ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Eurartesim 160 mg/20 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 160 mg piperaquine tetraphosphate (as the tetrahydrate; PQP) and 20 mg artenimol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

White oblong biconvex film-coated tablet (dimension 11.5x5.5mm / thickness 4.4mm) with a break-line and marked on one side with the letters “S” and “T”.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Eurartesim is indicated for the treatment of uncomplicated *Plasmodium falciparum* malaria in adults, adolescents, children and infants 6 months and over and weighing 5 kg or more.

Consideration should be given to official guidance on the appropriate use of antimalarial medicinal products, including information on the prevalence of resistance to artenimol/piperaquine in the geographical region where the infection was acquired (see section 4.4).

4.2 Posology and method of administration

Posology

Eurartesim should be administered over three consecutive days for a total of three doses taken at the same time each day.

Dosing should be based on body weight as shown in the table below.

Body weight (kg)	Daily dose (mg)		Tablet strength and number of tablets per dose
	PQP	Artenimol	
5 to <7	80	10	½ x 160 mg / 20 mg tablet
7 to <13	160	20	1 x 160 mg / 20 mg tablet
13 to <24	320	40	1 x 320 mg / 40 mg tablet
24 to <36	640	80	2 x 320 mg / 40 mg tablets
36 to <75	960	120	3 x 320 mg / 40 mg tablets
> 75*	1,280	160	4 x 320 mg / 40 mg tablets

* see section 5.1

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, alternative antimalarial therapy 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.

There is no data on a second course of treatment.
No more than two courses of Eurartesim may be given within a 12 month period (see sections 4.4 and 5.3).
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 (see sections 4.4 and 5.2).

Special populations

Elderly
Clinical studies of Eurartesim did not include patients aged 65 years and over, therefore no dosing recommendation can be made. Considering the possibility of age-associated decrease in hepatic and renal function, as well as a potential for heart disorders (see sections 4.3 and 4.4), caution should be exercised when administering the product to the elderly.

Hepatic and renal impairment
Eurartesim has not been evaluated in subjects with moderate or severe renal or hepatic insufficiency. Therefore, caution is advised when administering Eurartesim to these patients (see section 4.4).

Paediatric population
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. No data are available for these paediatric subsets.

Method of administration

Eurartesim should be taken orally with water and without food.
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, such as infants and young children, Eurartesim may be crushed and mixed with water. The mixture should be used immediately after preparation.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Severe malaria according to WHO definition.
- Family history of sudden death or of congenital prolongation of the QTc interval.
- Known congenital prolongation of the QTc-interval or any clinical condition known to prolong the QTc interval.
- History of symptomatic cardiac arrhythmias or with clinically relevant bradycardia.
- Any predisposing cardiac conditions for arrhythmia such as severe hypertension, left ventricular hypertrophy (including hypertrophic cardiomyopathy) or congestive cardiac failure accompanied by reduced left ventricle ejection fraction.
- Electrolyte disturbances, particularly hypokalaemia, hypocalcaemia or hypomagnesaemia.
- 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), antidepressive medicinal products.
    - Certain antimicrobial medicinal products, including medicinal products of the following classes:
        - macrolides (e.g. erythromycin, clarithromycin),
        - fluoroquinolones (e.g. moxifloxacin, sparfloxacin),
        - imidazole and triazole antifungal medicinal products,
        - and also pentamidine and saquinavir.
    - Certain non-sedating antihistamines (e.g. terfenadine, astemizole, mizolastine).
    - Cisapride, droperidol, domperidone, bepridil, diphemanil, probucol, levomethadyl, methadone, vinca alkaloids, arsenic trioxide.
- Recent treatment with medicinal products known to prolong the QTc interval that may still be circulating at the time that Eurartesim is commenced (e.g. mefloquine, halofantrine, lumefantrine, chloroquine, quinine and other antimalarial medicinal products) taking into account their elimination half-life.

4.4 Special warnings and precautions for use

Eurartesim should not be used to treat severe falciparum malaria (see section 4.3) and, due to insufficient data, should not be used to treat malaria due to *Plasmodium vivax, Plasmodium malariae* or *Plasmodium ovale.*

The long half-life of piperaquine (about 22 days) should be kept in mind in the event that another anti-malarial agent is started due to treatment failure or a new malaria infection (see below and sections 4.3 and 4.5).

Piperaquine is a mild inhibitor of CYP3A4. Caution is recommended when co-administering Eurartesim with medicinal products exhibiting variable patterns of inhibition, induction or competition

for CYP3A4 as the therapeutic and/or toxic effects of some co-administered medicinal products could be altered.

Piperaquine is also a substrate of CYP3A4. A moderate increase of piperaquine plasma concentrations (<2-fold) was observed when co-administered with strong CYP3A4 inhibitors, resulting in a potential exacerbation of the effect on QTc prolongation (see section 4.5).

Exposure to piperaquine may also be increased when co-administered with mild or moderate CYP3A4-inhibitors (e.g. oral contraceptives). Therefore, caution should be applied when co-administering Eurartesim with any CYP3A4-inhibitor and ECG monitoring should be considered.

Due to the lack of multiple dose PK data for piperaquine, administration of any strong CYP3A4-inhibitors should be discouraged after initiation (i.e. the first dose) of Eurartesim (see sections 4.5 and 5.2).

Eurartesim should not be used during the 1st trimester of pregnancy in situations where other suitable and effective antimalarials are available (see section 4.6).

In the absence of carcinogenicity study data, and due to lack of clinical experience with repeated courses of treatment in humans, no more than two courses of Eurartesim should be given in a 12-month period (see sections 4.2 and 5.3).

Effects on cardiac repolarization
In clinical trials with Eurartesim limited ECGs were obtained during treatment. These showed that QTc prolongation occurred more frequently and to a larger extent in association with Eurartesim therapy than with the comparators (see section 5.1 for details of the comparators). Analysis of cardiac adverse events in clinical trials showed that these were reported more frequently in Eurartesim treated patients than in those treated with comparator antimalarial (see section 4.8). Before the third dose of Eurartesim, in one of the two Phase III studies 3/767 patients (0.4%) were reported to have a QTcF value of >500 ms versus none in the comparator group.

The potential for Eurartesim to prolong the QTc interval was investigated in parallel groups of healthy volunteers who took each dose with high (~1000 Kcal) or low (~400 Kcal) fat/calorie meals or in fasting conditions. Compared to placebo, the maximum mean increases in QTcF on Day 3 of dosing with Eurartesim were 45.2, 35.5 and 21.0 msec under respective dosing conditions. The QTcF prolongation observed under fasting conditions lasted between 4 and 11 hours after the last dose was administered on Day 3. The mean QTcF prolongation compared to placebo decreased to 11.8 msec at 24 hours and to 7.5 msec at 48 hours. No healthy subject dosed in fasting conditions showed a QTcF greater than 480 msec or an increase over baseline greater than 60 msec. The number of subjects with QTcF greater than 480 msec after dosing with low fat meals was 3/64, while 10/64 had QTcF values over this threshold after dosing with high fat meals. No subject had a QTcF value greater than 500 msec in any of the dosing conditions.

An ECG should be obtained as early as possible during treatment with Eurartesim and ECG monitoring should be applied in patients who may have a higher risk of developing arrhythmia in association with QTc prolongation (see below).

When clinically appropriate, consideration should be given to obtaining an ECG from all patients before the last of the three daily doses is taken and approximately 4-6 hours after the last dose, since the risk of QTc interval prolongation may be greatest during this period (see section 5.2). QTc intervals of more than 500 ms 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.

Compared to adult males, female patients and elderly patients have longer QTc intervals. Therefore, they may be more sensitive to the effects of QTc-prolonging medications such as Eurartesim so that special caution is required.

Delayed Haemolytic Anaemia
Delayed haemolytic anaemia has been observed up to one month following use of IV artesunate and oral artemisinin-based combination treatment (ACT) including Eurartesim, sometimes severe enough to require transfusion. Risk factors may include young age (children under 5 years of age) and previous treatment with IV artesunate.

Patients and caregivers should be advised to be vigilant for signs and symptoms of post-treatment haemolysis such as pallor, jaundice, dark-coloured urine, fever, fatigue, shortness of breath, dizziness and confusion.

Furthermore, as a subset of patients with delayed haemolytic anaemia after Eurartesim administration show evidence of autoimmune haemolytic anaemia, a direct antiglobulin test should be considered to determine whether therapy, e.g. with corticosteroids, is necessary.

Paediatric population
Special precaution is advised in young children when vomiting, as they are likely to develop electrolyte disturbances. These may increase the QTc-prolonging effect of Eurartesim (see section 4.3).

Hepatic and renal impairment
Eurartesim has not been evaluated in patients with moderate or severe renal or hepatic insufficiency (see section 4.2). Due to the potential for higher plasma concentrations of piperaquine to occur, caution is advised if Eurartesim is administered to patients with jaundice and/or with moderate or severe renal or hepatic insufficiency, and ECG and blood potassium monitoring are advised.

Geographical drug resistance
Drug resistance patterns of P. falciparum may vary geographically. Increased resistance in P. falciparum against artemisinins and/or piperaquine has been reported, predominantly in South-East Asia. In the event of proven or suspected recrudescent malaria infections after treatment with artenimol/piperaquine patients should be treated with a different antimalarial.

4.5 Interaction with other medicinal products and other forms of interaction

Eurartesim is contraindicated in patients already taking other medicinal products that are known to prolong the QTc interval due to the risk of a pharmacodynamic interaction leading to an additive effect on the QTc interval (see sections 4.3 and 4.4).

A limited number of drug-drug pharmacokinetic interaction studies with Eurartesim have been performed in healthy adult subjects. Therefore the assessment of the potential for drug-drug interactions to occur is based on either *in vivo* or *in vitro* studies.

Effect of Eurartesim on co-administered medicinal products
Piperaquine is metabolised by, and is an inhibitor of CYP3A4. The concurrent administration of oral Eurartesim with 7.5 mg oral midazolam, a CYP3A4 probe substrate, led to a modest increase (≤2-fold) in midazolam and its metabolites exposures in healthy adult subjects. This inhibitory effect was no longer evident one week after last administration of Eurartesim. Therefore, particular attention should be paid when medicinal products that have a narrow therapeutic index (e.g. antiretroviral medicinal products and cyclosporine) are co-administered with Eurartesim.

From *in vitro* data, piperaquine undergoes a low level of metabolism by CYP2C19, and is also an inhibitor of this enzyme. There is the potential for reducing the rate of metabolism of other substrates

of this enzyme, such as omeprazole, with consequent increase of their plasma concentration, and therefore, of their toxicity.

Piperaquine has the potential to increase the rate of metabolism for CYP2E1 substrates resulting in a decrease in the plasma concentrations of substrates such as paracetamol or theophylline, and the anaesthetic gases enflurane, halothane and isoflurane. The main consequence of this interaction could be a reduction of efficacy of the co-administered medicinal products.

Artenimol administration may result in a slight decrease in CYP1A2 activity. Caution is therefore, advised when Eurartesim is administered concomitantly with medicinal products metabolised by this enzyme that have a narrow therapeutic index, such as theophylline. Any effects are unlikely to persist beyond 24 hours after the last intake of artenimol.

Effect of co-administered medicinal products on Eurartesim
Piperaquine is metabolised by CYP3A4 *in vitro.* The concurrent administration of a single dose of oral clarithromycin, (a strong CYP3A4 inhibitor probe) with a single dose of oral Eurartesim led to a modest increase (≤2-fold) in piperaquine exposure in healthy adult subjects. This increase in exposure to the antimalarial combination may result in an exacerbation of the effect on QTc (see section 4.4). Therefore, particular caution is required if Eurartesim is administered to patients taking potent CYP3A4 inhibitors (e.g. some HIV-protease inhibitors [atazanavir, darunavir, indinavir, lopinavir, ritonavir], or verapamil and ECG monitoring should be considered due to the risk of higher plasma concentrations of piperaquine (see section 4.4).

