Paediatric Drug Optimization (PADO) for malaria (June 2025)

Summary of outcomes

<table>
<tr><th colspan="2">PADO ACCESS LIST
Includes products that are developed, approved and recommended by WHO
Goal: Advocate for greater access, uptake and roll out (through multiple activities depending on the product)</th></tr>
<tr><td>Artemether
Oily injection
20 mg/mL</td><td>Background information
WHO guidelines: If artesunate is not available, artemether should be used in preference to quinine for treating children and adults with severe malaria.[i]
WHO Essential Medicines Lists: the 2023 WHO EML and EMLc include a 80 mg/mL (in 1 mL ampoule) formulation of artemether. [ii]
A proposal was submitted to replace the 80 mg/mL in 1 mL ampoule formulation listed on the WHO EMLc with 20 mg/mL; 40 mg/mL in 1 mL formulations, which were identified in some markets. Lower strength formulations are more suitable to support the administration of WHO recommended doses in children (initial dose: 3.2 mg/kg IM; maintenance dose: 1.6 mg/kg IM without dilution).[iii]
Registration at Stringent Regulatory Authorities (SRA)/WHO Listed Authorities (WLAs), WHO Prequalification and market considerations: Artemether oily injection could not be found registered at any of the SRA/WLA reviewed and it is not prequalified by WHO. Several strengths of the oily injection (20 mg/ml; 40 mg/ml; 80 mg/ml; 100 mg/ml) are included in the WHO Prequalification Expression of Interest for antimalarials.[iv]
Rationale for inclusion in the PADO access list
Artesunate is the preferred treatment for severe malaria and, according to WHO guidelines, can be administered both intravenously (IV) and intramuscularly (IM). However, PADO-malaria participants noted that artemether continues to be used in some countries, particularly in remote areas, as an option for IM administration. Participants indicated that based on their experience, this is often more practical than IV delivery in such settings, whereas artesunate is predominantly administered intravenously.
Given the recommended dose, the lower strength formulation (20 mg/mL) was prioritized for the listing in the PADO access list.</td></tr>
<tr><td colspan="2">➢ The listing in the PADO-malaria access list intends to encourage submission of artemether oily injection 20 mg/mL to WHO prequalification, to ensure that quality-assured formulations of this medicine become available.</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td>Primaquine
2.5 mg dispersible tablet (DT)</td><td>Background information
WHO guidelines: primaquine, alongside an ACT, is recommended for patients with P. falciparum malaria to reduce transmission in low-transmission areas, at a single dose of 0.25 mg/kg (low dose). G6PD testing is not required.</td></tr>
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	Primaquine is also recommended for radical cure of patients with uncomplicated *P. vivax* or *P. ovale* malaria at a high total dose (7mg/kg) at 0.5 mg/kg/day for 14 days or 1 mg/kg/day for 7 days.[i] • *WHO Essential Medicines Lists:* Primaquine is listed in the 2023 WHO EMLc as tablet: 7.5 mg; 15 mg.[ii] ○ A review of age-appropriateness of formulations listed on the WHO EMLc highlighted that conventional tablets are not appropriate to dose young children, as they have limited dose flexibility and low acceptability.[1] • *Registration at SRA/WLA, WHO Prequalification and market considerations::* Dispersible tablets of primaquine (2.5 mg, 5 mg, 7.5 mg DT) are being developed. Despite not being registered by SRA/WLA we, they are invited for prequalification and currently under evaluation by WHO prequalification (all three strengths). **Rationale for inclusion in the PADO access list** • The group agreed to list the 2.5 mg DT of primaquine to the PADO access list, as this specific strength is particularly important for the indication of transmission reduction, where primaquine is given at a lower dose. • Tablet burden for older children (eg, up to 3 tablets for a 30kg child) was not of concern, especially as the tablets are intended to be dispersed in water, facilitating administration. • The broad availability of a 2.5 mg dispersible tablet would also enable the administration of higher doses for radical cure, as multiple tablets can be administered in water. • Formulation consolidation around only one dosage form with scoring line(s) that would enable the required dose flexibility was not deemed a priority.
➢ **The listing in the PADO-malaria access list intends to advocate for broad access to this formulation of primaquine, which is a key priority for reducing transmission, particularly in regions where artemisin resistance is prevalent. Once developed and approved, the submission of an application for the inclusion of primaquine dispersible tablets, particularly the 2.5 mg dispersible tablet formulation, to the 2027 WHO EMLc will be a key step towards increased access.**	
Tafenoquine 50 mg dispersible tablet	**Background information** • *WHO guidelines:* tafenoquine is recommended as an alternative to primaquine (3.5 mg/kg total dose) for preventing relapses of *P. vivax* in patients ≥ 2years of age, who have ≥ 70% G6PD activity and who receive chloroquine treatment. These recommendations pertain only to South America. Tafenoquine is given as a single dose, while primaquine is a seven-day cure.

