FANEXIN DIHYDROARTEMISININ/PIPERAQUINE TABLETS
FANEXIN DIHYDROARTEMISININ/PIPERAQUINE SUSPENSION

1. Name of the medicinal product

FANEXIN Dihydroartemisinin/Piperaquine Tablets, 40mg/320mg
FANEXIN Dihydroartemisinin/Piperaquine Suspension, 80mg/640mg, 80mL

2. Qualitative and quantitative composition

Each FANEXIN tablet contains 40 mg of dihydroartemisinin and 320 mg of Piperaquine.
Each 80 mL FANEXIN Suspension after reconstitution Contains Dihydroartemisinin 80 mg, Piperaquine Phosphate 640 mg.

3. Pharmaceutical form

FANEXIN Tablet is Film-coated tablet (tablet), White oblong biconvex film-coated tablet with a break-line, and the tablet can be divided into equal doses.
FANEXIN Suspension is light yellow granules.

4. Clinical particulars

4.1 Therapeutic indications

FANEXIN 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.

4.2 Posology and method of administration

Posology

FANEXIN 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	DHA	
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 to 100	1,280	160	4 x 320 mg / 40 mg tablets
>100	There are no data on which to base a dose recommendation in patients weighing >100 kg.		

If a patient vomits within 30 minutes of taking FANEXIN, 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 FANEXIN 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 FANEXIN may be given within a 12 month period (see sections 4.4 and 5.3).

A second course of FANEXIN 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 FANEXIN 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

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

Paediatric population

The safety and efficacy of FANEXIN 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

FANEXIN 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, FANEXIN suspension is suggested for use.

Dosage by age should be:

Age	First Day (Dose/mL)	Daily dose for 6 days (mL)	**Total volume required (Ml)**	**Recommended No. of bottles**
0 to 1 years	10ml	5ml	40ml	1 Bottle
1 to 3 years	15ml	7.5ml	60ml	1 Bottle
4 to 6 years	20ml	10ml	80ml	1 Bottle

Note: The reconstituted suspension can be stored for 14 days in refrigerator and 7 days at room temperature.

Preparation and conservation of the Oral Suspension:
1. Shake the bottle before opening it.
2. Open the bottle, fill the dosing cap with water (mineral water is recommended) and pour it inside the bottle in order to solve the recommend powder.
3. A bottle of FANEXIN Oral Suspension is a complete six days treatment only for infants and children not up to 6 years.
4. For adults and children older than 6 years, it is advisable to use FANEXIN® tablets.
5. After each use, clean carefully the dosing cap and keep it together with the bottle in the refrigerator.

4.3 Contraindications

- 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 antifungalmedicinal 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 FANEXIN 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

FANEXIN 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 FANEXIN 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 FANEXIN 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 FANEXIN (see sections 4.5 and 5.2).

FANEXIN should not be used during 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 FANEXIN should be given in a 12-month period (see sections 4.2 and 5.3).

Effects on cardiac repolarization

In clinical trials with FANEXIN limited ECGs were obtained during treatment. These showed that QTc prolongation occurred more frequently and to a larger extent in association with FANEXIN 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 FANEXIN treated patients than in those treated with comparator antimalarial (see section

4.8). Before the third dose of FANEXIN, 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 FANEXIN 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 FANEXIN 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 FANEXIN 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 FANEXIN 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 FANEXIN so that special caution is required.

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 FANEXIN (see section 4.3).

Hepatic and renal impairment

FANEXIN 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 FANEXIN is administered to patients with jaundice and/or with moderate or severe renal or hepatic insufficiency, and ECG and blood potassium monitoring are advised.

4.5 Interaction with other medicinal products and other forms of interaction

FANEXIN 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 FANEXIN 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 FANEXIN on co-administered medicinal products

Piperaquine is metabolised by, and is an inhibitor of CYP3A4. The concurrent administration of oral FANEXIN 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 FANEXIN. 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 FANEXIN.

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.

Dihydroartemisinin administration may result in a slight decrease in CYP1A2 activity. Caution is therefore, advised when FANEXIN 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 Dihydroartemisinin.