Enzyme inducing medicinal products such as rifampicin, carbamazepine, phenytoin, phenobarbital, St. John's wort (*Hypericum perforatum*) are likely to lead to reduced piperaquine plasma concentrations. The concentration of artenimol may also be reduced.

When co-administered with efavirenz, the plasma concentration of piperaquine was decreased by 43%. Reduced plasma concentrations of piperaquine and/or artenimol may lead to therapeutic failure. Therefore, concomitant treatment with such medicinal products is not recommended.

Paediatric population
Drug-drug interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known. The above mentioned interactions for adults and the warnings in section 4.4 should be taken into account for the paediatric population.

Oral contraceptives
When co-administered to healthy women, Eurartesim exerted only a minimum effect on an estrogen/progestinic combination oral contraceptive treatment increasing the ethynilestradiol rate of absorption (expressed by geometric mean C_{max}) of about 28% but not significantly changing the exposure to ethynilestradiol and levonorgestrel and not influencing contraception activity as demonstrated by the similar plasma concentrations of follicle stimulating hormone (FSH), luteinizing hormone (LH) and progesterone observed after oral contraceptive treatment with or without concomitant Eurartesim administration.

Food interaction
Absorption of piperaquine is increased in the presence of fatty food (see sections 4.4 and 5.2) which may increase its effect on QTc interval. Therefore, Eurartesim should be taken with water only as described in section 4.2. Eurartesim should not be taken with grapefruit juice as it is likely to lead to increased piperaquine plasma concentrations.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are only limited (n=3) amount of data from the use of artenimol/piperaquine during the 1st trimester of pregnancy.
Based on animal data, Eurartesim is suspected to cause serious birth defects when administered during

the first trimester of pregnancy (see sections 4.4 and 5.3). Reproductive studies with artemisinin derivatives have demonstrated teratogenic potential with an increased risk during early gestation (see section 5.3). Piperaquine was not teratogenic in the rat or rabbit.
Therefore Eurartesim should not be used during the 1st trimester of pregnancy in situations where other suitable and effective anti-malarials are available (see section 4.4).
A large amount of data (more than 3000 exposed outcomes) from the use of artenimol/piperaquine during the 2nd and 3rd trimester indicate no fetotoxicity. In perinatal and postnatal studies in rats, piperaquine was associated with delivery complications. However, there was no delay in neonatal development following exposure in utero or via milk (see section 5.3).
Consequently, if Eurartesim is more suitable for a pregnant woman than other artemisinin-based combination therapies with a higher range of experience (or sulfadoxine–pyrimethamine), Eurartesim may be used in the 2nd and 3 trimester.

Breast-feeding
Animal data suggest excretion of piperaquine into breast milk but no data are available in humans.
Women taking Eurartesim should not breast-feed during their treatment.

Fertility
There are no specific data relating to the effects of piperaquine on fertility, however, to date no adverse events have been reported during clinical use. Moreover, data obtained in animal studies show that fertility is unaffected by artenimol in both females and males.

4.7 Effects on ability to drive and use machines

Adverse event data collected in clinical trials suggest that Eurartesim has no influence on the ability to drive and operate machines once the patient has recovered from the acute infection.

4.8 Undesirable effects

Summary of the safety profile
The safety of Eurartesim has been evaluated in two phase III open-label studies involving 1,239 paediatric patients up to 18 years and 566 adult patients >18 years treated with Eurartesim.

In a randomised trial in which 767 adults and children with uncomplicated *P. falciparum* malaria were exposed to Eurartesim, 25% of subjects were judged to have experienced an adverse drug reaction (ADR). No single type of ADR occurred at an incidence of ≥5%. The most frequent ADRs observed at an incidence ≥1.0% were: Headache (3.9%), Electrocardiogram QTc Prolonged (3.4%), *P. falciparum* infection (3.0%), Anaemia (2.8%), Eosinophilia (1.7%), Haemoglobin decreased (1.7%), Sinus tachycardia (1.7%), Asthenia (1.6%), Haematocrit [decreased] (1.6%), Pyrexia (1.5%), Red Blood Cell Count decreased (1.4%). A total of 6 (0.8%) subjects had serious ADRs in the study.

In a second randomised trial, 1,038 children, aged between 6 months and 5 years, were exposed to Eurartesim and 71% were judged to have experienced an ADR. The following ADRs were observed at an incidence of ≥5.0%: Cough (32%), Pyrexia (22.4%), Influenza (16.0%), *P. falciparum* infection (14.1%), Diarrhoea (9.4%), Vomiting (5.5%) and Anorexia (5.2%). A total of 15 (1.5%) subjects had serious ADRs in the study.

Tabulated list of adverse reactions
In the tables below, ADRs are listed under system organ class (SOC), and ranked by headings of frequency. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness, using the following convention: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known

(cannot be estimated from the available data). The table in this section is for adult patients only. A corresponding table for paediatric patients is presented in the specific section below.

Frequency of ADRs in adult patients participating in clinical studies with Eurartesim and post-marketing data:

SOC	Very Common	Common	Uncommon	**Not known**
Infections and infestations		*P. falciparum* infection	Respiratory tract infection Influenza	
Blood and lymphatic system disorders		Anaemia		Autoimmune haemolytic anaemia Delayed haemolytic anaemia
Metabolism and nutrition disorders			Anorexia	
Nervous system disorders		Headache	Convulsion Dizziness	
Cardiac disorders		QTc prolonged Tachycardia	Cardiac conduction disorders Sinus arrhythmias Bradycardia	
Respiratory, thoracic and mediastinal disorders			Cough	
Gastrointestinal disorders			Vomiting Diarrhoea Nausea Abdominal pain	
Hepatobiliary disorders			Hepatitis Hepatocellular injury Hepatomegaly Abnormal liver function tests	
Skin and subcutaneous Tissue disorders			Pruritis	
Musculoskeletal and connective tissue disorders			Arthralgia Myalgia	
General disorders and administration site conditions		Asthenia Pyrexia		

Description of selected adverse reactions

The ADRs noted for Eurartesim were generally mild in severity, 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 effect on prolongation of the QTc interval was observed on Day 2, and had resolved by Day 7 (the next time point at which ECGs were performed).

Paediatric population
A tabular overview of the frequency of the ADRs in paediatric patients is given below. The majority of paediatric experience is derived from African children aged 6 months to 5 years.

Frequency of ADRs in paediatric patients participating in clinical studies with Eurartesim and post-marketing data:

SOC	Very Common	Common	Uncommon	Not known
Infections and infestations	Influenza *P. falciparum* infection	Respiratory tract infection Ear infection		
Blood and lymphatic system disorders		Thrombocytopenia Leukopenia/neutropenia Leukocytoses NEC Anaemia	Thrombocythaemia Splenomegaly Lymphadenopathy Hypochromasia	Autoimmune haemolytic anaemia Delayed haemolytic anaemia
Metabolism and nutrition disorders		Anorexia		
Nervous system disorders			Convulsion Headache	
Eye disorders		Conjunctivitis		
Cardiac disorders		QT/QTc prolonged Heart rate irregular	Cardiac conduction disorders Cardiac murmur	
Respiratory, thoracic and mediastinal disorders	Cough		Rhinorrhoea Epistaxis	
Gastrointestinal disorders		Vomiting Diarrhoea Abdominal pain	Stomatitis Nausea	
Hepatobiliary disorders			Hepatitis Hepatomegaly Abnormal liver function tests Jaundice	
Skin and subcutaneous Tissue disorders		Dermatitis Rash	Acanthosis Pruritis	
Musculoskeletal and connective tissue disorders			Arthralgia	
General disorders and administration site conditions	Pyrexia	Asthenia		

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V

4.9 Overdose

In clinical trials, nine patients received double the cumulative intended dose of Eurartesim. The safety profile of these patients did not differ from that of patients receiving the recommended dose, with no patient reporting SAEs.

In cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate, including ECG monitoring because of the possibility of QTc interval prolongation (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiprotozoals, antimalarials, artemisinin and derivatives, combinations, ATC code: P01BF05

Pharmacodynamic effects
Artenimol is able to reach high concentrations within the parasitized erythrocytes. Its endoperoxide bridge is thought to be essential for its antimalarial activity, causing free-radical damage to parasite membrane systems including:

- Inhibition of *falciparum* sarcoplasmic-endoplasmic reticulum calcium ATPase,
- Interference with mitochondrial electron transport
- Interference with parasite transport proteins
- Disruption of parasite mitochondrial function

The exact mechanism of action of piperaquine is unknown, but it likely mirrors that of chloroquine, a close structural analogue. Chloroquine binds to toxic haeme (derived from the patient's haemoglobin) within the malaria parasite, preventing its detoxification via a polymerisation step.

Piperaquine is a bisquinoline, and this class has shown good antimalarial activity against chloroquine-resistant *Plasmodium* strains *in vitro*. The bulky bisquinolone structure may be important for activity against chloroquine-resistant strains, and may act through the following mechanisms:

- Inhibition of the transporters that efflux chloroquine from the parasite food vacuole
- Inhibition of haem-digestion pathway in the parasite food vacuole.

Resistance to piperaquine (when used as monotherapy) has been reported.

The efficacy and safety of Eurartesim have been assessed in two large randomised, open-label clinical trials:

Study DM040010 was conducted in Asian adult and paediatric patients with uncomplicated *P. falciparum* malaria. Eurartesim treatment was compared with Artesunate + Mefloquine (AS + MQ). The primary end-point was the PCR-corrected cure rate at Day 63.

Study DM040011 was conducted in African paediatric patients with uncomplicated *P. falciparum* malaria. Eurartesim treatment was compared with Artemether + Lumefantrine (A + L). The primary end-point was PCR-corrected cure rate at Day 28.

The results for the primary endpoint in the modified intent to treat (m-ITT) populations (defined as all randomised patients who received at least one dose of the study treatment, with the exclusion of those patients lost to follow up for unknown reasons) were as follows:

Study	PCR-corrected cure rate (m-ITT)			
	Eurartesim	**AS + MQ**	**A + L**	**95 % two-sided CI on the treatment difference (Eurartesim - Comparator); p-value**
DM040010 (n=1087)	97.0%	95.3%	-	(-0.84, 4.19) %; p=0.161
DM040011 (n=1524)	92.7%	-	94.8%	(-4.59, 0.45) %; p=0.128

In each case the results confirmed that Eurartesim was not inferior to the comparator medicinal product. In both studies, the true treatment failure rate was below the 5% efficacy threshold set by WHO.

The age-specific PCR-corrected cure rates in the m-ITT populations are tabulated below for the Asian and African studies, respectively:

Study	PCR-corrected cure rate (m-ITT)			
	Eurartesim	**AS + MQ**	**A + L**	**95% two-sided CI on the treatment difference (Eurartesim - Comparator); p-value**
DM04010 (n=1087)				
≤5 years	100.0%	100.0%	-	-
>5 to ≤12 years	98.2%	96.5%	-	(-3.67, 7.09)%; 0.605
>12 to ≤18 years	97.3%	100.0%	-	(-6.40, 0.99)%; 1.000
>18 to ≤64 years	96.6%	94.4%	-	(-0.98, 5.30)%; 0.146
DM04011 (n=1524)				
≤1 year	91.5%	-	98.5%	(-12.66, -1.32)%[(1)]; 0.064
>1 to ≤2 years	92.6%	-	94.6%	(-6.76, 2.63)%; 0.413
>2 to ≤5 years	93.0%	-	94.0%	(-4.41, 2.47)%; 0.590

[(1)] This CI is asymptotic because the exact CI could not be computed

In the European Safety Registry 25 patients weighing ≥ 100 kg (range 100 -121 kg) were treated with 4 tablets 320/40 mg PQP/artenimol for 3 days. Twenty-two of these patients were shown to be parasitic free at the last microscopic analysis of the blood sample; three patients did not complete parasitological blood analysis. All patients were clinically cured.

5.2 Pharmacokinetic properties

Pharmacokinetic profiles of artenimol and piperaquine have been investigated in animal models and in different human populations (healthy volunteers, adult patients and paediatric patients).

