# Eurartesim®

# (piperaquine tetraphosphate/ dihydroartemisinin)

# Guide for Healthcare Professionals

# (Physician Leaflet)

## REVISED EDITION 2016

**This guide is intended to provide you with information regarding the safe use of Eurartesim and to support you in providing information and counseling to your patients.**

## About Eurartesim

Eurartesim tablets contain two active antimalarial ingredients: dihydroartemisinin (DHA) and piperaquine tetraphosphate (PQP). The formulation meets WHO recommendations, which advise combination treatment for *Plasmodium falciparum* malaria to reduce the risk of resistance development, with artemisinin-based preparations regarded as the 'policy standard'.

Eurartesim is effective against *Plasmodium falciparum* malaria in adults and children. Data are available from large clinical trials that involved over 2600 patients in Africa and Asia, of whom over 1000 were children under 5 years of age. The studies were designed to compare the safety and efficacy of Eurartesim with the established artemisinin combination therapies artemether/lumefantrine (in Africa) and artesunate/mefloquine (in Asia). Eurartesim was shown to be at least as effective as the comparator agents and well tolerated, overall.

The DHA component of Eurartesim reaches high concentrations within the parasitised erythrocytes and shows rapid schizontocidal activity by means of free-radical damage to parasite membrane systems. The exact mechanism of action of the PQP component is unknown, but is thought to mirror that of chloroquine, a close structural analogue. PQP has shown good activity against chloroquine-resistant *Plasmodium* strains *in vitro* and has a long half-life (20–22 days) resulting in a sustained antimalarial effect.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

## Patients eligible for Eurartesim

- Eurartesim is indicated for the treatment of uncomplicated *Plasmodium falciparum* malaria in adults, children and infants aged ≥6 months and weighing ≥5kg.
- Eurartesim is contraindicated for the treatment of severe *Plasmodium falciparum* malaria (according to the WHO definition) and should not be used to treat malaria caused by *Plasmodium vivax*, *Plasmodium malariae* or *Plasmodium ovale*.
- Eurartesim is contraindicated in patients with a history of clinical conditions that may lead to QTc interval prolongation and in patients taking drugs that are known to prolong the QTc interval.
- Caution is advised when administering Eurartesim to patients aged ≥65 years and to those with moderate or severe hepatic/renal impairment, because these groups were not studied in Eurartesim trials.

## Key safety issues

### *QTc prolongation*

In clinical trials, electrocardiograms (ECGs) obtained during treatment showed that prolongation of the QTc interval occurred with Eurartesim. QTc interval prolongation may be associated with an increased likelihood of severe cardiac arrhythmia, such as torsades de pointes (TdP), which was not observed during the development of Eurartesim.

QTc prolongation was shown to be correlated to the piperaquine plasma concentration which, in its turn, is correlated with food administration. Therefore, QTc prolongation is more significant when Eurartesim is taken with food. For this reason, Eurartesim should be taken between meals (at least 3

hours before and after meals), with water only. See section “How Eurartesim should be taken” for details.

Compared to adult males, female patients and elderly patients have longer QTc intervals. Therefore special caution is required in these patients, as they may be more sensitive to the effects of QTc-prolonging medications such as Eurartesim. Special precaution is also advised in young children when vomiting as they are likely to develop electrolyte disturbances which may increase the QTc-prolonging effect of Eurartesim.

Administration of Eurartesim is contraindicated in patients taking medicinal products that are known to prolong the QTc interval. These include (but are not limited to):

- Antiarrhythmics (e.g. amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, hydroquinidine, sotalol).
- Neuroleptics (e.g. phenothiazines, sertindole, sultopride, chlorpromazine, haloperidol, mesoridazine, pimozide, or thioridazine) and antidepressive agents.
- Certain antimicrobial agents, including agents of the following classes:
  - macrolides (e.g. erythromycin, clarithromycin),
  - fluoroquinolones (e.g. moxifloxacin, sparfloxacin),
  - imidazole and triazole antifungal agents,
  - pentamidine and saquinavir.
- Certain non-sedating antihistamines (e.g. terfenadine, astemizole, mizolastine).
- Cisapride, droperidol, domperidone, bepridil, diphemanil, probucol, levomethadyl, methadone, vinca alkaloids, arsenic trioxide.

