Brand Name : PYMAL SUSPENSION **Generic Name : Dihydroartemisinin and Piperaquine Phosphate Suspension**	**2018**
Module 1 : Administrative Information **1.3 :** Product information **1.3.1 :** Summary of Product Characteristics (SmPC)	**Confidential**

1.3.1 Summary of Product Characteristics (SmPC)

1- Name of the Medicinal Product:

1.1 Product Name

- **Generic Name or International Non-Proprietary Name (INN)**

  Dihydroartemisinin and Piperaquine Phosphate Suspension

- **Brand Name**

  PYMAL SUSPENSION

1.2 Dosage Strength

Each 80 ml after reconstitution contains
Dihydroartemisinin……..80mg
Piperaquine Phosphate……640 mg
Excipients……q.s.

1.3 Dosage Form

Dry powder for Suspension

2- Quality and Quantitative Composition:

2.1 Qualitative Declaration

Each 80 ml after reconstitution contains
Dihydroartemisinin……..80mg
Piperaquine Phosphate……640 mg
Excipients……q.s.

2.2 Quantitative Declaration

Composition:

Batch Size - 10,000 Bottles.

Sr. No:	Ingredients	Specification	gm/Nos.	Overages %	Qty/Batch 10,000 nos. in Kg
Dry mixing					
1.	Dihydroartemisinin	IHS	0.080	---	0.800
2.	Piperaquine Phosphate	IHS	0.640	---	6.400
3.	Sodium citrate anhydrous	BP	0.900	---	9.000
4.	Sugar (Pharma grade)	BP	16.476	---	164.760
5.	Colloidal Silicon Dioxide	BP	0.600	---	6.000
6.	Xanthum gum	BP	0.100	---	1.000
7.	Flavour orange dry powder	BP	0.900	---	9.000
8.	Aspartame	BP	1.000	---	10.000
9.	Sodium Benzoate	BP	0.300	---	3.000
10.	Sunset yellow supra	BP	0.0040	---	0.040
Average Wt. of Dry Powder			**21.0 gm**	**Limit: 21.00gm ± 5 %**	

NOTE: Active material is to be calculated on Assay / Potency basis.
BP = British Pharmacopoeia.
IHS = In-house Specification

3- Pharmaceutical Form:

A White to off white colour free flowing granules. This is converted to white colour suspension after addition of water & makes volume up to 80 ml.

4- Clinical Particulars:

4.1 Therapeutic indications

P-ALAXIN 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

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

Dosage

For children and infants. Add proper water until the volume of bottle (80 ml) to reconstitute oral suspension. Shake well before use. Recap the bottle immediately after use. The treatment duration is 2 days. Dosage should be adapted according to weight.

If a patient vomits within 30 minutes of taking P-ALAXIN, 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 P-ALAXIN 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 P-ALAXIN may be given within a 12 month period A second course of P-ALAXIN should not be given within 2 months after the first course due to the long elimination half-life of piperaquine

Hepatic and renal impairment

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

Elderly

Clinical studies of P-ALAXIN tablets 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.

Paediatric population

See posology table above.

The safety and efficacy of P-ALAXIN in children 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

P-ALAXIN 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, P-ALAXIN may be crushed and mixed with water. The mixture should be used immediately after preparation.

4.3 Contraindications

- Hypersensitivity to any of the active substances or to any of the excipients.
- 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.
- Recent treatment with medicinal products known to prolong the QTc interval that may still be circulating at the time that Pipart is commenced (e.g. mefloquine, halofantrine, lumefantrine, chloroquine, quinine and other antimalarial agents) taking into account their elimination half-life.

4.4 Special warning and precautions for use

P-ALAXIN should not be used to treat severe falciparum malaria 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

Piperaquine is an inhibitor of CYP3A4. Caution is recommended when co-administering P-ALAXIN 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

Effects on cardiac repolarization

In clinical trials with P-ALAXIN limited ECGs were obtained during treatment. These showed that QTc prolongation occurred more frequently and to a larger extent in association with P-ALAXIN therapy than with the comparators Analysis of cardiac adverse events in clinical trials showed that these were reported more frequently in P-ALAXIN treated patients than in those treated with comparator antimalarial. Before the third dose of P-ALAXIN, 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 P-ALAXIN 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 P-ALAXIN 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 P-ALAXIN and ECG monitoring should be applied in patients who may have a higher risk of developing arrhythmia in association with QTc prolongation

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 P-ALAXIN 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 P-ALAXIN so that special caution is required.