Absorption

Artenimol is very rapidly absorbed, T_{max} being approximately 1-2 hrs after single and multiple dosing. In patients, mean C_{max} (CV %) and AUC_{INF} of artenimol (observed after the first dose of Eurartesim) were 752 (47%) ng/ml and 2,002 (45%) ng/ml*h, respectively.

Artenimol bioavailability appears to be higher in malaria patients than in healthy volunteers, possibly because malaria *per se* has an effect on artenimol disposition. This may reflect malaria-associated impairment of hepatic function, causing an increase in artenimol bioavailability (reduction of first hepatic effect) without affecting its apparent elimination half-life, which is absorption rate limited. In

healthy male volunteers under fasting conditions, mean C_{max} and AUC_{INF} of artenimol ranged between 180-252 ng/ml and 516-684 ng/ml*h, respectively.

The systemic exposure to artenimol was slightly lower following the last dose of Eurartesim (lower than after the first dose by up to 15%). Artenimol pharmacokinetic parameters were found to be similar in healthy volunteers of Asian and Caucasian origin. artenimol systemic exposure on the last day of treatment was higher in females than in males, the difference being within 30%.

In healthy volunteers, artenimol exposure was increased by 43% when administered with a high fat/high calorie meal.

Piperaquine, a highly lipophilic compound, is slowly absorbed. In humans, piperaquine has a T_{max} of approximately 5 hours following a single and repeated dose. In patients mean (CV %) C_{max} and AUC_{0-24} (observed after the first dose of Eurartesim) were 179 (62%) ng/ml and 1,679 (47%) ng/ml*h, respectively. Due to its slow elimination, piperaquine accumulates in plasma after multiple doses with an accumulation factor of approximately 3. Piperaquine pharmacokinetic parameters were found to be similar in healthy volunteers of Asian and Caucasian origin. On the other hand, on the last day of Eurtartesim treatment, the piperaquine maximum plasma concentration was higher in female than in male healthy volunteers, the difference being in the order of 30 to 50%.

In healthy volunteers, piperaquine exposure is increased approximately 3-fold when administered with a high fat/high calorie meal. This pharmacokinetic effect is accompanied by an increased effect on prolongation of the QT interval. Accordingly, Eurartesim should be administered with water no less than 3 hours after the last food intake, and no food should be taken within 3 hours after each dose (see section 4.2).

Distribution
Both piperaquine and artenimol are highly bound to human plasma proteins: the protein binding observed in *in vitro* studies was 44-93% for artenimol and >99% for piperaquine. Moreover, from *in vitro* and *in vivo* data in animals, piperaquine and artenimol tend to accumulate in RBC.

Artenimol was observed to have a small volume of distribution in humans (0.8 l/kg; CV 35.5%). Pharmacokinetic parameters observed for piperaquine in humans indicate that this active substance has a large volume of distribution (730 l/kg; CV 37.5%).

Biotransformation
Artenimol is principally converted to α-artenimol-β-glucuronide (α-artenimol-G). Studies in human liver microsomes showed that artenimol was metabolised by the UDP-glucuronosyltransferase (UGT1A9 and UGT2B7) to α-artenimol-G with no cytochrome P450-mediated metabolism. *In vitro* drug-drug interaction studies revealed that artenimol is an inhibitor of CYP1A2; therefore, there is the potential for artenimol to increase plasma concentrations of CYP1A2 substrates (see section 4.5).

In vitro metabolism studies demonstrated that piperaquine is metabolised by human hepatocytes (approximately 85% of piperaquine remained after 2 hours incubation at 37°C). Piperaquine was mainly metabolised by CYP3A4 and to a lesser extent by CYP2C9 and CYP2C19. Piperaquine was found to be an inhibitor of CYP3A4 (also in a time-dependent way) and to a lesser extent of CYP2C19, while it stimulated the activity of CYP2E1.

No effect on the metabolite profile of piperaquine in human hepatocytes was observed when piperaquine was co-incubated with artenimol. The piperaquine major metabolites were a carboxyl acid cleavage product, and a mono-N-oxidated product.
In human studies, piperaquine was found to be a mild inhibitor of CYP3A4 enzyme while potent inhibitors of CYP3A4 activity caused mild inhibition of piperaquine metabolism (see section 4.5).

Elimination
The elimination half-life of artenimol is approximately 1 hour. The mean oral clearance for adult patients with malaria was 1.34 l/h/kg. The mean oral clearance was slightly higher for paediatric

patients, however the differences were minor in magnitude (<20%). Artenimol is eliminated by metabolism (mainly glucuroconjugation). Its clearance was found to be slightly lower in female than in male healthy volunteers. Data regarding artenimol excretion in humans are scarce. However, it is reported in the literature that the excretion of unchanged active substance in human urine and faeces is negligible for artemisinin derivatives.

The elimination half-life of piperaquine is around 22 days for adult patients and around 20 days for paediatric patients. The mean oral clearance for adult patients with malaria was 2.09 l/h/kg, while in paediatric patients was 2.43 l/h/kg. Due to its long elimination half-life, piperaquine accumulates after multiple dosing.

Animal studies showed that radiolabelled piperaquine is excreted by the biliary route, while urinary excretion is negligible.

Pharmacokinetics in special patient populations
No specific pharmacokinetic studies have been performed in patients with hepatic or renal insufficiency, or in elderly people.

In a paediatric pharmacokinetic study, and based on very limited sampling, minor differences were observed for artenimol pharmacokinetics between the paediatric and adult populations. The mean clearance (1.45 l/h/kg) was slightly faster in the paediatric patients than in the adult patients (1.34 l/h/kg), while the mean volume of distribution in the paediatric patients (0.705 l/kg) was lower than in the adults (0.801 l/kg).
The same comparison showed that piperaquine absorption rate constant and terminal half-life in children were predominantly similar to those seen in adults. However, the apparent clearance was faster (1.30 versus 1.14 l/h/kg) and the apparent total volume of distribution was lower in the paediatric population (623 versus 730 l/kg).

5.3 Preclinical safety data

General toxicity
Literature data concerning chronic toxicity of piperaquine in dogs and monkeys indicate some hepatotoxicity and mild reversible depression of total white cell and neutrophil counts.

The most important nonclinical safety findings after repeated dosing were the infiltration of macrophages with intracytoplasmic basophilic granular material consistent with phospholipidosis and degenerative lesions in numerous organs and tissues. These adverse reactions were seen in animals at exposure levels similar to clinical exposure levels, and with possible relevance to clinical use. It is not known whether these toxic effects are reversible.

Artenimol and piperaquine were not genotoxic/clastogenic based on *in vitro* and *in vivo* testing.

No carcinogenicity studies have been performed.

Artenimol causes embryolethality and teratogenicity in rats and rabbits.

Piperaquine did not induce malformation in rats and rabbits. In a perinatal and postnatal development study (segment III) in female rats treated with 80 mg/kg, some animals had a delay of delivery inducing mortality of the neonates. In females delivering normally the development, behaviour and growth of the surviving progeny was normal following exposure *in utero* or via milk.

No reproduction toxicity studies have been performed with the combination of artenimol and piperaquine.

Central nervous system (CNS) toxicity
There is potential for neurotoxicity of artemisinin derivatives in man and animals, which is strongly related to the dose, route and formulations of the different artenimol pro-drugs. In humans, the

potential neurotoxicity of orally administered artenimol can be considered highly unlikely, given the rapid clearance of artenimol, and its short exposure (3 days of treatment for malaria patients). There was no evidence of artenimol-induced lesions in the specific nuclei in rats or dogs, even at lethal dose.

Cardiovascular toxicity
Effects on blood pressure and on PR and QRS duration were observed at high piperaquine doses. The most important potential cardiac effect was related to cardiac conduction.

In the hERG test, the IC_{50} was 0.15 µmol for piperaquine and 7.7 µmol for artenimol. The association of artenimol and piperaquine does not produce hERG inhibition greater than that of the single compounds.

Phototoxicity
There are no phototoxicity concerns with artenimol, as it does not absorb in the range of 290-700 nm. Piperaquine has an absorption maximum at 352 nm. Since piperaquine is present in the skin (about 9% in the non-pigmented rat and only 3% in the pigmented rat), slight phototoxic reactions (swelling and erythema) were observed 24 hours after oral treatment in mice exposed to UV radiation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Pre-gelatinised starch
Dextrin
Hypromellose (E464)
Croscarmellose sodium
Magnesium stearate (E572)

Film coating
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Eurartesim tablets are packaged in PVC/PVDC/aluminium blisters containing 3 tablets.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Alfasigma S.p.A.
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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/716/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 October 2011
Date of latest renewal: 09 September 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Eurartesim 320 mg/40 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 320 mg piperaquine tetraphosphate (as the tetrahydrate; PQP) and 40 mg artenimol (artenimol).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

White oblong biconvex film-coated tablet (dimension 16x8mm / thickness 5.5mm) with a break-line and marked on one side with two "σ" letters.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Eurartesim is indicated for the treatment of uncomplicated *Plasmodium falciparum* malaria in adults, adolescents, children and infants 6 months and over and weighing 5 kg or more.

Consideration should be given to official guidance on the appropriate use of antimalarial medicinal products, including information on the prevalence of resistance to artenimol/piperaquine in the geographical region where the infection was acquired (see section 4.4).

4.2 Posology and method of administration

Posology

Eurartesim should be administered over three consecutive days for a total of three doses taken at the same time each day.

Dosing should be based on body weight as shown in the table below.

Body weight (kg)	**Daily dose (mg)**		**Tablet strength and number of tablets per dose**
	PQP	Artenimol	
5 to <7	80	10	½ x 160 mg / 20 mg tablet
7 to <13	160	20	1 x 160 mg / 20 mg tablet
13 to <24	320	40	1 x 320 mg / 40 mg tablet
24 to <36	640	80	2 x 320 mg / 40 mg tablets
36 to <75	960	120	3 x 320 mg / 40 mg tablets
> 75*	1,280	160	4 x 320 mg / 40 mg tablets

* see section 5.1

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, alternative antimalarial therapy 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.

There is no data on a second course of treatment.
No more than two courses of Eurartesim may be given within a 12 month period (see sections 4.4 and 5.3).
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 (see sections 4.4 and 5.2).

Special populations

Elderly
Clinical studies of Eurartesim did not include patients aged 65 years and over, therefore no dosing recommendation can be made. Considering the possibility of age-associated decrease in hepatic and renal function, as well as a potential for heart disorders (see sections 4.3 and 4.4), caution should be exercised when administering the product to the elderly.

Hepatic and renal impairment
Eurartesim has not been evaluated in subjects with moderate or severe renal or hepatic insufficiency. Therefore, caution is advised when administering Eurartesim to these patients (see section 4.4).

Paediatric population

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. No data are available for these paediatric subsets.

Method of administration

Eurartesim should be taken orally with water and without food.
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, such as infants and young children, Eurartesim may be crushed and mixed with water. The mixture should be used immediately after preparation.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Severe malaria according to WHO definition.
- Family history of sudden death or of congenital prolongation of the QTc interval.
- Known congenital prolongation of the QTc-interval or any clinical condition known to prolong the QTc interval.
- History of symptomatic cardiac arrhythmias or with clinically relevant bradycardia.
- Any predisposing cardiac conditions for arrhythmia such as severe hypertension, left ventricular hypertrophy (including hypertrophic cardiomyopathy) or congestive cardiac failure accompanied by reduced left ventricle ejection fraction.
- Electrolyte disturbances, particularly hypokalaemia, hypocalcaemia or hypomagnesaemia.
- 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), antidepressive medicinal products.
    - Certain antimicrobialmedicinal products, including medicinal products of the following classes:
        - macrolides (e.g. erythromycin, clarithromycin),
        - fluoroquinolones (e.g. moxifloxacin, sparfloxacin),
        - imidazole and triazole antifungal medicinal products,
        - and also pentamidine and saquinavir.
    - Certain non-sedating antihistamines (e.g. terfenadine, astemizole, mizolastine).
    - Cisapride, droperidol, domperidone, bepridil, diphemanil, probucol, levomethadyl, methadone, vinca alkaloids, arsenic trioxide.
- Recent treatment with medicinal products known to prolong the QTc interval that may still be circulating at the time that Eurartesim is commenced (e.g. mefloquine, halofantrine, lumefantrine, chloroquine, quinine and other antimalarial medicinal products) taking into account their elimination half-life.