[1] https://cdn.who.int/media/docs/default-source/2025-eml-expert-committee/reviews/r.1_emlc-review_attachment1.pdf?sfvrsn=af5f13d5_1

	• *WHO Essential Medicines Lists:* tafenoquine is not listed on the 2023 WHO EML and EMLc. ○ A review of this formulation using the quality Target Product Profile (qTPP) toolconcluded that it is appropriate for delivering the indicated dose to children (10-20 kg: 100 mg; 20 to <35kg: 200 mg) and acceptable for the target patient population (two tablets can be dispersed in 3-5 mL of water).[v] No additional concerns were identified regarding excipients, storage, or administration. • *Registration at SRA/WLA, WHO Prequalification and market considerations:* Tafenoquine 50 mg dispersible tablets are approved by the Australian TGA, included in the WHO PQ EOI and prequalified by WHO. It is an expensive single source product. Despite not being protected by patents, no generic version is available. The restrictive WHO recommendation (in terms of age and geography), the need for G6PD testing, and the availability of primaquine for use for the same indication, have not made this product attractive for generic manufacturers. **Rationale for inclusion in the PADO access list** • The group acknowledged the added value of tafenoquine as an option for single-dose radical cure. However, it noted that key remaining research gaps need to be addressed to clarify market size and stimulate demand. • Despite acknowledging the 100 mg minimum dose for the recommended indication and that a dose lower than 100 mg may be needed for children below 2 years of age, formulation consolidation (eg, 100 mg scored dispersible tablets) was not deemed a priority to discuss at this point in time, considering existing evidence gaps on tafenoquine (dosing, including for children younger than 2 years of age, use with ACTs).
➢ **The listing of tafenoquine 50 mg dispersible tablets to the PADO-malaria access list intends to promote the implementation of studies to fill key research gaps, that may inform a broader use of tafenoquine. Submission for inclusion of tafenoquine in the 2027 WHO EML will have to consider the additional scientific evidence generated by that time.**	
Artesunate + pyronaridine Granules: 20 mg + 60 mg	**Background information** • *WHO guidelines:* ASPY is recommended as one of the ACT options for children and adults with uncomplicated *P. falciparum* malaria.i • *WHO Essential Medicines Lists:* ASPY granules are included in the WHO EMLc and they are appropriate to deliver the WHO-recommended dose in children.[ii] • *Registration at SRA/WLA, WHO Prequalification and market considerations:* approved by stringent regulatory authorities including EMA, as well as in other countries and prequalified by WHO. Currently supplied by a single manufacturer and not under patent. Currently, at least five manufacturers are developing generic ASPY products and plan to submit dossiers for WHO prequalification within the next two years.

	Rationale for inclusion in the PADO access list • Despite its increasingly important role in the treatment of uncomplicated malaria, its uptake has been limited primarily due to its high price. • There is a need to advocate for and support stakeholders' actions to increase the uptake of this product. In the short term, this includes efforts such as volume negotiations and volume guarantees. In the medium term, initiatives may need to focus on encouraging generic manufacturers to enter the market by supporting more efficient manufacturing and process chemistry. This strategy, combined with the introduction of generic competition, is expected to drive down the final cost.
➢ **The listing of ASPY granules to the PADO-malaria access list intends to underscore the importance of ensuring affordable access to this paediatric formulation, including by promoting ongoing stakeholders' action towards increased access to ASPY granules both in the short and in the medium term.**	