### *Potential teratogenic effects*

Eurartesim should not be used during pregnancy if other suitable and effective antimalarials are available. In addition, women should not breastfeed during treatment with Eurartesim. These limitations come from findings from animal studies with artemisinin derivatives, such as DHA.

A pregnancy registry is in place to monitor the pregnancy outcomes of patients inadvertently or deliberately exposed to Eurartesim while pregnant. Information on this pregnancy registry can be obtained via the following registry website www.malariapregnancyregistry.org.

See section “Safety and pregnancy registries” for details.

## Potential risks associated with Eurartesim

The safety of Eurartesim has been evaluated in two Phase III studies involving both adults (>18 years of age) and children (mainly aged 6 months to 5 years). The adverse drug reactions (ADRs) reported and their frequencies are shown in the following tables.

| **Adult patients (n=566)** | |
|---|---|
| **Frequency** | **Adverse drug reaction** |
| Very common<br>≥1 in 10 | None |
| Common<br>≥1 in 100 to <1 in 10 | Headache, QTc prolongation, tachycardia, anaemia, asthenia, pyrexia |
| Uncommon<br>≥1 in 1000 to <1 in 100 | Influenza, respiratory tract infection, anorexia, dizziness, convulsion, cardiac conduction disorders, sinus arrhythmias, bradycardia, cough, vomiting, abdominal pain, diarrhoea, nausea, hepatitis, hepatomegaly, liver function tests increased, pruritis, arthralgia, myalgia |

| **Paediatric patients (n=1,239)** | |
|---|---|
| **Frequency** | **Adverse drug reaction** |
| Very common<br>≥1 in 10 | Influenza, cough, pyrexia |
| Common<br>≥1 in 100 to <1 in 10 | Diarrhoea, vomiting, anorexia, respiratory tract infection, ear infection, anaemia, leukopenia/neutropenia, leukocytosis/necrotizing enterocolitis, thrombocytopenia, conjunctivitis, irregular heart rate, QT/QTc prolongation, abdominal pain, dermatitis, rash, asthenia |
| Uncommon<br>≥1 in 1000 to <1 in 100 | Hypochromasia, lymphadenopathy, splenomegaly, thrombocythaemia, convulsion, headache, cardiac murmur, cardiac conduction disorders, epistaxis, rhinorrhoea, nausea, stomatitis, hepatitis, hepatomegaly, jaundice, liver function tests increased, pruritis, acanthosis, arthralgia |

The ADRs were generally mild and the majority were non-serious. Reactions such as cough, pyrexia, headache, *P. falciparum* infection, anaemia, asthenia, anorexia and the observed changes in blood cell parameters are consistent with those expected in patients with acute malaria. The QTc prolongation was observed on Day 2 and had resolved by Day 7 (the next time point at which ECGs were performed).

Patients should be counselled about the benefit/risk profile of Eurartesim and referred to the Patient Information Leaflet (PIL), which lists the ADRs most commonly encountered. Please advise patients that if any ADR becomes severe or they experience an ADR not listed in the PIL they should inform their physician or pharmacist as soon as possible.

## Possible drug interactions

Eurartesim is contraindicated in patients already taking other drugs known to prolong the QTc interval owing to the risk of an additive effect. In addition, the interaction of Eurartesim with the cytochrome P450 enzymes means that Eurartesim may affect or be affected by other medications, which are also substrates and/or inhibitors of these enzymes, as detailed below.

### *Effect of Eurartesim on concomitant drugs*

- **CYP3A4**: PQP is metabolised by, and inhibits, CYP3A4. Therefore, it has the potential to increase the plasma concentration of other s ubstrates for this enzyme, such as statins, with the risk of heightened toxicity. It is particularly important to be vigilant when co-administering drugs with a narrow therapeutic index such as cyclosporine and antiretroviral medication.
- **CYP2C19**: PQP undergoes a low level of metabolism by CYP2C19 and is also an inhibitor of this enzyme. Other substrates of this enzyme, such as omeprazole, may have their rate of metabolism reduced by Eurartesim, with a consequent increase of their plasma concentration and toxicity.
- **CYP2E1**: PQP has the potential to increase the metabolic rate for CYP2E1 substrates resulting in a decrease in the plasma concentrations of substrates such as paracetamol and the anaesthetic gases enflurane, halothane and isoflurane. The main consequence of this interaction could be a reduction in efficacy of the co-administered products.
- **CYP1A2**: DHA administration may result in a slight decrease in CYP1A2 activity. Caution is therefore advised when Eurartesim is administered concomitantly with medications that are metabolised by this enzyme and have a narrow therapeutic index, such as theophylline. Any effects are unlikely to persist beyond 24 hours after the last intake of DHA.

### *Effect of concomitant drugs on Eurartesim*

Concomitant treatment with drugs that inhibit CYP3A4 may lead to a marked increase of PQ plasma concentrations, resulting in exacerbation of QTc prolongation. Therefore, particular caution is required if Eurartesim is given to patients taking products such as nefazodone, verapamil and some protease inhibitors (e.g. amprenavir, atazanavir, indinavir, nelfinavir, ritonavir). ECG monitoring is advisable in these cases.

Enzyme-inducing drugs such as rifampicin, carbamazepine, phenytoin, phenobarbital and St John's Wort (*Hypericum perforatum*) are likely to lead to reduced PQ concentrations and may also lower DHA levels. Concomitant treatment with such products is not recommended.

All these potential interactions should be kept in mind when treating patients with Eurartesim and, because of the long half-life of PQ, for up to 3 months after treatment.

*Please refer to the comprehensive contraindicated concomitant medications checklist provided, which should be reviewed in the patient's presence.*

*Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via: HPRA Pharmacovigilance, Earlsfort Terrace, IRL-Dublin 2; Tel: +3531 6764971; Fax: +3531 6762517. Website: www.hpra.ie; Adverse events should also be reported to Sigma-Tau Industrie Farmaceutiche Riunite S.p.A,*

*email: Pharmacovigilance@sigma-tau.it,*

*Fax: +39 06 9139 4007*

*Phone: +39 06 9139 3360.*

## Before prescribing Eurartesim

Due to the propensity for Eurartesim to prolong the QTc interval, there are a number of important contraindications to its use. These include any pre-existing conditions, past conditions, family history and use of concomitant medications that may predispose the patient to QTc prolongation or cardiac arrhythmia.

*Please refer to the comprehensive contraindicated concomitant medications checklist provided, which should be reviewed in the patient's presence.*

## Counselling your patient

As part of your discussions with patients or their carer, please ensure that you provide the following:

- a copy of the patient information leaflet;
- a full description of the benefit/risk profile of Eurartesim;
- counselling regarding contraceptive methods and pregnancy prevention appropriate for their sex and child-bearing status;
- adverse event reporting instructions including the list of adverse events potentially associated with QTc prolongation (see section "Key safety issues" for details).

Additional information can be found in the summary of product characteristics.

## Dosing schedule

- Eurartesim should be taken over 3 consecutive days for a total of three doses taken at the same time each day. The tablets are available in two strengths: PQP 160mg/DHA 20mg and PQP 320mg/DHA 40mg.
- Dosing should be based on body weight as shown in the table below.
- A second course of Eurartesim should not be given within 2 months of the first course and no more than two courses may be given within a 12-month period.