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

Piperaquine is metabolised by and is an inhibitor of CYP3A4. There is a potential for a several-fold increase of piperaquine plasma concentrations when it is co-administered with other CYP3A4 substrates (due to competition) and, especially, with CYP3A4 inhibitors, resulting in an exacerbation of the effect on QTc prolongation.

Therefore, particular caution is required if P-ALAXIN is administered to patients taking such medicinal products, and ECG monitoring is advised due to the risk of higher plasma concentrations of piperaquine

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

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

Effects on cardiac repolarization

In clinical trials with P-ALAXIN limited ECGs were obtained during treatment. These showed that QTc prolongation occurred more frequently and to a larger extent in association with P-ALAXIN 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 P-ALAXIN treated patients than in those treated with comparator antimalarial (see section 4.8). Before the third dose of P-ALAXIN, 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 P-ALAXIN 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 P-ALAXIN 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 P-ALAXIN 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 P-ALAXIN 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 P-ALAXIN 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 P-ALAXIN.

Hepatic and renal impairment

P-ALAXIN 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 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 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 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 P-ALAXIN on co-administered medicinal products

Piperaquine is metabolised by, and is an inhibitor of CYP3A4. The concurrent administration of oral P-ALAXIN 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 P-ALAXIN. 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.

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 P-ALAXIN 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 P-ALAXIN

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 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 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 artenimol 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, P-ALAXIN 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 P-ALAXIN 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 should

be taken with water only as described in section 4.2. P-ALAXIN 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 artenimol and piperaquine in pregnant women. Based on animal data, P-ALAXIN 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 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 P-ALAXIN 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 machine

Adverse event data collected in clinical trials suggest that P-ALAXIN 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 P-ALAXIN 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 P-ALAXIN.

In a randomized trial in which 767 adults and children with uncomplicated *P. falciparum* malaria were exposed to P-ALAXIN, 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 P-ALAXIN 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:

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 P-ALAXIN were generally mild in severity, and the majority was 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:

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 and treatment

In clinical trials, nine patients received double the cumulative intended dose of P-ALAXIN. 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

DHA 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 P-ALAXIN 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. P-ALAXIN 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. P-ALAXIN 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

	PCR-corrected cure rate (m-ITT)			
Study	**P-ALAXIN**	**AS + MQ**	**A + L**	**95 % two-sided CI on the treatment difference (P-ALAXIN - 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 P-ALAXIN 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)			
	P-ALAXIN	**AS + MQ**	**A + L**	**95% two-sided CI on the treatment difference (P-ALAXIN - Comparator); p-value**
DM04010 (n=1087) ≤ 5 years >5 to ≤12 years > 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

This CI is asymptotic because the exact CI could not be computed

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 P-ALAXIN) 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 P-ALAXIN (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 P-ALAXIN) 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, P-ALAXIN 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 withartenimol. 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 ofartenimol, 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 withartenimol, 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

Sodium citrate anhydrous
Sugar
Colloidal Silicon Dioxide
Xanthan gum
Flavour orange dry powder
Aspartame
Sodium Benzoate
Sunset yellow supra

6.2 Incompatibilities

None known

6.3 Shelf life

36 months from the date of manufacture.

6.4 Special precautions for storage

Store in a cool and dry place, protected from light

6.5 Nature and contents of container

1 Bottle packed in a one printed monocarton along with its package insert.

Note: All pack style may not be marketed.

7- Marketing Authorization Holder:

- Name : **GLOBELA PHARMA PVT. LTD.**

- Address : Plot No. 357, G.I.D.C.,
Sachin,
Surat – 394 230,
Gujarat,
India.

- Phone : +91– 261–2398058
- Fax : +91– 261–2398058
- E-mail : info@globelapharma.com

8- Marketing Authorization Number (s):

Product license / registration Number (s)

9- Manufacturer Name:

- Name : **GLOBELA PHARMA PVT. LTD.**

- Address : Plot No. 357, G.I.D.C.,
Sachin,
Surat – 394 230,
Gujarat,
India.

- Phone : +91– 261–2398058
- Fax : +91– 261–2398058
- E-mail : info@globelapharma.com

10- Date of first authorization/renewal of the authorization:

11- Date of revision of the text:
