R.1 Review of age-appropriateness of formulations on the EMLc

Reviewer summary	☒ Supportive of the proposal (with some queries) ☐ Not supportive of the proposal Justification (based on considerations of the dimensions described below): There were 18 items of the EMLc list in which the decisions proposed by the Secretariat left room for some questions or additional aspects to consider. Seven of these were subsequently resolved by the GAP-f "Report of a comprehensive review of the age appropriateness of formulations on the WHO Model List of Essential Medicines for Children Identification of potential changes and formulation gaps"; while five were partially resolved. Six remain unresolved, because, in my view, the report has not fully explained the proposed change or given the necessary justification according to the same rationale applied to other formulations of the EMLc. The box below summarizes the review. Box 1 – Issues pertaining to EMLc formulations and status.

Medicine (EMLc section)	Aspect to consider	Resolved in Report?	Justification
Acetylcysteine (4.2)	Deletion of oral liquid	Yes	As a specific antidote for paracetamol (not as a mucolytic adjuvant)
Acetylsalycilic acid (29.3)	Why remove suppository 50mg while adding 75mg dispersible tablet?	Yes	No product registered.
Artemether (6.5.3.1)	Apparent problems with registration and prequalification of oily injection.	Partially	"Artemether oily injection could not be found registered at any of the SRAs that were reviewed" (…) "This formulation has also not been prequalified by WHO" but o prequalification expression of interest. 20mg ad 40mg only available in some markets.
Artemether- lumefantrine (6.5.3.1)	Why remove age restriction footnote?	Yes	New WHO recommendations
Artesunate (6.5.3.1)	Why remove rectal dosage form?	Yes	Rectal dosage form of 100mg to e maintained.
Artesunate + pyronaridine (6.5.3.1)	Why remove age restriction footnote?	Partially	Reason not explicit. New WHO recommendations?
Chloroquine (6.5.3.1)	Why not recommend 40 or 50mg tablet?	Partially	Even if oral liquid formulation is not ideal, it must be kept. Low dose tablet should be considered, alternatively, for crushing and extemporaneous formulation.
Desmopressin (10.2)	"actuation" (spray) and not dose	Partially	Keeping the required dose relative to indication in addition to "actuation" (or actual spray delivery) might be explanatory
Dihydroartemisinin + piperaquine phosphate (6.5.3.1)	Why remove age restriction footnote?	No	There is only mention of "5 to < 8 kg" on p.67. Even if "In line with what proposed across section 6.5.3.1" that age restrictions be lifted form the section.
Levetiracetam (5.1)	The solution for infusion appears to be available in only one of the SRA territories interrogated (USA) and the shelf life of the product is not known.	No	Very scarce availability and unknown shelf-life. Furthermore, safety of concentrate for infusion may be questioned due to possibility of medication error.
Lidocaine + epinephrine (1.2)	Why not include age restriction?	No	"…depending on market and concentration its use in children under 1 year is not recommended (use of 1% recommended in children)" (p.14)
Mefloquine (6.5.3.1)	Removal of 250mg tablet	Yes	Use in combination with artesunate
Methadone (2.2)	No mention of age restrictions	No	Age restriction to those < 18yrs may be considered (p. 20 Report)
Morphine (2.2)	Are granules to be excluded?	Partially	Granules not deletions. Proposed changes in dosages. But not available. Kept due to request of NGO.
Neostigmine (20)	Why delete tablet?	Yes	Pyridostigmine first-line for MG.
Primaquine (6.5.3.1)	O 5mg tablet listed	No	Tablet registered by other RA (not SRA)[1,2]
Spironolactone (16)	Why remove other liquid forms?	Yes	No availability other than only the 25 mg/5 mL concentration could be found.
Valganciclovir (6.4.3)	No regulatory approval for CMVr in children	No	Potential teratogen and carcinogen

Additionally, the work was carried out considering the list of Stringent Regulatory Authorities, recognized by WHO. It includes mostly European countries, with only Australia, Japan and the USA as non-European counterparts. ICH membership is broader and reference RA in some continents (Africa, South and Central America) were not considered. It is noteworthy to point out that the SRA concept is in transition to WHO Listed Authorities (WLA) (until 2027)3,4. This has narrowed the market availability of some formulations

	that might otherwise be recognized as available, because they have been registered by some of these WHA or by authorities recognized as mature.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? (**https://list.essentialmeds.org/**)	☐ Yes ☐ No ☒ Not applicable
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;)	☐ Yes ☐ No ☒ Not applicable
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;)	☐ Yes ☐ No ☒ Not applicable
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms?	☐ Yes ☐ No ☒ Not applicable
Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☐ Yes ☐ No ☒ Not applicable
Are there any issues regarding price, cost-effectiveness and budget implications in different settings?	☐ Yes ☐ No ☒ Not applicable
Is the medicine available and accessible across countries? (e.g. shortages, generics and biosimilars, pooled procurement programmes, access programmes)	☐ Yes ☐ No ☒ Not applicable
Does the medicine have wide regulatory approval?	☐ Yes, for the proposed indication ☐ Yes, but only for other indications (off-label for proposed indication) ☐ No ☒ Not applicable

Additional references

1. Brasil. Ministério da Saúde. Fundação Oswaldo Cruz. Instituto de Tecnologia em Fármacos (Farmaguinhos). Farmanguinhos obtém registro da Primaquina 5mg. Available at: https://www.far.fiocruz.br/2022/03/farmanguinhos-obtem-registro-de-medicamento-inovador-contra-a-malaria/

2. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. GT-MALÁRIA/CGZV. Esquemas recomendados para o tratamento da malária não complicada no Brasil. Available at: https://www.gov.br/saude/pt-br/centrais-de-conteudo/publicacoes/svsa/malaria/tratamento/esquemas-tratamento-malaria

3. WHO. WHO Listed Authorities. March 1, 2024. Available at: https://www.who.int/news-room/questions-and-answers/item/who-listed-authorities#:~:text=The%20WLA%20replaces%20the%20Stringent,the%20scope%20for%20the%20listing).

4. WHO. A Framework for evaluating and publicly designating regulatory authorities as WHO Listed Authorities (WLA). 2024. Available at: https://www.who.int/initiatives/who-listed-authority-reg-authorities