Summary of Product Characteristics

P-ALAXIN Dispersible (Dihydroartemisinin 20/40 mg & Piperaquine Phosphate 160/320 mg Dispersible Tablets)

1. NAME OF THE MEDICINAL PRODUCT

P-ALAXIN Dispersible (Dihydroartemisinin 20/40 mg & Piperaquine 160/320 mg Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains:

Dihydroartemisinin Ph.Int …….. 20/40 mg

Piperaquine Phosphate IH…… 160/320 mg

Excipients….q.s.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Oral tablet

P-ALAXIN Dispersible 20/160:

White to off White coloured, round shaped, beveled edge, flat faced tablet, debossed with "TT" "21" separated with break line on one side and plain on other side.

P-ALAXIN Dispersible 40/320:

White to off White coloured, round shaped, beveled edge, flat faced tablet, debossed with "TT" "22" separated with break line on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

P-ALAXIN Dispersible is indicated for the treatment of uncomplicated malaria in children and infants6 months and over and weighing 5kg or more.

Dihydroartemisinin 20/40 mg & Piperaquine 160/320 mg Dispersible Tablets is active against all Plasmodium parasites that cause malaria in humans.

Consideration should be given to official guidance on the appropriate use of antimalarial medicinalproducts.

4.2 Posology and method of administration

Posology

P-ALAXIN Dispersible 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 following table:

Body weight	Number of Tablets	Daily dose	
		Piperaquine	Dihydroartemisinin
5kg to less than 8kg	1 tablet per day for 3 days	160mg	20mg
8 kg to less than 11 kg	1½ tablets per day for 3 days	240mg	30mg
11 kg to less than 17 kg	2 tablets per day for 3 days	320mg	40mg
17 kg to less than 25 kg	3 tablets per day for 3 days	480mg	60mg

The safety and efficacy of P-ALAXIN Dispersible in infants aged less than 6 months and in children weighing less than5 kg has not been established.

For patients weighing more than 25 kg, a higher strength tablet is available and should be used if required.

Special populations Elderly

Clinical studies of dihydroartemisinin/piperaquine 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 caution should be exercised when administering the product to the elderly.

Hepatic and renal impairment

Dihydroartemisinin/piperaquine has not been evaluated in subjects with moderate or severe renal orhepatic insufficiency. Therefore, caution is advised when administering P-ALAXIN Dispersible to these patients

Method of administration

P-ALAXIN Dispersible Tablets should be taken orally with water and without food:

- Each dose should be taken no less than three hours after the last food intake.
- No food should be taken within 3 hours after each dose.

The tablets should be dispersed in drinking water before administration of the dose. Each tablet shouldbe dispersed in a minimum of 10 mL water; the maximum volume of water recommended for dispersion of a dose is 50 mL.

If a patient vomits within 30 minutes of taking P-ALAXIN Dispersible Tablets, 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 Dihydroartemisinin/piperaquine Tablets should not be attempted more than once. If the second dose is vomited,alternative antimalarial therapy should be started.

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

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

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,
        - 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 started (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

P-ALAXIN Dispersible Tablets should not be used to treat complicated malaria.

The long half-life of piperaquine (about 22 days) should be kept in mind in the event that another antimalarial 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 P-ALAXIN Dispersible Tablets with medicinal products exhibiting variable patterns of inhibition, induction or competition for CYP3A4 as the therapeutic and/or toxic effects of some coadministered 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 P-ALAXIN Dispersible Tablets 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 P-ALAXIN Dispersible Tablets.

P-ALAXIN Dispersible Tablets should not be used during pregnancy in situations where other suitable and effective antimalarials are available.

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 P-ALAXIN Dispersible Tablets should be given in a 12-month period.

Effects on cardiac repolarization

In clinical trials with piperaquine/dihydroartemisinin limited ECGs were obtained during treatment. These showed that QTc prolongation occurred more frequently and to a larger extent in association with piperaquine/dihydroartemisinin 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 piperaquine/dihydroartemisinin-treated patients than in those treated with

comparator antimalarial. Before the third dose of piperaquine/dihydroartemisinin, in one of the two Phase III studies 3/767 patients (0.4%) were reported to have a QTcF value of >500 milliseconds (ms) versus none in the comparator group.

The WHO guidelines no longer recommend performing an ECG before prescribing piperaquine/dihydroartemisinin. However, piperaquine/dihydroartemisinin should not be used in patients with known congenital long QT interval syndromes or those who have a clinical condition or are taking a medication that prolongs the QT interval.

There has been no evidence of piperaquine-related cardiotoxicity in large randomized trials or in extensive deployment in the field.

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 reports involving piperaquine/dihydroartemisinin. Risk factors may include young age (children under 5 years old) 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.

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 P-ALAXIN Dispersible Tablets.

Hepatic and renal impairment

Piperaquine/dihydroartemisinin has not been evaluated in patients with moderate or severe renal or hepatic insufficiency Due to the potential for higher plasma concentrations of piperaquine to occur, caution is advised if P-ALAXIN Dispersible Tablets 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

P-ALAXIN Dispersible Tablets 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.

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

Effect of P-ALAXIN Dispersible Tablets *on co-administered medicinal products*

Piperaquine is metabolised by, and is an inhibitor of, CYP3A4. The concurrent administration of oral P-ALAXIN Dispersible Tablets with 7.5 mg oral midazolam, a CYP3A4 probe substrate, led to a modest increase (≤2- fold) in midazolam and its metabolites exposure in healthy adult subjects. This inhibitory effect was no longer evident one week after last administration of P-ALAXIN Dispersible Tablets. 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 P-ALAXIN Dispersible Tablets.

