Management of treatment failure (recrudescence) in falciparum malaria

ACMP interim guidance

This guidance covers adults and children with falciparum malaria or mixed infections including *Plasmodium falciparum.*

Countries and regions with higher risk of reduced sensitivity to artemisinins

The prevalence of K13 and other falciparum malaria resistance mutations that result in a reduced sensitivity to artemisinin combination therapies (ACT) is increasing globally. As a result, treatment failure can now be seen in African countries including Uganda, Kenya, Tanzania, Rwanda, Ethiopia and Eritrea[a]. This list is likely to increase: check www.who.int and other relevant sources. Established artemisinin resistance continues to exist in the Greater Mekong Subregion[1].

IV artesunate and oral artemisinin combination therapies (ACT) are still effective, but parasites with K13 and other resistance mutations have reduced sensitivity to ACT, so parasitaemia may reduce more slowly following treatment, and late treatment failure (recrudescence) is more likely.

Treatment of a second episode of falciparum malaria without intervening travel to malaria-endemic country (presumed recrudescence)

Discuss all cases with an infection consultant with malaria expertise

Severe malaria

- Treat with IV artesunate as per national guidelines[b]
- IV artesunate plus IV quinine combination therapy is recommended by the World Health Organization (WHO) in areas with established artemisinin resistance (parts of Cambodia, the Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam)[B]. It is rarely needed outside of these areas.
    - See national guidelines for quinine monitoring[b]
    - Do not stop the artesunate

Non-severe falciparum malaria or oral continuation therapy following treatment of severe malaria

Use an oral agent which was NOT used to treat the primary infection, and which was not used for prophylaxis. Options include:

- Eurartesim (piperaquine tetraphosphate / artenimol) PO 3 days (check contra-indications, annex 1). Do not delay treatment whilst waiting for Eurartesim; use an alternative or drug combination or continue IV artesunate until Eurartesim is available.
- Riamet (artemether- lumefantrine) PO **5 day course**
- Malarone (atovaquone-proguanil)
- Quinine + clindamycin

Send EDTA blood urgently to the Malaria Reference Laboratory (telephone 020 7927 2427 in advance), with report form including travel history and highlighting that this is a recrudescent case. The referral form is at https://www.gov.uk/government/publications/malaria-report-form

Safety net: tell the patient that the malaria could come back. If they have a fever after finishing treatment, they need to attend an emergency department for a same day malaria film.

Version 1, Advisory Committee on Malaria Prevention, UK 01/11/24
Revision 1, Correction in Eurartesim dosing table: piperaquine and artenimol doses were labelled incorrectly 04/02/25

Additional notes

Prevention advice is even more important in people planning to travel to these areas

- https://assets.publishing.service.gov.uk/media/65a16fc674ae66000d738a64/guidelines-for-malaria-prevention-in-travellers-from-the-UK-2023.pdf
- https://www.uclh.nhs.uk/our-services/find-service/tropical-and-infectious-diseases/travel-clinic-services

In-country monitoring for drug failure is patchy, so African countries not on the list above may also be affected.

Annex 1: Use of Eurartesim (piperaquine tetraphosphate / artenimol)

Contraindications

- Severe malaria (use parenteral therapy)
- Unable to tolerate oral treatment (use parenteral therapy)
- History of allergy to Eurartesim
- History of ventricular arrythmias associated with prolonged QTc syndromes
- Family history of sudden death or of congenital prolongation of the QTc interval
- History of symptomatic cardiac arrhythmia or clinically relevant bradycardia
- Any predisposing cardiac conditions for arrhythmia[2]