Effect of co-administered medicinal products on FANEXIN

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 FANEXIN 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 FANEXIN is administered to patients taking potent CYP3A4 inhibitors (e.g. some protease inhibitors [amprenavir, atazanavir, indinavir, nelfinavir, ritonavir], nefazodone 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 Dihydroartemisinin may also be reduced. 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, FANEXIN 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 FANEXIN 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, FANEXIN should be taken with water only as described in section 4.2. FANEXIN 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 insufficient data on the use of Dihydroartemisinin and piperaquine in pregnant women. Based on animal data, FANEXIN 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. 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.

FANEXIN should not be used during pregnancy in situations where other suitable and effective anti-malarials are available (see section 4.4).

Breast-feeding

Animal data suggest excretion of piperaquine into breast milk but no data are available in humans. Women taking FANEXIN 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 Dihydroartemisinin in both females and males.

4.7 Effects on ability to drive and use machines

Adverse event data collected in clinical trials suggest that FANEXIN 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 FANEXIN 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 FANEXIN.

In a randomized trial in which 767 adults and children with uncomplicated *P. falciparum* malaria were exposed to FANEXIN, 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 randomized trial, 1,038 children, aged between 6 months and 5 years, were exposed to FANEXIN 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 FANEXIN:

SOC	Very Common	Common	Uncommon
Infections and infestations		P falciparum infection	Respiratory tract infection Influenza
Blood and lymphatic system disorders		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 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 FANEXIN 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 FANEXIN:

SOC	Very Common	Common	Uncommon
Infections and infestations	Influenza P. falciparum infection	Respiratory tract infection Ear infection	
Blood and lymphatic system disorders		Thrombocytopenia Leukopenias/neutropenia Leuckocytoses NEC Anaemia	Thrombocythaemia Splenomegaly Lymphadenopathy Hypochromasia
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 the Yellow Card Scheme at the website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

In clinical trials, nine patients received double the cumulative intended dose of FANEXIN. 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

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

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

5.2 Pharmacokinetic properties

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

Absorption

Dihydroartemisinin 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 Dihydroartemisinin (observed after the first dose of FANEXIN) were 752 (47%) ng/ml and 2,002 (45 %) ng/ml*h, respectively.

Dihydroartemisinin bioavailability appears to be higher in malaria patients than in healthy volunteers, possibly because malaria *per se* has an effect on Dihydroartemisinin disposition. This may reflect malaria-associated impairment of hepatic function, causing an increase in Dihydroartemisinin 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 Dihydroartemisinin ranged between 180-252 ng/ml and 516-684 ng/ml*h, respectively.

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

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

Dihydroartemisinin 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

Dihydroartemisinin is principally converted to α- Dihydroartemisinin-β-glucuronide (α- Dihydroartemisinin-G). Studies in human liver microsomes showed that Dihydroartemisinin was metabolised by the UDP-glucuronosyltransferase (UGT1A9 and UGT2B7) to α- Dihydroartemisinin-G with no cytochrome P450-mediated metabolism.

In vitro drug-drug interaction studies revealed that Dihydroartemisinin is an inhibitor of CYP1A2; therefore, there is the potential for Dihydroartemisinin 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 withDihydroartemisinin. 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 Dihydroartemisinin 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%). Dihydroartemisinin is eliminated by metabolism (mainly glucuroconjugation). Its clearance was found to be slightly lower in female than in male healthy volunteers. Data regarding Dihydroartemisinin 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 Dihydroartemisinin 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.

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

No carcinogenicity studies have been performed.

Dihydroartemisinin 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 Dihydroartemisinin 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 Dihydroartemisinin pro-drugs. In humans, the potential neurotoxicity of orally administered Dihydroartemisinin can be considered highly unlikely, given the rapid clearance ofDihydroartemisinin, and its short exposure (3 days of treatment for malaria patients). There was no evidence of Dihydroartemisinin-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 forDihydroartemisinin. The association of Dihydroartemisinin and piperaquine does not produce hERG inhibition greater than that of the single compounds.

Phototoxicity

There are no phototoxicity concerns withDihydroartemisinin, 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. Storage

Do not store above 30°C.
KEEP MEDICINES OUT OF REACH OF CHILDREN.

7. Manufacturer:

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