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 P-ALAXIN Dispersible Tablets 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 P-ALAXIN Dispersible Tablets

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 P-ALAXIN Dispersible 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 P-ALAXIN Dispersible Tablets 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 interactions documented above for adults and the warnings in section 4.4 should be considered for the paediatric population.

Oral contraceptives

When co-administered to healthy women, P-ALAXIN Dispersible Tablets [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}) by 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 P-ALAXIN Dispersible Tablets 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, P-ALAXIN Dispersible Tablets should be taken with water only, as described in section 4.2. P-ALAXIN Dispersible Tablets should not be taken with grapefruit juice as it is likely to lead to increased piperaquine plasma concentrations.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

There are insufficient data on the use of dihydroartemisinin and piperaquine in pregnant women. Based on animal data, piperaquine/dihydroartemisinin 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.

P-ALAXIN Dispersible should not be used during pregnancy in situations where other suitable and effective antimalarials 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 P-ALAXIN Dispersible 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 P-ALAXIN Dispersible 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 piperaquine/dihydroartemisinin 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 piperaquine/dihydroartemisinin.

In a randomized trial in which 767 adults and children with uncomplicated *P. falciparum* malaria were exposed to piperaquine/dihydroartemisinin, 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 piperaquine/dihydroartemisinin 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 P-ALAXIN Dispersible Tablets

SOC	Very common	Common	Uncommon
Infections and infestations		*P. falciparum* infection	Respiratory tract infection;
Blood and lymphatic system disorders		Anaemia	
Metabolism and nutrition disorders			Anorexia
Nervous system disorders		Headache	Convulsion; dizziness
Cardiac disorders		QTc interval prolongation; tachycardia	Cardiac conduction disorders; sinus arrhythmia;
Respiratory, thoracic and mediastinal			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		Asthenia; pyrexia	

Description of selected adverse reactions

The ADRs noted for piperaquine/dihydroartemisinin 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 P-ALAXIN Dispersible Tablets

SOC	Very common	Common	Uncommon
Infections and infestations	Influenza; *P. falciparum* infection	Respiratory tract infection; ear infection	
Blood and lymphatic system disorders		Thrombocytopenia; leukopenia/neutropenia; leukocytosis; anaemia	Thrombocytosis; splenomegaly; lymphadenopathy; hypochromasia
Metabolism and nutrition disorders		Anorexia	
Nervous system disorders			Convulsion; headache
Eye disorders		Conjunctivitis	
Cardiac disorders		QTc interval prolongation; heart rate irregular	Cardiac conduction disorders; cardiac murmur
Respiratory, thoracic and mediastinal	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	Pyrexia	Asthenia	

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. Health care professionals are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose

In clinical trials, nine patients received double the cumulative intended dose of piperaquine/dihydroartemisinin. 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.

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 haem (derived from the patient's haemoglobin) within the malaria parasite, preventing its detoxification via a polymerisation step.

Piperaquine is a bisquinolone, 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.

5.2 Pharmacokinetic properties

The absorption characteristics of P-ALAXIN Dispersible Tablets have been determined after administration of Dihydroartemisinin/ Piperaquine Tetraphosphate 40/320 mg FDC tablets in healthy volunteers in the fasting state as follows:

	Dihydroartemisinin	**Piperaquine**
General		
	Bioavailability is higher in patients with malaria compared to healthy Volunteers.	
Absorption		
Absolute bioavailability	NA	NA
Oral Bioavailability	NA	NA
Food effect	Exposure increased by 43% with a high fat/high calorie meal	Exposure increased approximately 3-fold with a high fat/high calorie meal
Distribution		
Volume of distribution (mean)	0.8 L/kg	730 L/kg
Plasma protein binding *in vitro*	44–93%	> 99%
Tissue distribution	Accumulates in red blood cells	Accumulates in red blood cells
Metabolism		
	Hepatic glucuronidation to α- artenimol-β-glucuronide	Hepatic: major metabolites are a carboxyl acid cleavage product and a mono-N-
Elimination		
Mean elimination half-life	1 hour	22 days
Mean oral clearance	1.34	2.1 L/h/kg
% of dose excreted in urine	Negligible as intact drug	NA
% of dose excreted in faeces	Negligible as intact drug	NA
Pharmacokinetic linearity	NA	NA
Drug interactions *(in vitro)*		
Transporters	NA	NA
Metabolising enzymes	UGT1A9 and UGT2B7	CYP3A4 (mainly), CYP2C9 and CYP2C19
	Inhibitor of CYP1A2	Mild inhibitor of CYP3A4 and CYP2C19 Inducer of CYP2E1
Special populations		
Renal impairment	NA	NA
Hepatic impairment	NA	NA
Elderly patients	NA	NA

NA: Not available

Patients with hepatic or renal insufficiency

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

Paediatrics

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 of dihydroartemisinin, 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 IC50 was 0.15 μmol for piperaquine and 7.7 μmol for dihydroartemisinin. The association of dihydroartemisinin and piperaquine does not produce hERG inhibition greater than that of the single compounds.

Phototoxicity

There are no phototoxicity concerns with dihydroartemisinin, 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

Pregelatinised Starch, Microcrystalline cellulose , Crospovidone, Sucralose, Dextrine, Powdarome Strawberry Premium Flavour, Colloidal anhydrous silica, Magnesium Stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C. Protect from light and moisture.

6.5 Nature and contents of container

3 Tablets packed in Alu/Alu blister, one/two such blisters packed in a carton along with a leaflet.

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bliss GVS Pharma Ltd., Saki Vihar Road,

Andheri (East), Mumbai - 400 072