4.4 Special warnings and precautions for use

Eurartesim should not be used to treat severe falciparum malaria (see section 4.3) and, due to insufficient data, should not be used to treat malaria due to *Plasmodium vivax, Plasmodium malariae* or *Plasmodium ovale.*

The long half-life of piperaquine (about 22 days) should be kept in mind in the event that another anti-malarial agent is started due to treatment failure or a new malaria infection (see below and sections 4.3 and 4.5).

Piperaquine is a mild inhibitor of CYP3A4. Caution is recommended when co-administering Eurartesim with medicinal products exhibiting variable patterns of inhibition, induction or competition for CYP3A4 as the therapeutic and/or toxic effects of some co-administered medicinal products could be altered.

Piperaquine is also a substrate of CYP3A4. A moderate increase of piperaquine plasma concentrations (<2-fold) was observed when co-administered with strong CYP3A4 inhibitors, resulting in a potential exacerbation of the effect on QTc prolongation (see section 4.5).

Exposure to piperaquine may also be increased when co-administered with mild or moderate CYP3A4-inhibitors (e.g. oral contraceptives). Therefore, caution should be applied when co-administering Eurartesim with any CYP3A4-inhibitor and ECG monitoring should be considered.

Due to the lack of multiple dose PK data for piperaquine, administration of any strong CYP3A4-inhibitors should be discouraged after initiation (i.e. the first dose) of Eurartesim (see sections 4.5 and 5.2).

Eurartesim should not be used during the 1st trimester of pregnancy in situations where other suitable and effective antimalarials are available (see section 4.6).

In the absence of carcinogenicity study data, and due to lack of clinical experience with repeated courses of treatment in humans, no more than two courses of Eurartesim should be given in a 12-month period (see sections 4.2 and 5.3).

Effects on cardiac repolarization

In clinical trials with Eurartesim limited ECGs were obtained during treatment. These showed that QTc prolongation occurred more frequently and to a larger extent in association with Eurartesim therapy than with the comparators (see section 5.1 for details of the comparators). Analysis of cardiac adverse events in clinical trials showed that these were reported more frequently in Eurartesim treated patients than in those treated with comparator antimalarial (see section 4.8). Before the third dose of Eurartesim, in one of the two Phase III studies 3/767 patients (0.4%) were reported to have a QTcF value of >500 ms versus none in the comparator group.

The potential for Eurartesim to prolong the QTc interval was investigated in parallel groups of healthy volunteers who took each dose with high (~1000 Kcal) or low (~400 Kcal) fat/calorie meals or in fasting conditions. Compared to placebo, the maximum mean increases in QTcF on Day 3 of dosing with Eurartesim were 45.2, 35.5 and 21.0 msec under respective dosing conditions. The QTcF prolongation observed under fasting conditions lasted between 4 and 11 hours after the last dose was administered on Day 3. The mean QTcF prolongation compared to placebo decreased to 11.8 msec at 24 hours and to 7.5 msec at 48 hours. No healthy subject dosed in fasting conditions showed a QTcF greater than 480 msec or an increase over baseline greater than 60 msec. The number of subjects with QTcF greater than 480 msec after dosing with low fat meals was 3/64, while 10/64 had QTcF values over this threshold after dosing with high fat meals. No subject had a QTcF value greater than 500 msec in any of the dosing conditions.

An ECG should be obtained as early as possible during treatment with Eurartesim and ECG monitoring should be applied in patients who may have a higher risk of developing arrhythmia in association with QTc prolongation (see below).

When clinically appropriate, consideration should be given to obtaining an ECG from all patients before the last of the three daily doses is taken and approximately 4-6 hours after the last dose, since the risk of QTc interval prolongation may be greatest during this period (see section 5.2). QTc intervals of more than 500 ms 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.

Compared to adult males, female patients and elderly patients have longer QTc intervals. Therefore, they may be more sensitive to the effects of QTc-prolonging medications such as Eurartesim so that special caution is required.

Delayed Haemolytic Anaemia
Delayed haemolytic anaemia has been observed up to one month following use of IV artesunate and oral artemisinin-based combination treatment (ACT) including Eurartesim, sometimes severe enough to require transfusion. Risk factors may include young age (children under 5 years of age) and previous treatment with IV artesunate.

Patients and caregivers should be advised to be vigilant for signs and symptoms of post-treatment haemolysis such as pallor, jaundice, dark-coloured urine, fever, fatigue, shortness of breath, dizziness and confusion.

Furthermore, as a subset of patients with delayed haemolytic anaemia after Eurartesim administration show evidence of autoimmune haemolytic anaemia, a direct antiglobulin test should be considered to determine whether therapy, e.g. with corticosteroids, is necessary.

Paediatric population
Special precaution is advised in young children when vomiting, as they are likely to develop electrolyte disturbances. These may increase the QTc-prolonging effect of Eurartesim (see section 4.3).

Hepatic and renal impairment
Eurartesim has not been evaluated in patients with moderate or severe renal or hepatic insufficiency (see section 4.2). Due to the potential for higher plasma concentrations of piperaquine to occur, caution is advised if Eurartesim is administered to patients with jaundice and/or with moderate or severe renal or hepatic insufficiency, and ECG and blood potassium monitoring are advised.

Geographical drug resistance
Drug resistance patterns of P. falciparum may vary geographically. Increased resistance in P. falciparum against artemisinins and/or piperaquine has been reported, predominantly in South-East Asia. In the event of proven or suspected recrudescent malaria infections after treatment with artenimol/piperaquine patients should be treated with a different antimalarial.

4.5 Interaction with other medicinal products and other forms of interaction

Eurartesim is contraindicated in patients already taking other medicinal products that are known to prolong the QTc interval due to the risk of a pharmacodynamic interaction leading to an additive effect on the QTc interval (see section 4.3 and 4.4).

A limited number of drug-drug pharmacokinetic interaction studies with Eurartesim have been performed in healthy adult subjects. Therefore the assessment of the potential for drug-drug interactions to occur is based on either *in vivo* or *in vitro* studies.

Effect of Eurartesim on co-administered medicinal products
Piperaquine is metabolised by, and is an inhibitor of CYP3A4. The concurrent administration of oral Eurartesim with 7.5 mg oral midazolam, a CYP3A4 probe substrate, led to a modest increase (≤2-fold) in midazolam and its metabolites exposures in healthy adult subjects. This inhibitory effect was no longer evident one week after last administration of Eurartesim. Therefore, particular attention should be paid when medicinal products that have a narrow therapeutic index (e.g. antiretroviral medicinal products and cyclosporine) are co-administered with Eurartesim.

From *in vitro* data, piperaquine undergoes a low level of metabolism by CYP2C19, and is also an inhibitor of this enzyme. There is the potential for reducing the rate of metabolism of other substrates of this enzyme, such as omeprazole, with consequent increase of their plasma concentration, and therefore, of their toxicity.

Piperaquine has the potential to increase the rate of metabolism for CYP2E1 substrates resulting in a decrease in the plasma concentrations of substrates such as paracetamol or theophylline, and the anaesthetic gases enflurane, halothane and isoflurane. The main consequence of this interaction could be a reduction of efficacy of the co-administered medicinal products.

Artenimol administration may result in a slight decrease in CYP1A2 activity. Caution is therefore, advised when Eurartesim is administered concomitantly with medicinal products metabolised by this enzyme that have a narrow therapeutic index, such as theophylline. Any effects are unlikely to persist beyond 24 hours after the last intake of artenimol.

Effect of co-administered medicinal products on Eurartesim
Piperaquine is metabolised by CYP3A4 *in vitro.* The concurrent administration of a single dose of oral clarithromycin, (a strong CYP3A4 inhibitor probe) with a single dose of oral Eurartesim led to a modest increase (≤2-fold) in piperaquine exposure in healthy adult subjects. This increase in exposure to the antimalarial combination may result in an exacerbation of the effect on QTc (see section 4.4). Therefore, particular caution is required if Eurartesim is administered to patients taking potent CYP3A4 inhibitors (e.g. some HIV-protease inhibitors [atazanavir, darunavir, indinavir, lopinavir, ritonavir], or verapamil and ECG monitoring should be considered due to the risk of higher plasma concentrations of piperaquine (see section 4.4).

Enzyme inducing medicinal products such as rifampicin, carbamazepine, phenytoin, phenobarbital, St. John's wort (*Hypericum perforatum*) are likely to lead to reduced piperaquine plasma concentrations. The concentration of artenimol may also be reduced.

When co-administered with efavirenz, the plasma concentration of piperaquine was decreased by 43%. Reduced plasma concentrations of piperaquine and/or artenimol may lead to therapeutic failure. Therefore, concomitant treatment with such medicinal products is not recommended.

Paediatric population
Drug-drug interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known. The above mentioned interactions for adults and the warnings in section 4.4 should be taken into account for the paediatric population.

Oral contraceptives
When co-administered to healthy women, Eurartesim exerted only a minimum effect on an estrogen/progestinic combination oral contraceptive treatment increasing the ethynilestradiol rate of absorption (expressed by geometric mean C_{max}) of about 28% but not significantly changing the exposure to ethynilestradiol and levonorgestrel and not influencing contraception activity as demonstrated by the similar plasma concentrations of follicle stimulating hormone (FSH), luteinizing hormone (LH) and progesterone observed after oral contraceptive treatment with or without concomitant Eurartesim administration.

Food interaction
Absorption of piperaquine is increased in the presence of fatty food (see sections 4.4 and 5.2) which may increase its effect on QTc interval. Therefore, Eurartesim should be taken with water only as described in section 4.2. Eurartesim should not be taken with grapefruit juice as it is likely to lead to increased piperaquine plasma concentrations.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are only limited (n=3) amount of data from the use of artenimol/piperaquine during the 1st trimester of pregnancy.
Based on animal data, Eurartesim is suspected to cause serious birth defects when administered during the first trimester of pregnancy (see sections 4.4 and 5.3). Reproductive studies with artemisinin derivatives have demonstrated teratogenic potential with an increased risk during early gestation (see section 5.3). Piperaquine was not teratogenic in the rat or rabbit.
Therefore Eurartesim should not be used during the 1st trimester of pregnancy in situations where other suitable and effective anti-malarials are available (see section 4.4).
A large amount of data (more than 3000 exposed outcomes) from the use of artenimol/piperaquine during the 2nd and 3rd trimester indicate no fetotoxicity. In perinatal and postnatal studies in rats, piperaquine was associated with delivery complications. However, there was no delay in neonatal development following exposure in utero or via milk (see section 5.3).
Consequently, if Eurartesim is more suitable for a pregnant woman than other artemisinin-based combination therapies with a higher range of experience (or sulfadoxine–pyrimethamine), Eurartesim may be used in the 2nd and 3rd trimester.

Breast-feeding
Animal data suggest excretion of piperaquine into breast milk but no data are available in humans.
Women taking Eurartesim should not breast-feed during their treatment.

Fertility
There are no specific data relating to the effects of piperaquine on fertility, however, to date no adverse events have been reported during clinical use. Moreover, data obtained in animal studies show that fertility is unaffected by artenimol in both females and males.

4.7 Effects on ability to drive and use machines

Adverse event data collected in clinical trials suggest that Eurartesim has no influence on the ability to drive and operate machines once the patient has recovered from the acute infection.

4.8 Undesirable effects

Summary of the safety profile
The safety of Eurartesim has been evaluated in two phase III open-label studies involving 1,239 paediatric patients up to 18 years and 566 adult patients >18 years treated with Eurartesim.