| Body weight (kg) | Daily dose (mg) | | Number of tablets per dose and tablet strength |
|---|---|---|---|
| | PQP | DHA | |
| 5 to <7 | 80 | 10 | ½ x 160mg/20mg tablet |
| 7 to <13 | 160 | 20 | 1 x 160mg/20mg tablet |
| 13 to <24 | 320 | 40 | 1 x 320mg/40mg tablet |
| 24 to <36 | 640 | 80 | 2 x 320mg/40mg tablets |
| 36 to <75 | 960 | 120 | 3 x 320mg/40mg tablets |
| 75 to 100 | 1,280 | 160 | 4 x 320mg/40mg tablets |
| >100 | There are no data on which to base a dose recommendation in patients weighing >100kg | | |

## How Eurartesim should be taken

- Patients should take Eurartesim orally with water only (no other fluids) on an empty stomach.
- Each dose should be taken no less than 3 hours after the last food intake.
- No food should be taken within 3 hours after each dose.
- For patients unable to swallow the tablets, they may be crushed and mixed with water. The mixture should be taken immediately after preparation.
- If a patient vomits within 30 minutes of taking Eurartesim, the whole dose should be re-administered. If vomiting occurs within 30–60 minutes, half the dose should be re-administered. Re-dosing should not be attempted more than once. If the second dose is vomited, alternative antimalarial therapy should be given.
- If a dose is missed, it should be taken as soon as it is remembered on the same day. If the patient forgets to take it on the same day, they should take the next dose at their usual time on the following day and then continue the recommended regimen until the full course of treatment has been completed. Patients should not take two doses on the same day to make up for a missed dose.

Please advise the patient that details of how to take Eurartesim are included in the PIL.

## ECG monitoring

In patients who may have a higher risk of developing arrhythmia in association with QTc prolongation, an ECG should be obtained as early as possible during treatment with Eurartesim and ECG monitoring should be applied. ECG monitoring is also advised in patients who are co-administered with CYP3A4 inhibitors.

An ECG and blood potassium monitoring are advised in patients with jaundice and/or with moderate or severe renal or hepatic insufficiency. When clinically appropriate, consideration should be given to obtaining an ECG from patients before the last of the three daily doses is taken and approximately 4–6 hours after the last dose because the risk of QTc interval prolongation may be greatest during this period.

QTc intervals of more than 500ms are associated with a pronounced risk for potentially life-threatening ventricular tachyarrhythmias. Therefore, ECG monitoring during the following 24–48 hours should be applied for patients found to have a prolongation to this extent. These patients should not receive another dose of Eurartesim and alternative antimalarial therapy should be instituted.

## Safety and pregnancy registries

Sigma Tau has set up two European multicentre registries to collect data on cardiovascular safety and on the outcome of pregnancies in patients exposed to Eurartesim.

- The **safety registry** will assess the association between QTc prolongation induced by Eurartesim and various factors, co-morbidities and concomitant medications, and will monitor patterns of drug utilisation in 300 patients receiving Eurartesim. It will also investigate, as a secondary objective, the incidence of treatment-emergent adverse events of special interest. These are TdP, sudden death, ventricular tachycardia, ventricular fibrillation and flutter, syncope, seizures and sustained arrhythmias.
- The **pregnancy registry** will monitor the outcome of pregnancies in women who, inadvertently or otherwise, receive Eurartesim while pregnant or within 1 month prior to conception, or whose partner was treated with Eurartesim within this timeframe. The registry will collect information on neonatal mortality, infant birth defects/development and maternal complications.

*For further details on these registries and for information on how to enrol patients, please see the details below:*

***Malaria Pregnancy Registry***

www.MALARIAPREGNANCYREGISTRY.NET

www.MALARIAPREGNANCYREGISTRY.COM

www.MALARIAPREGNANCYREGISTRY.INFO

www.malariapregnancyregistry.org

Phone: +44(0)1908 363 454

Email: eurartesimregistry@mapigroup.com

***Malaria Safety Registry***

www.MALARIASAFETYREGISTRY.ORG

www.MALARIASAFETYREGISTRY.NET

www.MALARIASAFETYREGISTRY.COM

www.MALARIASAFETYREGISTRY.MOBI

www.malariaregistry.org

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