Cautions

- Avoid in the first trimester of pregnancy (insufficient data)
- Avoid breastfeeding while taking Eurartesim
- >65 years old: caution with respect to cardiac risk factors
- Known condition causing prolongation of the QTc interval
- Check ECG: if QTcB > 450 admit the patient for treatment and discuss with cardiologist. Use Bazett formula for calculation
- Increased ECG monitoring is advised for drugs that could prolong the QT interval
- Use with caution if significant cardiac history[2]
- Review family history; use with caution if positive for congenital prolongation of the QT interval or sudden death
- Check electrolytes: use with caution in the presence of electrolyte disturbances, particularly hypokalaemia, hypocalcaemia or hypomagnesaemia. First dose of Eurartesim can be given before electrolytes are available if there is no reason to suspect derangement
- Use with caution in moderate/ severe renal or hepatic impairment (insufficient data)
- The safety and efficacy of Eurartesim in infants aged less than 6 months and in children weighing less than 5 kg has not been established. Discuss with a consultant paediatrician before using in these groups. Tablets may be crushed and mixed with water.

Drug interactions[3]

- **Avoid if the patient is currently taking or has recently taken other medications known to prolong the QT interval[4]**.

- **Caution if patient is taking medications exhibiting inhibition, induction or competition for CYP3A4[5], CYP2E1[6], CYP2C19[7] or CYP1A2[8]**; levels of Eurartesim and other drugs may be increased or decreased. Review the SPC[d] p3) for information on drug interactions.
- **Piperaquine has a half-life of 22 days, and effects could theoretically persist up to 16 weeks after stopping Eurartesim.** Caution prescribing other QT prolonging drugs[3]or drugs that may interact over this period. **Inform patient and GP (give patient leaflet and/ or use discharge smartphrase)**

Dosing schedule based on weight[9]

Give over 3 consecutive days, for a total of 3 doses taken at roughly the same time each day

Body weight (kg)*	Daily dose (mg)		Tablet strength and number of tablets per dose
	PQP#	Artenimol	
5 - <8	160	20	½ x 320 mg / 40 mg tablets OD for 3 days
8 - <11	240	30	¾ x 320 mg / 40 mg tablets OD for 3 days+
11 - < 17	320	40	1 x 320 mg / 40 mg tablets OD for 3 days
17 - < 25	480	60	1.5 x 320 mg / 40 mg tablets OD for 3 days
25 - < 36	640	80	2 x 320 mg / 40 mg tablets OD for 3 days
36 to <75	960	120	3 x 320 mg / 40 mg tablets OD for 3 days
> 75	1280	160	4 x 320 mg / 40 mg tablets OD for 3 days

* For individuals with a weight up to **<60kg**, the WHO dosing schedule[c] is recommended in preference to the manufacturer's Summary of Product Characteristics[d] (SPC) on the basis of superior efficacy of a higher dose together with good safety data in this population[c]. The WHO also suggests higher dosing in individuals with a weight >60kg. We recommend using the manufacturer's dose recommendations outlined in the product SPC in this group instead of the WHO recommendation until there is sufficient safety data in this population.
# PQP: piperaquine
+ It is recommended that a 320mg/ 40mg tablet of Eurartesim is crushed and dissolved in water, eg a volume of 10ml, and then ¾ of the volume of the suspension, eg 7.5ml, is administered. **Caution:** it may take a few minutes for the tablet to dissolve; parents and carers should be warned of this.

Administration

First check cardiac history, drug history and review ECG.

Eurartesim should be taken orally with water and on an empty stomach (3 hours after the last food intake) and no food should then be taken within 3 hours after each dose. Avoid grapefruit juice. Piperaquine absorption is significantly increased if taken with fat.

If a patient vomits within 30 minutes of taking Eurartesim, the whole dose should be re-administered; if a patient vomits within 30-60 minutes, half the dose should be re-administered. Re-dosing with Eurartesim should not be attempted more than once. If the second dose is vomited, parenteral artesunate should be instituted.

If a dose is missed, it should be taken as soon as realised and then the recommended regimen continued until the full course of treatment has been completed.

No more than two courses of Eurartesim may be given within a 12-month period. A second course of Eurartesim should not be given within 2 months after the first course due to the long elimination half-life of piperaquine.