In a randomised trial in which 767 adults and children with uncomplicated *P. falciparum* malaria were exposed to Eurartesim, 25% of subjects were judged to have experienced an adverse drug reaction (ADR). No single type of ADR occurred at an incidence of ≥5%. The most frequent ADRs observed at an incidence ≥1.0% were: Headache (3.9%), Electrocardiogram QTc Prolonged (3.4%), *P. falciparum* infection (3.0%), Anaemia (2.8%), Eosinophilia (1.7%), Haemoglobin decreased (1.7%), Sinus tachycardia (1.7%), Asthenia (1.6%), Haematocrit [decreased] (1.6%), Pyrexia (1.5%), Red Blood Cell Count decreased (1.4%). A total of 6 (0.8%) subjects had serious ADRs in the study.

In a second randomised trial, 1,038 children, aged between 6 months and 5 years, were exposed to Eurartesim and 71% were judged to have experienced an ADR. The following ADRs were observed at an incidence of ≥5.0%: Cough (32%), Pyrexia (22.4%), Influenza (16.0%), *P. falciparum* infection (14.1%), Diarrhoea (9.4%), Vomiting (5.5%) and Anorexia (5.2%). A total of 15 (1.5%) subjects had serious ADRs in the study.

Tabulated list of adverse reactions
In the tables below, ADRs are listed under system organ class (SOC), and ranked by headings of frequency. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness, using the following convention: Very common (≥1/10), common (≥1/100 to <1/10),

uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). The table in this section is for adult patients only. A corresponding table for paediatric patients is presented in the specific section below.

Frequency of ADRs in adult patients participating in clinical studies with Eurartesim and post-marketing data:

SOC	Very Common	Common	Uncommon	**Not known**
Infections and infestations		*P. falciparum* infection	Respiratory tract infection Influenza	
Blood and lymphatic system disorders		Anaemia		Autoimmune haemolytic anaemia Delayed haemolytic anaemia
Metabolism and nutrition disorders			Anorexia	
Nervous system disorders		Headache	Convulsion Dizziness	
Cardiac disorders		QTc prolonged Tachycardia	Cardiac conduction disorders Sinus arrhythmias Bradycardia	
Respiratory, thoracic and mediastinal disorders			Cough	
Gastrointestinal disorders			Vomiting Diarrhoea Nausea Abdominal pain	
Hepatobiliary disorders			Hepatitis Hepatocellular injury Hepatomegaly Abnormal liver function tests	
Skin and subcutaneous Tissue disorders			Pruritis	
Musculoskeletal and connective tissue disorders			Arthralgia Myalgia	
General disorders and administration site conditions		Asthenia Pyrexia		

Description of selected adverse reactions

The ADRs noted for Eurartesim were generally mild in severity, 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 effect on prolongation of the QTc interval was observed on Day 2, and had resolved by Day 7 (the next time point at which ECGs were performed).

Paediatric population
A tabular overview of the frequency of the ADRs in paediatric patients is given below. The majority of paediatric experience is derived from African children aged 6 months to 5 years.

Frequency of ADRs in paediatric patients participating in clinical studies with Eurartesim and post-marketing data:

SOC	Very Common	Common	Uncommon	Not known
Infections and infestations	Influenza *P. falciparum* infection	Respiratory tract infection Ear infection		
Blood and lymphatic system disorders		Thrombocytopenia Leukopenia/neutropenia Leukocytoses NEC Anaemia	Thrombocythaemia Splenomegaly Lymphadenopathy Hypochromasia	Autoimmune haemolytic anaemia Delayed haemolytic anaemia
Metabolism and nutrition disorders		Anorexia		
Nervous system disorders			Convulsion Headache	
Eye disorders		Conjunctivitis		
Cardiac disorders		QT/QTc prolonged Heart rate irregular	Cardiac conduction disorders Cardiac murmur	
Respiratory, thoracic and mediastinal disorders	Cough		Rhinorrhoea Epistaxis	
Gastrointestinal disorders		Vomiting Diarrhoea Abdominal pain	Stomatitis Nausea	
Hepatobiliary disorders			Hepatitis Hepatomegaly Abnormal liver function tests Jaundice	
Skin and subcutaneous Tissue disorders		Dermatitis Rash	Acanthosis Pruritis	
Musculoskeletal and connective tissue disorders			Arthralgia	
General disorders and administration site conditions	Pyrexia	Asthenia		

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In clinical trials, nine patients received double the cumulative intended dose of Eurartesim. The safety profile of these patients did not differ from that of patients receiving the recommended dose, with no patient reporting SAEs.

In cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate, including ECG monitoring because of the possibility of QTc interval prolongation (see section 4.4)

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiprotozoals, antimalarials, Artemisinin and derivatives, combinations, ATC code: P01BF05.

Pharmacodynamic effects
Artenimol is able to reach high concentrations within the parasitized erythrocytes. Its endoperoxide bridge is thought to be essential for its antimalarial activity, causing free-radical damage to parasite membrane systems including:

- Inhibition of *falciparum* sarcoplasmic-endoplasmic reticulum calcium ATPase,
- Interference with mitochondrial electron transport
- Interference with parasite transport proteins
- Disruption of parasite mitochondrial function

The exact mechanism of action of piperaquine is unknown, but it likely mirrors that of chloroquine, a close structural analogue. Chloroquine binds to toxic haeme (derived from the patient's haemoglobin) within the malaria parasite, preventing its detoxification via a polymerisation step.

Piperaquine is a bisquinoline, and this class has shown good antimalarial activity against chloroquine-resistant *Plasmodium* strains *in vitro*. The bulky bisquinolone structure may be important for activity against chloroquine- resistant strains, and may act through the following mechanisms:

- Inhibition of the transporters that efflux chloroquine from the parasite food vacuole
- Inhibition of haem-digestion pathway in the parasite food vacuole.

Resistance to piperaquine (when used as monotherapy) has been reported.

The efficacy and safety of Eurartesim have been assessed in two large randomised, open-label clinical trials:

Study DM040010 was conducted in Asian adult and paediatric patients with uncomplicated *P. falciparum* malaria. Eurartesim treatment was compared with Artesunate + Mefloquine (AS + MQ). The primary end-point was the PCR-corrected cure rate at Day 63.

Study DM040011 was conducted in African paediatric patients with uncomplicated *P. falciparum* malaria. Eurartesim treatment was compared with Artemether + Lumefantrine (A + L). The primary end-point was PCR-corrected cure rate at Day 28.

The results for the primary endpoint in the modified intent to treat (m-ITT) populations (defined as all randomised patients who received at least one dose of the study treatment, with the exclusion of those patients lost to follow up for unknown reasons) were as follows:

Study	PCR-corrected cure rate (m-ITT)			
	Eurartesim	**AS + MQ**	**A + L**	**95 % two-sided CI on the treatment difference (Eurartesim - Comparator); p-value**
DM040010 (n=1087)	97.0%	95.3%	-	(-0.84, 4.19)%; p=0.161
DM040011 (n=1524)	92.7%	-	94.8%	(-4.59, 0.45)%; p=0.128

In each case the results confirmed that Eurartesim was not inferior to the comparator medicinal product. In both studies, the true treatment failure rate was below the 5% efficacy threshold set by WHO.

The age-specific PCR-corrected cure rates in the m-ITT populations are tabulated below for the Asian and African studies, respectively:

Study	PCR-corrected cure rate (m-ITT)			
	Eurartesim	**AS + MQ**	**A + L**	**95% two-sided CI on the treatment difference (Eurartesim - Comparator); p-value**
DM04010 (n=1087)				
≤5years	100.0%	100.0%	-	-
>5 to ≤12years	98.2%	96.5%	-	(-3.67, 7.09)%; 0.605
>12 to ≤18 years	97.3%	100.0%	-	(-6.40, 0.99)%; 1.000
>18 to ≤64 years	96.6%	94.4%	-	(-0.98, 5.30)%; 0.146
DM04011 (n=1524)				
≤1 year	91.5%	-	98.5%	(-12.66, -1.32)%[(1)]; 0.064
>1 to ≤ 2 years	92.6%	-	94.6%	(-6.76, 2.63)%; 0.413
>2 to ≤5 years	93.0%	-	94.0%	(-4.41, 2.47)%; 0.590

[(1)] This CI is asymptotic because the exact CI could not be computed

In the European Safety Registry 25 patients weighing ≥ 100 kg (range 100 -121 kg) were treated with 4 tablets 320/40 mg PQP/artenimol for 3 days. Twenty-two of these patients were shown to be parasitic free at the last microscopic analysis of the blood sample; three patients did not complete parasitological blood analysis. All patients were clinically cured.

5.2 Pharmacokinetic properties

Pharmacokinetic profiles of artenimol and piperaquine have been investigated in animal models and in different human populations (healthy volunteers, adult patients and paediatric patients).

Absorption
Artenimol is very rapidly absorbed, T_{max} being approximately 1-2 hrs after single and multiple dosing. In patients, mean C_{max} (CV%) and AUC_{INF} of artenimol (observed after the first dose of Eurartesim) were 752 (47%) ng/ml and 2,002 (45 %) ng/ml*h, respectively.

Artenimol bioavailability appears to be higher in malaria patients than in healthy volunteers, possibly because malaria *per se* has an effect on artenimol disposition. This may reflect malaria-associated impairment of hepatic function, causing an increase in artenimol bioavailability (reduction of first hepatic effect) without affecting its apparent elimination half-life, which is absorption rate limited. In healthy male volunteers under fasting conditions, mean C_{max} and AUC_{INF} of artenimol ranged between 180-252 ng/ml and 516-684 ng/ml*h, respectively.

The systemic exposure to artenimol was slightly lower following the last dose of Eurartesim (lower than after the first dose by up to 15%). Artenimol pharmacokinetic parameters were found to be similar in healthy volunteers of Asian and Caucasian origin. Artenimol systemic exposure on the last day of treatment was higher in females than in males, the difference being within 30%.

In healthy volunteers, artenimol exposure was increased by 43% when administered with a high fat/high calorie meal.

Piperaquine, a highly lipophilic compound, is slowly absorbed. In humans, piperaquine has a T_{max} of approximately 5 hours following a single and repeated dose. In patients mean (CV%) C_{max} and AUC_{0-24} (observed after the first dose of Eurartesim) were 179 (62%) ng/ml and 1,679 (47%) ng/ml*h, respectively. Due to its slow elimination, piperaquine accumulates in plasma after multiple doses with an accumulation factor of approximately 3. Piperaquine pharmacokinetic parameters were found to be similar in healthy volunteers of Asian and Caucasian origin. On the other hand, on the last day of Eurtartesim treatment, the piperaquine maximum plasma concentration was higher in female than in male healthy volunteers, the difference being in the order of 30 to 50%.

In healthy volunteers, piperaquine exposure is increased approximately 3-fold when administered with a high fat/high calorie meal. This pharmacokinetic effect is accompanied by an increased effect on prolongation of the QT interval. Accordingly, Eurartesim should be administered with water no less than 3 hours after the last food intake, and no food should be taken within 3 hours after each dose (see section 4.2).

Distribution
Both piperaquine and artenimol are highly bound to human plasma proteins: the protein binding observed in *in vitro* studies was 44-93% for artenimol and >99% for piperaquine. Moreover, from *in vitro* and *in vivo* data in animals, piperaquine and artenimol tend to accumulate in RBC.

Artenimol was observed to have a small volume of distribution in humans (0.8 l/kg; CV 35.5%). Pharmacokinetic parameters observed for piperaquine in humans indicate that this active substance has a large volume of distribution (730 l/kg; CV 37.5%).

Biotransformation
Artenimol is principally converted to α- artenimol-β-glucuronide (α- artenimol-G). Studies in human liver microsomes showed that artenimol was metabolised by the UDP-glucuronosyltransferase (UGT1A9 and UGT2B7) to α- artenimol-G with no cytochrome P450-mediated metabolism. *In vitro* drug-drug interaction studies revealed that artenimol is an inhibitor of CYP1A2; therefore, there is the potential for artenimol to increase plasma concentrations of CYP1A2 substrates (see section 4.5).

