PENTA surveys of health professionals, it was reported that oral liquid formulations of enalapril and other ACE inhibitors (eg captopril) are extemporaneously prepared from other dosage forms.

Recommendation for the EMLc pathway

- To reduce tablet burden for older children who are given a higher enalapril dose of up to 20 mg daily, we recommend considering the inclusion of a 10 mg tablet to the EMLc. It should be noted that such a strength is also not listed on the WHO Model List but could be worth considering for addition to both lists given its potential utility in both older children and adults.
- To enable administration of the recommended dose of enalapril in children below 20-30 kg and increase acceptability in this subgroup, we recommend considering the inclusion of enalapril 1 mg/mL oral solution, upon assessment of its characteristics especially in terms of excipient safety.
- Further information on the availability of dispersible tablet formulations of enalapril is recommended, including monitoring of the EMA-approved paediatric investigation plan for an age-appropriate solid oral dosage form, with a view to considering the inclusion of such formulations on the EMLc in the future.

Section 12.4 Medicines used in heart failure

Digoxin

Current listing in section 12.4	Proposed listing in section 12.4 (complementary list)
Injection: 250 micrograms/mL in 2 mL ampoule. Oral liquid: 50 micrograms/mL. Tablet: 62.5 micrograms; 250 mg micrograms	Injection: **100 micrograms/mL in 1 mL ampoule**; 250 micrograms/mL in 2 mL ampoule. Oral liquid: 50 micrograms/mL. Tablet: 62.5 micrograms; **125 micrograms;** 250 mg micrograms

Assessment findings

- Digoxin is an old drug with narrow therapeutic margin and toxicity issues, but it is still widely used.
- The availability of several dosage forms covers the needs of the paediatric population. Indeed, tablets are not dispersible and can be used to dose children above 6 years of age. For younger children, the oral liquid formulation can be used. Slow intravenous infusion is the preferred parenteral route when oral administration is not indicated. Solutions for injection include some excipients of concern, especially ethanol, 10% v/v.
- Additional strengths of the solution for injection were found in some markets, including 50 microgram/2 mL, 100 microgram/mL.
- An additional tablet strength was found in some markets, ie: 125 micrograms, which could enable more precise dosing across the paediatric age spectrum.

Recommendation for the EMLc pathway

- Considering that digoxin should be administered in specialized settings and given its potential toxicity, we recommend considering whether it should be moved to the Complementary List of section 12.4.
- Solution for injection at lower concentrations, found in some markets could facilitate dosing in children and reduce vial wastage. Inclusion on the EMLc of the 100 micrograms/mL strength formulation is proposed.
- Given that the dose should be adjusted depending on the age/weight, phase of the treatment (loading dose or maintenance) and response to treatment, available strengths need to allow for a high dose flexibility. Therefore, we recommend considering the inclusion of a 125 mg microgram tablet, which was found in some markets, to increase dose precision.

Furosemide

Current listing in section 12.4	Proposed listing in section 12.4
Injection: 10 mg/mL in 2 mL ampoule. Oral liquid: 20 mg/5 mL. Tablet: 40 mg	Injection: 10 mg/mL in 2 mL or **5 mL** ampoule. Oral liquid: 20 mg/5 mL, **50 mg/5 mL** Tablet: **20 mg;** 40 mg

Assessment findings

- Parenteral administration should be reserved for patients unable to take oral medication or for patients in emergency clinical situations. Product labels indicate that there should be a switch to oral therapy as soon as possible. Furosemide injections could also be found available in 5 mL ampoules.
- Furosemide oral liquid did not meet the target for excipient safety, including 12% of ethanol as well as sorbitol and benzoates. The preparation of ethanol-free solutions has been reported in the literature.[34] Other (higher) strengths of the oral liquid formulation could be found in some markets, including: 40 mg/5 mL and 10 mg/mL (=50 mg/5 mL), which could be used to dose older children (20 kg and above) who have challenges swallowing tablets whole, as the 20 mg/5 mL strength would result in excessive volumes. For older children who are able to swallow, tablets can also be used.
- Furosemide 20 mg tablets were found in some markets. This tablet strength is already listed in the EMLc (section 16. Diuretics). A 20 mg tablet strength could enable a higher dose precision, especially in the maintenance phase depending on initial treatment response.
- A 10 mg furosemide tablet (listed in section 16. Diuretics) could not be found in any market.

Recommendation for the EMLc pathway

- Given the availability of furosemide injection in both 2 mL and 5 mL ampoules, we recommend adding the 5 mL size in the EMLc listing. This change applies also to furosemide as listed in section 16. Diuretics.
- Given the availability of more concentrated solutions of furosemide oral liquid which could potentially be used to dose older children who cannot swallow tablets whole, by minimizing the volume of liquid to administer, we recommend considering inclusion of 10 mg/mL strength oral solution on the EMLc, mindful of the fact that availability multiple strengths may potentially lead to dosing errors. For this reason, it is proposed to describe this strength as 50 mg/5 mL. Considerations on whether more concentrated solutions are worth including, should also be done for section 16. Diuretics.
- A 20 mg furosemide tablet is already listed in section 16 and we recommend its inclusion also in section 12.4 given its added value to increase dose precision and flexibility, especially in the maintenance phase.
- Given that a 10 mg furosemide tablet could not be found, we recommend removing the 10 mg strength from the listing in section 16.
- The proposed modifications apply also to furosemide as listed in section 16. Diuretics.

Recommendation for the GAP-f pathway

- We recommend considering the development of an improved formulation to dose younger children, in particular an oral liquid formulation with an improved excipient profile or a dispersible tablet formulation.

Section 13.1 Antifungal medicines (topical)

No modifications proposed.

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