PADO PRIORITY LIST

- **Paediatric formulation is missing or under development, or approved but not yet endorsed by HO normative work (guidelines, EMLs)**
- **Goal: Advocate for accelerated development, approval or consideration for policy inclusion**

Artemether-lumefantrine <5kg 2.5/30 mg DT	**Background information** • *WHO guidelines:* artemether-lumefantrine (AL) is recommended by WHO for children and adults with uncomplicated *P. falciparum* malaria as one of the ACT options. Guidelines acknowledge that decreased exposure to lumefantrine has been documented in young children (<3y). The specific formulation designed for newborns and infants <5kg is not included in WHO guidelines. [i] • *WHO Essential Medicines Lists:* AL is included in the WHO EMLc as dispersible tablets, but not in this specific drug ratio. • *Registration at SRA/WLA, WHO Prequalification and market considerations:* this specific formulation received approval by Swissmedic in July 2025. It is not included in the WHO Prequalification EOI for antimalarials. **Rationale for inclusion in the PADO priority list** • This specific drug ratio of AL represents the first malaria treatment approved specifically for newborns and young infants. It provides the necessary flexibility, and it is acceptable for this population, as the tablets are designed to be dispersed in a very small volume of water. • Considerations for optimizing the formulation toward a 5/60 mg dispersible tablet would be valuable, as this corresponds to the dose required for newborns and infants weighing less than 5 kg.
➢ **The inclusion of this specific formulation of AL in the PADO priority list underscores the importance of promoting access to this formulation, acknowledging the need to develop appropriate access strategies, given the very limited market size for this indication. Essential actions would include enabling submissions of regulatory approvals in relevant high-burden countries and listing this specific formulation on the WHO PQ EOI to encourage generic manufacturing. Additionally, a submission for inclusion of this formulation in the 2027 WHO Model List of Essential Medicines for Children (EMLc), pending a WHO policy update, would further support efforts to expand access.**	
Artesunate + amodiaquine 25/67.5 mg and 50/135 mg child-appropriate oral dosage forms such as coated micropellets, dispersible tablets	**Background information** • *WHO guidelines:* ASAQ is recommended as one of the ACT options for children and adults with uncomplicated *P. falciparum* malaria. [i] • *WHO Essential Medicines Lists:* Conventional tablets of ASAQ are listed on the WHO EML and EMLc, but they have limited acceptability for children who are unable to swallow tablets whole. Product labels indicate that tablets can be crushed and mixed with water, which can lead to dosing errors and negatively affect adherence due to issues with taste and palatability. No information on the palatability of crushed tablets is available.

	• *Registration at SRA/WLA, WHO Prequalification and market considerations:* dispersible tablets of ASAQ are not available on the market. A 25/67.5 mg dispersible tablet formulation is invited by WHO for prequalification in the PQ EOI.[iv] **Rationale for inclusion in the PADO priority list** • Considering the need to increase the armamentarium of ACTs to enable countries to implement multiple first-line therapies (MFT) to prolong the lifespan of ACTs in ways that minimize the risk of resistance; and considering that ASAQ is widely used in LMICs, especially in Sub-Saharan Africa, the availability of a child-friendly formulation of ASAQ was deemed a priority for development. Two strengths of oral dosage forms were prioritized to enable administration of WHO-recommended dose. • The group noted that child-friendly formulations (25/67.5mg and 50/135mg) are currently under development, consisting of micropellets of artesunate and amodiaquine mixed together, with each drug individually coated to ensure stability of artesunate and mask the taste of amodiaquine. These are packaged in stick packs for direct administration into the mouth. However, the group also recognized that other age-appropriate formulations could be explored. • The group noted that the price of adult formulations of ASAQ is comparable to that of AL, enabling countries to implement MFTs that include both ACTs without significant cost implications. In contrast, other ACTs are generally more expensive. Therefore, the group emphasized that the final cost of the paediatric formulation of ASAQ should not become a barrier to its inclusion in MFT strategies.
➢ **The listing of ASAQ in the PADO priority list signals that the development of an age-appropriate formulation of this ACT is a priority, noting a higher urgency compared to other formulations. The listing also flags the need to pursue public health-oriented approaches, such as voluntary licensing, to ensure that the final product has an affordable price.**	
Atovaquone + proguanil 62.5/25 mg DT	**Background information** • *WHO guidelines*: recommended as chemoprophylaxis for travelers, in children and adults. • *WHO Essential Medicines Lists:* not included. In the 2023 WHO EML, proguanil was listed in section 6.5.3.2 Chemoprevention. As part of a comprehensive assessment for age-appropriateness of the WHO EMLc conducted in 2023-2024, it was proposed to remove proguanil from this section, and to consider the inclusion of atovaquone + proguanil in fixed-dose combination in a new proposed section of the EMLc for chemoprophylaxis.[iii] It is noted that this would require a full application to be submitted to the EML Expert Committee. • *Registration at SRA/WLA, WHO Prequalification and market considerations:* n/a, no development programme ongoing. Not listed on the WHO PQ EOI.