In vitro metabolism studies demonstrated that piperaquine is metabolised by human hepatocytes (approximately 85% of piperaquine remained after 2 hours incubation at 37°C). Piperaquine was mainly metabolised by CYP3A4 and to a lesser extent by CYP2C9 and CYP2C19. Piperaquine was found to be an inhibitor of CYP3A4 (also in a time-dependent way) and to a lesser extent of CYP2C19, while it stimulated the activity of CYP2E1.

No effect on the metabolite profile of piperaquine in human hepatocytes was observed when piperaquine was co-incubated with artenimol. The piperaquine major metabolites were a carboxyl acid cleavage product, and a mono-N-oxidated product.

In human studies, piperaquine was found to be a mild inhibitor of CYP3A4 enzyme while potent inhibitors of CYP3A4 activity caused mild inhibition of piperaquine metabolism (see section 4.5).

Elimination
The elimination half-life of artenimol is approximately 1 hour. The mean oral clearance for adult patients with malaria was 1.34 l/h/kg. The mean oral clearance was slightly higher for paediatric patients, however the differences were minor in magnitude (<20%). artenimol is eliminated by metabolism (mainly glucuroconjugation). Its clearance was found to be slightly lower in female than

in male healthy volunteers. Data regarding artenimol excretion in humans are scarce. However, it is reported in the literature that the excretion of unchanged active substance in human urine and faeces is negligible for artemisinin derivatives.

The elimination half-life of piperaquine is around 22 days for adult patients and around 20 days for paediatric patients. The mean oral clearance for adult patients with malaria was 2.09 l/h/kg, while in paediatric patients was 2.43 l/h/kg. Due to its long elimination half-life, piperaquine accumulates after multiple dosing.

Animal studies showed that radiolabelled piperaquine is excreted by the biliary route, while urinary excretion is negligible.

Pharmacokinetics in special patient populations
No specific pharmacokinetic studies have been performed in patients with hepatic or renal insufficiency, or in elderly people.

In a paediatric pharmacokinetic study, and based on very limited sampling, minor differences were observed for artenimol pharmacokinetics between the paediatric and adult populations. The mean clearance (1.45 l/h/kg) was slightly faster in the paediatric patients than in the adult patients (1.34 l/h/kg), while the mean volume of distribution in the paediatric patients (0.705 l/kg) was lower than in the adults (0.801 l/kg).

The same comparison showed that piperaquine absorption rate constant and terminal half-life in children were predominantly similar to those seen in adults. However, the apparent clearance was faster (1.30 versus 1.14 l/h/kg) and the apparent total volume of distribution was lower in the paediatric population (623 versus 730 l/kg).

5.3 Preclinical safety data

General toxicity
Literature data concerning chronic toxicity of piperaquine in dogs and monkeys indicate some hepatotoxicity and mild reversible depression of total white cell and neutrophil counts.

The most important nonclinical safety findings after repeated dosing were the infiltration of macrophages with intracytoplasmic basophilic granular material consistent with phospholipidosis and degenerative lesions in numerous organs and tissues. These adverse reactions were seen in animals at exposure levels similar to clinical exposure levels, and with possible relevance to clinical use. It is not known whether these toxic effects are reversible.

Artenimol and piperaquine were not genotoxic/clastogenic based on *in vitro* and *in vivo* testing.

No carcinogenicity studies have been performed.

Artenimol causes embryolethality and teratogenicity in rats and rabbits.

Piperaquine did not induce malformation in rats and rabbits. In a perinatal and postnatal development study (segment III) in female rats treated with 80 mg/kg, some animals had a delay of delivery inducing mortality of the neonates. In females delivering normally the development, behaviour and growth of the surviving progeny was normal following exposure *in utero* or via milk.

No reproduction toxicity studies have been performed with the combination of artenimol and piperaquine.

Central nervous system (CNS) toxicity
There is potential for neurotoxicity of artemisinin derivatives in man and animals, which is strongly related to the dose, route and formulations of the different artenimol pro-drugs. In humans, the potential neurotoxicity of orally administered artenimol can be considered highly unlikely, given the

rapid clearance of artenimol, and its short exposure (3 days of treatment for malaria patients). There was no evidence of artenimol-induced lesions in the specific nuclei in rats or dogs, even at lethal dose.

Cardiovascular toxicity
Effects on blood pressure and on PR and QRS duration were observed at high piperaquine doses. The most important potential cardiac effect was related to cardiac conduction.

In the hERG test, the IC_{50} was 0.15 µmol for piperaquine and 7.7 µmol forartenimol. The association of artenimol and piperaquine does not produce hERG inhibition greater than that of the single compounds.

Phototoxicity
There are no phototoxicity concerns with artenimol, as it does not absorb in the range of 290-700 nm. Piperaquine has an absorption maximum at 352 nm. Since piperaquine is present in the skin (about 9% in the non-pigmented rat and only 3% in the pigmented rat), slight phototoxic reactions (swelling and erythema) were observed 24 hours after oral treatment in mice exposed to UV radiation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Pre-gelatinised starch
Dextrin
Hypromellose (E464)
Croscarmellose sodium
Magnesium stearate (E572)

Film coating
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Eurartesim tablets are packaged in PVC/PVDC/aluminium blisters containing 3, 6, 9, 12, 270 or 300 tablets.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Alfasigma S.p.A.
Via Ragazzi del ’99, n. 5
40133 Bologna
Italy

Tel: +39 051 6489602
Fax: +39 051 388689
Email: regulatorycorporate@alfasigma.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/716/001
EU/1/11/716/002
EU/1/11/716/003
EU/1/11/716/004
EU/1/11/716/006
EU/1/11/716/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 October 2011
Date of latest renewal: 09 September 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Alfasigma S.p.A.
Via Pontina Km 30.400
IT-00071 Pomezia (RM)
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder shall ensure that all physicians who are expected to prescribe or use Eurartesim are provided with a healthcare profession educational pack containing the following:
- The Summary of Product Characteristics
- The Patient Information Leaflet
- The Physician Leaflet including the Contraindicated Conditions of Use and Contraindicated Concomitant Medication checklist

The Physician Leaflet should contain the following key messages:

- That Eurartesim has a potential to prolong the QTc interval that may lead to potentially lethal arrhythmias.
- That piperaquine absorption is increased in the presence of food, therefore to reduce this risk of QTc interval prolongation, the patients should be advised to take the tablets with water, without food, no less than three hours after the last food intake. No food should be taken within 3 hours after each dose.
- That Eurartesim is contraindicated in patients with severe malaria according to WHO definition and 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.
- The ECG monitoring recommendations.
- The scope and use of the Contraindicated Conditions of Use and Contraindicated Concomitant Medication checklist
- That there is a potential risk of teratogenicity and so Eurartesim should not be used in the 1st trimester of pregnancy in situations where other suitable and effective anti-malarials are available.
- The need to counsel patients on important risks associated with Eurartesim therapy and appropriate precautions when using the medicine.
- That patients should be advised to contact their doctor about adverse events and that physicians/pharmacists should report suspected adverse reactions to Eurartesim, and in particular, those associated with a QT prolongation.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Eurartesim 160 mg/20 mg film-coated tablets
piperaquine tetraphosphate/artenimol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 160 mg of piperaquine tetraphosphate (as the tetrahydrate) and 20 mg of artenimol.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
3 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Take at least 3 hours before or after food.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C
Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Alfasigma S.p.A.
Via Ragazzi del ’99, n. 5 40133 Bologna
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/716/005 3 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Eurartesim

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number} [product code]
SN: {number} [serial number]
NN: {number} [national reimbursement number or other national number identifying the medicinal product]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Eurartesim 160 mg/20 mg tablets
piperaquine tetraphosphate/artenimol

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Alfasigma S.p.A.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Eurartesim 320 mg/40 mg film-coated tablets
piperaquine tetraphosphate / artenimol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 320 mg of piperaquine tetraphosphate (as the tetrahydrate) and 40 mg of artenimol.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets. 3 tablets
Film-coated tablets. 6 tablets
Film-coated tablets. 9 tablets
Film-coated tablets. 12 tablets
Film-coated tablets. 270 tablets
Film-coated tablets. 300 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Take at least 3 hours before or after food.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C
Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Alfasigma S.p.A.
Via Ragazzi del ’99, n. 5 40133 Bologna
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/716/001 3 film-coated tablets
EU/1/11/716/002 6 film-coated tablets
EU/1/11/716/003 9 film-coated tablets
EU/1/11/716/004 12 film-coated tablets
EU/1/11/716/006 270 film-coated tablets
EU/1/11/716/007 300 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Eurartesim

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number} [product code]
SN: {number} [serial number]
NN: {number} [national reimbursement number or other national number identifying the medicinal product]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Eurartesim 320 mg/40 mg tablets
piperaquine tetraphosphate / artenimol

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Alfasigma S.p.A

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: information for the user

Eurartesim 160 mg/20 mg film-coated tablets
Piperaquine tetraphosphate/artenimol

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Eurartesim is and what it is used for

Eurartesim contains the active substances piperaquine tetraphosphate and artenimol. It is used to treat uncomplicated malaria when use of a medicine given by mouth is appropriate.

Malaria is caused by infection with a parasite called *Plasmodium*, spread by the bite of an infected mosquito.There are different types of *Plasmodium* parasite. Eurartesim kills the *Plasmodium falciparum* parasite.

The medicine can be taken by adults, adolescents, children and infants over 6 months old who weigh 5 kilograms or more.

2. What you need to know before you or your child takes Eurartesim

Do not take Eurartesim if you or your child:
- is allergic to the active substances, piperaquine tetraphosphate or artenimol, or to any of the other ingredients of this medicine (listed in section 6);
- has a severe type of malaria infection which has affected parts of the body such as the brain, lungs or kidneys;
- has a heart condition, such as changes to the rhythm or rate of heart beat, or heart disease;
- knows that any member of your family (parents, grandparents, brothers or sisters) died suddenly due to a heart problem or was born with heart problems;
- suffers from changes to the levels of salts in the body (electrolyte imbalances);
- is taking other medicines that can have an effect on heart rhythm, such as:

- quinidine, disopyramide, procainamide, amiodarone, dofetilide, ibutilide, hydroquinidine or sotalol;
- medicines used to treat depression such as amitriptyline, fluoxetine or sertraline;
- medicines used to treat mental health problems such as phenothiazines, sertindole, sultopride, chlorpromazine, haloperidol, mesoridazine, pimozide, or thioridazine;
- medicines used to treat infections. These include some of the types of medicines used to treat bacterial infections (macrolides [such as erythromycin or clarithromycin] and fluoroquinolones [such as moxifloxacin and sparfloxacin]) or fungal infections (including fluconazole and imidazole) as well as pentamidine (used to treat a specific type of pneumonia) and saquinavir (for treatment of HIV);
- antihistamines used to treat allergies or inflammation such as terfenadine, astemizole or mizolastine;
- certain medicines used to treat stomach problems such as cisapride, domperidone or droperidol;
- other medicines such as vinca alkaloids and arsenic trioxide (used to treat certain cancers), bepridil (used to treat angina), diphemanil (used to treat stomach disturbances), levomethadyl and methadone (used to treat drug addiction), and probucol (used to treat high blood cholesterol levels).

- has recently (for example within about one month) been treated for malaria with certain medicines or has taken certain medicines to prevent malaria. These medicines include: mefloquine, halofantrine, lumefantrine, chloroquine or quinine

If any of the above applies to you or your child or if you are unsure, tell your doctor or pharmacist before taking or giving Eurartesim.

Warnings and precautions
Talk to your doctor or pharmacist before taking this medicine if you or your child:
- has liver or kidney problems;
- has a malaria infection caused by a parasite other than *Plasmodium falciparum*;
- is taking or has taken any other medicines for the treatment of malaria (other than those mentioned above);
- is in the 1st trimester of pregnancy or breastfeeding (see below);
- is female, elderly (over 65 years) or vomiting;
- is taking certain other medicines which could cause possible metabolic interactions. Examples are listed in the section “Other medicines and Eurartesim”;
- if after treatment with Eurartesim malaria infection occurs again repeatedly or is not cured, your doctor may prescribe another medicine.