Annex 2: Obtaining a stock of Eurartesim

- **Supplies of Euratesim can be obtained from the wholesaler Mawdsleys.** If the organisation cannot obtain this promptly enough, UCLH Hospitals NHS Foundation Trust, London maintains a supply of Eurartesim 320/40mg tablets.
- **To request Eurartesim from UCLH during office hours (9am-5.00pm Monday to Friday):** please arrange for a pharmacist to contact the pharmacy procurement team on 020 3447 9731
- **For requests on weekdays between 5pm and 6pm or on bank holidays and weekends between 9am to 12.30pm:** please arrange for a pharmacist to contact the inpatient pharmacy department on 020 3447 4405 or 020 3447 3593
- **For requests between 6pm and 10pm on normal working days or after 12.30pm on weekends and bank holidays:** please arrange for a pharmacist to contact the on call pharmacist via switchboard (020 3456 7890).
- **For requests after 10pm (and to 9am the following day):** please continue interim management and contact pharmacy within the above hours

Footnotes

[1] **Reduced artemisinin sensitivity** is widespread in the Greater Mekong Subregion, where Eurartesim also has reduced efficacy. ***Discuss treatment of patients returning from this region with a consultant experienced in infectious diseases management; IV artesunate followed by oral combination treatment including Riamet (artemether-lumefantrine) and a second agent may be indicated.***

[2] **Significant cardiac history** includes history of symptomatic cardiac arrhythmias or predisposing conditions for arrhythmia such as severe hypertension, left ventricular hypertrophy (including hypertrophic cardiomyopathy) or congestive cardiac failure accompanied by reduced left ventricle ejection fraction.

[3] **Resources to check drug interactions** include: BNF (search "artenimol with piperaquine phosphate" as there is no entry for "Eurartesim" and check artenimol and piperaquine individually), Stockley's, the Eurartesim SPC and SPCs of other medicines taken by the patient. Crediblemeds.org is also useful in identifying drugs that can cause QT interval prolongation. If further advice is needed on drug interactions, please discuss with ID pharmacy team as Stockley's/BNF does not pick up some potential interactions and the below list is not exhaustive.

[4] **Medications that may prolong the QT interval** include but are not limited to fluconazole, methadone, moxifloxacin, amiodarone, ondansetron, domperidone, haloperidol, clarithromycin, ciprofloxacin, levofloxacin, venlafaxine, amitriptyline, tacrolimus.

[5] **Piperaquine inhibits CYP3A4** and could increase the level of CYP3A4 substrates such as atorvastatin, apixaban, rivaroxaban, edoxaban, ciclosporin. Note this interaction could persist 16 weeks after stopping Eurartesim. Piperaquine is metabolised by CYP3A4 and levels may be increased/decreased with CYP3A4 inhibitors/inducers e.g. verapamil, ritonavir, cobicistat, carbamazepine, rifampicin

[6] **Piperaquine may increase CYP2E1 metabolism** resulting in a decrease in levels of paracetamol or theophylline and the anaesthetic gases enflurane, halothane and isoflurane.

[7] **Piperaquine may inhibit CYP2C19** (which could decrease clopidogrel active levels or increase omeprazole levels). Note this interaction could persist 16 weeks after stopping Eurartesim.

[8] **Artenimol may inhibit CYP1A2** and could increase levels of drugs such as theophylline. Effects are unlikely to persist beyond 24 hours after the last dose of artenimol.

[9] https://www.ema.europa.eu/en/medicines/human/EPAR/eurartesim

References

a. WHO malaria resistance strategy 2022: https://www.who.int/publications-detail-redirect/9789240060265
b. UK malaria guidelines 2016: https://www.journalofinfection.com/article/S0163-4453(16)00047-5/pdf
c. World Health Organisation malaria guidelines 2023: https://www.who.int/publications/i/item/guidelines-for-malaria
d. Eurartesim SPC available online via EMA.europa.eu from: https://www.ema.europa.eu/en/documents/product-information/eurartesim-epar-product-information_en.pdf p3 (accessed 25/10/2024)
e. Stockleys accessed online on 31/01/2024 via MedicinesComplete — Dashboard (subscription required)