	Rationale for inclusion in the PADO priority list • The currently available formulation of atovaquone + proguanil is a 62.5/25mg film-coated tablet, which is not dispersible and should be swallowed whole or crushed and mixed with condensed milk prior to administration. This formulation is noted to be very expensive. • Considering the limited options for chemoprophylaxis in the pediatric population, and recognizing that manipulating tablets through crushing can lead to dosing errors and negatively affect adherence due to issues with taste and palatability, the group agreed to include a dispersible tablet formulation in the PADO priority list.The group noted that this is an unmet public health need, including for travelers across endemic countries in LMICs. • Other chemoprophylactic agents included in WHO EMLs were not discussed during PADO because no gaps in age-appropriate formulations were identified. Mefloquine was discussed but not prioritized given concerns around future use despite a formulation gap.
➢ **The inclusion of atovaquone + proguanil in the PADO priority list underscores the importance of developing a quality-assured, age-appropriate formulation of this chemoprophylactic agent for children, ensuring it is also affordable for LMICs. Submission for WHO prequalification, once the WHO PQ Expression of Interest (EOI) has been updated, will be a critical step to secure the availability of quality-assured products. Subsequently, an application can be pursued for inclusion in the WHO Model List of Essential Medicines for Children (EMLc), within the newly proposed section on chemoprophylaxis for travelers.**	

PADO WATCH LIST	
Category 1 **New combinations of existing products (not yet reviewed by WHO for guidelines in this specific combination)**	
Artemether + lumefantrine + amodiaquine 20/120/40 mg DT, taste masked	**Background information** • *WHO guidelines*: n/a. WHO has not yet reviewed evidence emerging from studies investigating this triple ACT. • *WHO Essential Medicines Lists:* not included. • *Registration at SRA/WLA, WHO Prequalification and market considerations:* n/a, still under development. Not included in the WHO PQ EOI. **Rationale for inclusion in the PADO priority list** • Triple ACTs have emerged as a viable alternative to combat declining efficacy due to multi-drug-resistant malaria • Recent randomized controlled trials have shown excellent safety and efficacy of artemether-lumefantrine-amodiaquine (ALAQ).[vi] Artemether-lumefantrine is the most commonly used antimalarial today and is being developed into a fixed-dose combination formulation with amodiaquine to address potential adherence issues associated with loose-tablet regimens.
Artesunate-piperaquine 50/320, 25/160, 12.5/80 mg DT	**Background information** • *WHO guidelines*: n/a. Scientific evidence reviewed by WHO so far from studies investigating artesunate + piperaquine (ASPQ) was not deemed sufficient for guideline consideration. • *WHO Essential Medicines Lists:* not included. • *Registration at SRA/WLA, WHO Prequalification and market considerations:* n/a, still under development. Not included in the WHO PQ EOI. **Rationale for inclusion in the PADO priority list** • The development of dispersible tablets of ASPQ would increase the armamentarium of ACTs that could be used in MFTs. The group acknowledged that the development of such dispersible tablets is ongoing. The group noted that drug combination is essentially equivalent to DHA-PPQ, as artesunate is metabolized into DHA in the body, and so its added value compared to DHA-PPQ and clinical positioning withih MFTs is uncertain. Also, DHA-PPQ is available in dispersible tablet formulations which are prequalified by WHO. Therefore, it was decided to note a relative lower priority of age-appropriate formulations of ASPQ compared to others listed in the PADO priority list.
Sulfadoxine-pyrimethamine + artesunate-pyronaridine (FDC), solid oral dosage form	**Background information** • *WHO guidelines*: n/a. WHO has not yet reviewed evidence emerging from studies investigating this combination of antimalarials. • *WHO Essential Medicines Lists:* not included.