If you are not sure about any of the above, please ask your doctor or pharmacist.

Talk to your doctor if following treatment specific symptoms of severe side effects occur: pale skin, general weakness, headache, shortness of breath and rapid heartbeat; particularly with exercise, confusion, dizziness, or dark-coloured urine (for details see section 4)

Children
Do not give this medicine to infants under 6 months or below 5 kg in weight.

Other medicines and Eurartesim
Tell your doctor or pharmacist if you or your child is taking, has recently taken or might take any other medicines. Some medicines can affect the way Eurartesim works and your doctor may decide that Eurartesim is not suitable or that extra checks are needed while you or your child is taking the medicines which could cause possible interactions. Examples are listed below (but there are several others):
- some medicines used to treat high cholesterol in the blood (such as atorvastatin, lovastatin, simvastatin);
- medicines used to treat hypertension and heart problems (such as diltiazem, nifedipine, nitrendipine, verapamil, felodipine, amlodipine);

- some medicines used to treat HIV (antiretroviral medicines): HIV-protease inhibitors (such as, atazanavir, darunavir, indinavir, lopinavir, ritonavir), non-nucleoside reverse transcriptase inhibitors (such as efavirenz, nevirapine);
- some medicines used to treat microbial infections (such as telithromycin, rifampicin, dapsone);
- medicines used to help you fall asleep: benzodiazepines (such as midazolam, triazolam, diazepam, alprazolam), zaleplon, zolpidem;
- medicines used to prevent/treat epileptic seizures: barbiturates (such as phenobarbital), carbamazepine or phenytoin;
- medicines used after organ transplantation and in autoimmune diseases (such as cyclosporin, tacrolimus);
- sex hormones, including those contained in hormonal contraceptives (such as gestodene, progesterone, estradiol), testosterone;
- glucocorticoids (hydrocortisone, dexamethasone);
- omeprazole (used to treat diseases related to gastric acid production);
- paracetamol (used to treat pain and fever);
- theophylline (used to improve bronchial air flow);
- nefazodone (used to treat depression);
- aprepitant (used to treat nausea);
- some gases (such as enflurane, halothane and isoflurane) used to give a general anaesthetic.

Eurartesim with food and drink
You should take the Eurartesim tablets with water only.
You should not take Eurartesim with grapefruit juice due to possible interactions.

Pregnancy and breast-feeding
Tell your doctor if you are in the 1st trimester of pregnancy, think you may be pregnant or become pregnant, or if you are breast-feeding. Based on animal data Eurartesim is suspected to harm the unborn child when used during the first three months of pregnancy. Therefore Eurartesim must not be used in the 1st trimester of pregnancy if your doctor can give you an alternative medicine. If you find out that you are pregnant within one month from taking Eurartesim, please inform your doctor. The exposure of pregnant women during the 2nd and 3rd trimester was not associated with any harm of the unborn child. If Eurartesim is more suitable for a pregnant woman than other artemisinin-based combination therapies with a higher range of experience (or sulfadoxine–pyrimethamine), Eurartesim may be used in the 2nd and 3rd trimester.

You should not breast-feed your baby while taking this medicine because the medicine may pass through breast milk to your baby.

If you are taking folate supplements to prevent possible neural tube birth defects, you can continue taking them at the same time as Eurartesim.

Ask your doctor or pharmacist for advice before taking any medicine during pregnancy or breast-feeding.

Driving and using machines
You can drive or use machines after taking Eurartesim once you have recovered from your illness.

3. How to take Eurartesim

Always take Eurartesim exactly as your doctor has told you to. Check with your doctor or pharmacist if you are not sure.

You or your child should take this medicine on an empty stomach. You or your child should take each dose no less than 3 hours after the last food intake, and no food should be taken within 3 hours after each dose of Eurartesim. You or your child can drink water at any time.

If the tablets are difficult to swallow, you can crush and mix them with water; drink the mixture immediately.

A course of Eurartesim lasts 3 consecutive days. Take one dose on each day. You should try to take the dose at about the same time on each of the three days.

The daily dose depends on the patient's **body weight**. Your doctor should have prescribed a dose that is appropriate for your weight or your child's weight as follows:

Body weight (kg)	Daily dose (mg)	Total number of tablets for treatment
5 to less than 7	Half 160 mg/20 mg tablet a day	1.5 tablet
7 to less than 13	One 160 mg/20 mg tablet a day	3 tablets
13 to less than 24	One 320 mg/40 mg tablet a day	3 tablets
24 to less than 36	Two 320 mg/40 mg tablets a day	6 tablets
36 to less than 75	Three 320 mg/40 mg tablets a day	9 tablets
>75	Four 320 mg/40 mg tablets a day	12 tablets

Vomiting when taking this medicine
If this happens within:
- 30 minutes of taking Eurartesim, the whole dose must be taken again.
- 31-60 minutes, half the dose must be taken again.

If you or your child vomit also the second dose, do not take or give your child another dose. Contact your doctor urgently to obtain an alternative treatment for malaria.

Taking this medicine, if the malaria infection returns
- If you or your child gets another attack of malaria, you may take a second course of Eurartesim within one year if your doctor thinks this is a suitable treatment. You or your child must not take more than two courses within one year. If this happens, talk to your doctor. You or your child should not take a second course of Eurartesim within 2 months of the first course.
- If you or your child is infected more than twice in a year, your doctor will prescribe an alternative treatment.

If you or your child takes more Eurartesim tablets than you should
If you or your child takes more than the recommended dose, tell your doctor. Your doctor may suggest special monitoring for you or your child because doses higher than those recommended may have an unwanted, severe effect on the heart (see also section 4).

If you or your child forgets to take Eurartesim
If you or your child forgets to take the second dose of Eurartesim at the right time, take it as soon as you remember. Then take the third (last) dose approximately 24 hours after the second dose.
If you or your child forgets to take the third (last) dose at the right time, take it as soon as you remember. Never take more than one dose on the same day to make up for a missed dose.
Check with your doctor or pharmacist if you are not sure.

If you or your child stops taking Eurartesim
For the medicine to work effectively, you or your child should take the tablets as instructed and should complete the 3 days course of treatment. If you or your child is not able to do this, talk to your doctor or pharmacist.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most of the side effects are not severe and normally disappear within a few days or weeks after treatment.

Heart problems
A heart problem, called QT prolongation, can occur while taking Eurartesim and for some days after taking the last dose. This can cause a life-threatening abnormality of the heart rhythm. Other hearth rhythm disturbances with symptoms such as fast heart beat (tachycardia) and a forceful heartbeat that may be rapid or irregular (palpitations) have been observed in adults and children. The frequency of these side effects is common (may affect up to 1 in 10 people).
Furthermore, irregular (sinus arrhythmias) or slow heart rate (bradycardia) has been observed in adults. The frequency of these side effects is uncommon (may affect up to 1 in 100 people).

If you notice anything different about your or your child's heart rhythm or have symptoms (such as palpitations or irregular heart beat) you should contact your doctor as soon as possible and before the next dose is due.
Your doctor may take electrical recordings of the heart (electrocardiogram, ECG) while you or your child is being treated and after the last dose is given. Your doctor will advise you when these readings will be taken.

Problems with red blood cells
Sometimes a problem with your red blood cells, called haemolytic anaemia can occur after receiving malaria treatment. This condition can be delayed, and may occur up to one month following use of Eurartesim (delayed haemolytic anaemia). In most cases, the anaemia recovers without specific treatment, but sometimes, in severe cases, a blood transfusion may be required. Your doctor will carry out regular blood tests. If the lack of red blood cells is suspected to be caused by your immune system (autoimmune haemolytic anaemia) these tests may include a direct antiglobulin test, to determine whether treatment, e.g. with corticosteroids, is necessary. The frequency of these side effects is not known (cannot be estimated from the available data). Contact your doctor immediately if you or your child develops one or more of the following symptoms after treatment with Eurartesim: pale skin, general weakness, headache, shortness of breath and rapid heartbeat; particularly with exercise, confusion, dizziness, or dark-coloured urine.

Other side effects in adults

Common (may affect up to 1 in 10 people)
Anaemia, headache, fever, general weakness.

Uncommon (may affect up to 1 in 100 people)
Influenza, respiratory infections, poor appetite or loss of appetite, dizziness, convulsions (fits), cough, vomiting, abdominal pain, diarrhoea, nausea, inflammation or enlargement of the liver, damaging of liver cells, abnormal liver function tests, itching, pain in the muscles or joints.

Other side effects in children

Very common (may affect more than 1 in 10 people)

Influenza, cough, fever.

Common (may affect up to 1 in 10 people)
Respiratory infections, ear infection, anaemia, abnormalities in various types of blood cells (white blood cells and platelets), poor appetite or loss of appetite, eye infection, abdominal pain, vomiting, diarrhoea, skin inflammation, rash, general weakness.

Uncommon (may affect up to 1 in 100 people)
Abnormalities in red blood cells, excessive numbers of platelets, enlargement of some organs (such as liver or spleen), swollen lymph glands, convulsions (fits), headache, abnormal heart sounds (heard by your doctor with a stethoscope), nose bleeds, runny nose, nausea, inflammation of the mouth, inflammation or enlargement of the liver, jaundice, abnormal liver function blood tests, skin itching and inflammation, pain in the joints.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Eurartesim

Keep this medicine out of the sight and reach of children.

Do not take this medicine after the expiry date which is stated on the package after 'EXP'. The expiry date refers to the last day of that month.

Do not store above 30°C.
Store in the original package in order to protect from light and moisture.

Do not use this medicine if you notice the blister is open.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Eurartesim contains
The active substances are piperaquine tetraphosphate and artenimol.
Each film-coated tablet contains 160 mg piperaquine tetraphosphate (as the tetrahydrate) and 20 mg artenimol.

The other ingredients are:
Tablet core: pre-gelatinised starch, dextrin, hypromellose (E464), croscarmellose sodium, magnesium stearate (E572).
Film coating: hypromellose, titanium dioxide (E171), macrogol 400.

What Eurartesim looks like and contents of the pack
Eurartesim are white film-coated tablets, embossed and with a break line along the middle.

The 160 mg/20 mg tablets have the letters 'S' and 'T' on one side and come in blisters containing 3 tablets.

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This leaflet was last revised in month YYYY

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu

Package leaflet: information for the user

Eurartesim 320 mg/40 mg film-coated tablets
Piperaquine tetraphosphate/artenimol

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Eurartesim is and what it is used for

Eurartesim contains the active substances piperaquine tetraphosphate and artenimol. It is used to treat uncomplicated malaria when use of a medicine given by mouth is appropriate.

Malaria is caused by infection with a parasite called *Plasmodium*, spread by the bite of an infected mosquito.There are different types of *Plasmodium* parasite. Eurartesim kills the *Plasmodium falciparum* parasite.

The medicine can be taken by adults, adolescents, children and infants over 6 months old who weigh 5 kilograms or more.

2. What you need to know before you or your child takes Eurartesim

Do not take Eurartesim if you or your child:
- is allergic to the active substances, piperaquine tetraphosphate or artenimol, or to any of the other ingredients of this medicine (listed in section 6);
- has a severe type of malaria infection which has affected parts of the body such as the brain, lungs or kidneys;
- has a heart condition, such as changes to the rhythm or rate of heart beat, or heart disease;
- knows that any member of your family (parents, grandparents, brothers or sisters) died suddenly due to a heart problem or was born with heart problems;
- suffers from changes to the levels of salts in the body (electrolyte imbalances);
- is taking other medicines that can have an effect on heart rhythm, such as:
  - quinidine, disopyramide, procainamide, amiodarone, dofetilide, ibutilide, hydroquinidine or sotalol;
  - medicines used to treat depression such as amitriptyline, fluoxetine or sertraline;
  - medicines used to treat mental health problems such as phenothiazines, sertindole, sultopride, chlorpromazine, haloperidol, mesoridazine, pimozide, or thioridazine;

- medicines used to treat infections. These include some of the types of medicines used to treat bacterial infections (macrolides [such as erythromycin or clarithromycin] and fluoroquinolones [such as moxifloxacin and sparfloxacin]) or fungal infections (including fluconazole and imidazole) as well as pentamidine (used to treat a specific type of pneumonia) and saquinavir (for treatment of HIV);
- antihistamines used to treat allergies or inflammation such as terfenadine, astemizole or mizolastine;
- certain medicines used to treat stomach problems such as cisapride, domperidone or droperidol;
- other medicines such as vinca alkaloids and arsenic trioxide (used to treat certain cancers), bepridil (used to treat angina), diphemanil (used to treat stomach disturbances), levomethadyl and methadone (used to treat drug addiction), and probucol (used to treat high blood cholesterol levels).