	• *Registration at SRA/WLA, WHO Prequalification and market considerations:* n/a, still under development. Not included in the WHO PQ EOI.[iv]
	• *Additional information:*
	  ○ This drug combination has been investigated as a single dose cure in a randomized controlled trial in Gabon, with AL as the standard of care. Preliminary results of the trial (unpublished) show promising efficacy results and no safety concern. The trial included more than 40% children aged below 10 yeras.
	  ○ There are plans to develop it as an FDC, including an age-appropriate formulation for children.
	
	Rationale for inclusion in the PADO priority list
	• A single-dose cure for the treatment of uncomplicated malaria was recognized as a potential game changer for antimalaria treatment, simplifying treatment delivery, potentially reducing the cost of treatment overall and helping to prevent the emergence of drug resistance.

➢ **The inclusion of ALAQ, ASPQ and the triple FDC of sulfadoxine-pyrimethamine + artesunate-pyronaridine in the PADO watch list underscores the need to continue monitoring the development of (taste-masked), age-appropriate formulations for children (e.g., dispersible tablets), while ensuring that equitable access to the final product is secured.**	
Category 2 **Product is under investigation in Phase 2 or 3** **GOAL: Advocate for accelerated investigation and approval pending confirmation of efficacy and safety**	
Ganaplacide-lumefantrine Cipargamin ZY 19489 + ferroquine M5717 + pyronaridine	• The PADO-malaria group agreed that all four products should be added to the watch list, signaling that ongoing studies will be monitored for emerging evidence.[vii] • These candidates have the potential to be used in drug-resistant uncomplicated malaria, as they have novel mechanisms of action that have shown activity against parasites that are resistant to current drugs. • Cipargamin is also being investigated as an IV treatment for severe malaria, to tackle the spread of artemisinin-resistance in *Plasmodium falciparum*, especially in Asian countries. • The group emphasized that child-appropriate formulations of any compounds emerging from the pipeline should be developed concurrently with ongoing studies, to avoid delays in providing children with access to new treatment options.
Long-acting technologies (LATs)	• The group discussed how LATs can potentially be transformative in malaria, particularly to tackle growing resistance to S/P and increase adherence, and how several use cases should be explored. • The group acknowledged that some candidates are currently being explored in phase 1. The listing in the PADO watch list signals that results emerging from ongoing studies should be closely monitored in the future.

[i] WHO guidelines for malaria, 30 November 2024. Geneva: World Health Organization; 2024. https://doi.org/10.2471/B09146. Licence: CC BY-NC-SA 3.0 IGO

[ii] WHO Model List of Essential Medicines for Children – 9th list, 2023. https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.03

[iii] Web Annex B. World Health Organization Model List of Essential Medicines for Children – 9th List, 2023. In: The selection and use of essential medicines 2023: Executive summary of the report of the 24th WHO Expert Committee on the Selection and Use of Essential Medicines, 24 – 28 April 2023. Geneva: World Health Organization; 2023 (WHO/MHP/HPS/EML/2023.03). Licence: CC BY-NC-SA 3.0 IGO. https://iris.who.int/bitstream/handle/10665/371091/WHO-MHP-HPS-EML-2023.03-eng.pdf?sequence=1

[iv] 22nd Invitation to Manufacturers of Antimalarial Medicines to Submit an Expression of Interest (EOI) for Product Evaluation to the WHO Prequalification Unit (PQT). 2023. https://extranet.who.int/prequal/sites/default/files/document_files/EOI-MalariaV22.pdf

[v] WHO paediatric quality product profile assessment tool. 2024. https://www.who.int/publications/m/item/who-paediatric-quality-product-profile-assessment-tool

[vi] van der Pluijm, R.W. et al. Lancet 395, 1345–1360 (2020); Peto, T.J. et al Lancet Infect. Dis. 22, 867–878 (2022); Tarning J, et al 2025, 117(5), 1248

[vii] https://www.mmv.org/sites/default/files/content/document/Global_portfolio_June2025.pptx