- has recently (for example within about one month) been treated for malaria with certain medicines or has taken certain medicines to prevent malaria. These medicines include: mefloquine, halofantrine, lumefantrine, chloroquine or quinine

If any of the above applies to you or your child or if you are unsure, tell your doctor or pharmacist before taking or giving Eurartesim.

Warnings and precautions
Talk to your doctor or pharmacist before taking this medicine if you or your child:
- has liver or kidney problems;
- has a malaria infection caused by a parasite other than *Plasmodium falciparum*;
- is taking or has taken any other medicines for the treatment of malaria (other than those mentioned above);
- is in the 1st trimester of pregnancy or breastfeeding (see below);
- is female, elderly (over 65 years) or vomiting;
- is taking certain other medicines which could cause possible metabolic interactions. Examples are listed in the section “Other medicines and Eurartesim”;
- if after treatment with Eurartesim malaria infection occurs again repeatedly or is not cured, your doctor may prescribe another medicine.

If you are not sure about any of the above, please ask your doctor or pharmacist.

Talk to your doctor if following treatment specific symptoms of severe side effects occur: pale skin, general weakness, headache, shortness of breath and rapid heartbeat; particularly with exercise, confusion, dizziness, or dark-coloured urine (for details see section 4)

Children
Do not give this medicine to infants under 6 months or below 5 kg in weight.

Other medicines and Eurartesim
Tell your doctor or pharmacist if you or your child is taking, has recently taken or might take any other medicines. Some medicines can affect the way Eurartesim works and your doctor may decide that Eurartesim is not suitable or that extra checks are needed while you or your child is taking the medicines which could cause possible interactions. Examples are listed below (but there are several others):
- some medicines used to treat high cholesterol in the blood (such as atorvastatin, lovastatin, simvastatin);
- medicines used to treat hypertension and heart problems (such as diltiazem, nifedipine, nitrendipine, verapamil, felodipine, amlodipine);
- some medicines used to treat HIV (antiretroviral medicines): HIV-protease inhibitors (such as, atazanavir, darunavir, indinavir, lopinavir, ritonavir), non-nucleoside reverse transcriptase inhibitors (such as efavirenz, nevirapine);
- some medicines used to treat microbial infections (such as telithromycin, rifampicin, dapsone);

- medicines used to help you fall asleep: benzodiazepines (such as midazolam, triazolam, diazepam, alprazolam), zaleplon, zolpidem;
- medicines used to prevent/treat epileptic seizures: barbiturates (such as phenobarbital), carbamazepine or phenytoin;
- medicines used after organ transplantation and in autoimmune diseases (such as cyclosporin, tacrolimus);
- sex hormones, including those contained in hormonal contraceptives (such as gestodene, progesterone, estradiol), testosterone;
- glucocorticoids (hydrocortisone, dexamethasone);
- omeprazole (used to treat diseases related to gastric acid production);
- paracetamol (used to treat pain and fever);
- theophylline (used to improve bronchial air flow);
- nefazodone (used to treat depression);
- aprepitant (used to treat nausea);
- some gases (such as enflurane, halothane and isoflurane) used to give a general anaesthetic.

Eurartesim with food and drink
You should take the Eurartesim tablets with water only.
You should not take Eurartesim with grapefruit juice due to possible interactions.

Pregnancy and breast-feeding
Tell your doctor if you are in the 1st trimester of pregnancy, think you may be pregnant or become pregnant, or if you are breast-feeding. Based on animal data Eurartesim is suspected to harm the unborn child when used during the first three months of pregnancy. Therefore Eurartesim must not be used in the 1st trimester of pregnancy if your doctor can give you an alternative medicine. If you find out that you are pregnant within one month from taking Eurartesim, please inform your doctor. The exposure of pregnant women during the 2nd and 3rd trimester was not associated with any harm of the unborn child. If Eurartesim is more suitable for a pregnant woman than other artemisinin-based combination therapies with a higher range of experience (or sulfadoxine–pyrimethamine), Eurartesim may be used in the 2nd and 3rd trimester.

You should not breast-feed your baby while taking this medicine because the medicine may pass through breast milk to your baby.

If you are taking folate supplements to prevent possible neural tube birth defects, you can continue taking them at the same time as Eurartesim.

Ask your doctor or pharmacist for advice before taking any medicine during pregnancy or breast-feeding.

Driving and using machines
You can drive or use machines after taking Eurartesim once you have recovered from your illness.

3. How to take Eurartesim

Always take Eurartesimexactly as your doctor has told you to. Check with your doctor or pharmacist if you are not sure.

You or your child should take this medicine on an empty stomach. You or your child should take each dose no less than 3 hours after the last food intake, and no food should be taken within 3 hours after each dose of Eurartesim. You or your child can drink water at any time.

If the tablets are difficult to swallow, you can crush and mix them with water; drink the mixture immediately.

A course of Eurartesim lasts 3 consecutive days. Take one dose on each day. You should try to take the dose at about the same time on each of the three days.

The daily dose depends on the patient's **body weight**. Your doctor should have prescribed a dose that is appropriate for your weight or your child's weight as follows:

Body weight (kg)	Daily dose (mg)	Total number of tablets for treatment
5 to less than 7	Half 160 mg/20 mg tablet a day	1.5 tablet
7 to less than 13	One 160 mg/20 mg tablet a day	3 tablets
13 to less than 24	One 320 mg/40 mg tablet a day	3 tablets
24 to less than 36	Two 320 mg/40 mg tablets a day	6 tablets
36 to less than 75	Three 320 mg/40 mg tablets a day	9 tablets
>75	Four 320 mg/40 mg tablets a day	12 tablets

Vomiting when taking this medicine
If this happens within:
- 30 minutes of taking Eurartesim, the whole dose must be taken again.
- 31-60 minutes, half the dose must be taken again.

If you or your child vomit also the second dose, do not take or give your child another dose. Contact your doctor urgently to obtain an alternative treatment for malaria.

Taking this medicine, if the malaria infection returns
- If you or your child gets another attack of malaria you may take a second course of Eurartesim within one year if your doctor thinks this is a suitable treatment. You or your child must not take more than two courses within one year. If this happens, talk to your doctor. You or your child should not take a second course of Eurartesim within 2 months of the first course.
- If you or your child is infected more than twice in a year, your doctor will prescribe an alternative treatment.

If you or your child takes more Eurartesim tablets than you should
If you or your child takes more than the recommended dose, tell your doctor. Your doctor may suggest special monitoring for you or your child because doses higher than those recommended may have an unwanted, severe effect on the heart (see also section 4).

If you or your child forgets to take Eurartesim
If you or your child forgets to take the second dose of Eurartesim at the right time, take it as soon as you remember. Then take the third (last) dose approximately 24 hours after the second dose.
If you or your child forgets to take the third (last) dose at the right time, take it as soon as you remember.
Never take more than one dose on the same day to make up for a missed dose.
Check with your doctor or pharmacist if you are not sure.

If you or your child stops taking Eurartesim
For the medicine to work effectively, you or your child should take the tablets as instructed and should complete the 3 days course of treatment. If you or your child is not able to do this, talk to your doctor or pharmacist.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most of the side effects are not severe and normally disappear within a few days or weeks after treatment.

Heart problems
A heart problem, called QT prolongation, can occur while taking Eurartesim and for some days after taking the last dose. This can cause a life-threatening abnormality of the heart rhythm. Other hearth rhythm disturbances with symptoms such as fast heart beat (tachycardia) and a forceful heartbeat that may be rapid or irregular (palpitations) have been observed in adults and children. The frequency of these side effects is common (may affect up to 1 in 10 people).
Furthermore, irregular (sinus arrhythmias) or slow heart rate (bradycardia) has been observed in adults. The frequency of these side effects is uncommon (may affect up to 1 in 100 people).

If you notice anything different about your or your child's heart rhythm or have symptoms (such as palpitations or irregular heart beat) you should contact your doctor as soon as possible and before the next dose is due.
Your doctor may take electrical recordings of the heart (electrocardiogram, ECG) while you or your child is being treated and after the last dose is given. Your doctor will advise you when these readings will be taken.

Problems with red blood cells
Sometimes a problem with your red blood cells, called haemolytic anaemia can occur after receiving malaria treatment. This condition can be delayed and may occur up to one month following use of Eurartesim (delayed haemolytic anaemia) In most cases, the anaemia recovers without specific treatment, but sometimes, in severe cases, a blood transfusion may be required. Your doctor will carry out regular blood tests. If the lack of red blood cells is suspected to be caused by your immune system (autoimmune haemolytic anaemia) these tests may include a direct antiglobulin test, to determine whether treatment, e.g. with corticosteroids, is necessary. The frequency of these side effects is not known (cannot be estimated from the available data). Contact your doctor immediately if you or your child develops one or more of the following symptoms after treatment with Eurartesim: pale skin, general weakness, headache, shortness of breath and rapid heartbeat; particularly with exercise, confusion, dizziness, or dark-coloured urine.

Other side effects in adults

Common (may affect up to 1 in 10 people)
Anaemia, headache, fever, general weakness.

Uncommon (may affect up to 1 in 100 people)
Influenza, respiratory infections, poor appetite or loss of appetite, dizziness, convulsions (fits), cough, vomiting, abdominal pain, diarrhoea, nausea, inflammation or enlargement of the liver, damaging of liver cells, abnormal liver function tests, itching, pain in the muscles or joints.

Other side effects in children

Very common (may affect more than 1 in 10 people)
Influenza, cough, fever.

Common (may affect up to 1 in 10 people)
Respiratory infections, ear infection, anaemia, abnormalities in various types of blood cells (white blood cells and platelets), poor appetite or loss of appetite, eye infection, abdominal pain, vomiting, diarrhoea, skin inflammation, rash, general weakness.

Uncommon (may affect up to 1 in 100 people)

Abnormalities in red blood cells, excessive numbers of platelets, enlargement of some organs (such as liver or spleen), swollen lymph glands, convulsions (fits), headache, abnormal heart sounds (heard by your doctor with a stethoscope), nose bleeds, runny nose, nausea, inflammation of the mouth, inflammation or enlargement of the liver, jaundice, abnormal liver function blood tests, skin itching and inflammation, pain in the joints.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Eurartesim

Keep this medicine out of the sight and reach of children.

Do not take this medicine after the expiry date which is stated on the package after 'EXP'. The expiry date refers to the last day of that month.

Do not store above 30°C.
Store in the original package in order to protect from light and moisture.

Do not use this medicine if you notice the blister is open.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Eurartesim contains
The active substances are piperaquine tetraphosphate and artenimol.
Each film-coated tablet contains 320 mg piperaquine tetraphosphate (as the tetrahydrate) and 40 mg artenimol.

The other ingredients are:
Tablet core: pre-gelatinised starch, dextrin, hypromellose (E464), croscarmellose sodium, magnesium stearate (E572).
Film coating: hypromellose, titanium dioxide (E171), macrogol 400.

What Eurartesim looks like and contents of the pack
Eurartesim are white film-coated tablets, embossed and with a break line along the middle.

The 320 mg/40 mg tablets have two 'σ' letters on one side and come in blisters containing 3, 6, 9, 12, 270 or 300 tablets.

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