Summary of Product Characteristics (SmPC)

(Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules)

1. NAME OF THE MEDICINAL PRODUCT : Zymat Capsules

1.1 Name of product:

Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules

1.2 Strength : Artemisinin 62.5 mg + Piperaquine Phosphate 375 mg

1.3 Pharmaceutical Dosage Form: Soft Gelatin Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITIONS:

Each Soft gelatin capsules contains

Artemisinin	62.5 mg
Piperaquine Phosphate	
Equivalent to Piperaquine	375 mg

3. PHARMACEUTICAL FORM :

Soft gelatin capsule

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules indicated for the treatment of uncomplicated Plasmodium falciparum malaria in adults, 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 agents.

4.2 Posology and method of administration

Posology
Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules should be administered over three consecutive days for a total of three doses taken at the same time each day.

Dosage

Dosing should be based on body weight of patient

If a patient vomits within 30 minutes of taking Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules, 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 Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules 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 Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules may be given within a 12 month period A second course of Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules should not be given within 2 months after the first course due to the long elimination half-life of piperaquine

Hepatic and renal impairment

Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules has not been evaluated in subjects with moderate or severe renal or hepatic insufficiency. Therefore, caution is advised when administering Artemisinin with Piperaquine Phosphate Soft Gelatin
Capsules to these patients

Elderly

Clinical studies of Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules 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

The safety and efficacy of Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules 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

Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules 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, Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules may be crushed and mixed with water. The mixture should be used immediately after preparation.

- Recommended route of administration:

Oral

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 DIHYDROARTEMISININ AND PIPERAQUINE PHOSPHATE TABLETS is commenced (e.g. mefloquine, halofantrine, lumefantrine, chloroquine, quinine and other antimalarial agents) taking into account their elimination half-life.

4.4 Special warnings and precautions for use

Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules 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 Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules 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 Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules limited ECGs were obtained during treatment. These showed that QTc prolongation occurred more frequently and to a larger extent in association with Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules therapy than with the comparators Analysis of cardiac adverse events in clinical trials showed that these were reported more frequently in Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules treated patients than in those treated with comparator antimalarial . Before the third dose of
Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules, 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 Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules 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 Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules 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 Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules 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 Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules 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 Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules 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 Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules

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 Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules is administered to patients taking such medicinal products, and ECG monitoring is advised due to the risk of higher plasma concentrations of piperaquine

Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules 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 Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules is administered to patients with jaundice and/or with moderate or severe renal or hepatic insufficiency, and ECG and blood potassium monitoring are advised.

Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules 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 Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules should be given in a 12- month period

4.5 Interaction with other medicinal products and other forms of interaction

Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules 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 Drug-drug pharmacokinetic interaction studies with Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules have not been performed. The assessment of the potential for drug-drug interactions to occur is based on in vitro studies.

Effect of Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules on co- administered medicinal products

Piperaquine is metabolised by, and is an inhibitor of CYP3A4. Therefore, it has the potential to increase plasma concentrations of other substrates for this enzyme (e.g. HMG CoA reductase inhibitors) with the risk of increased toxicity. 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 Artemisinin with

Piperaquine Phosphate Soft Gelatin Capsules

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.

DHA administration may result in a slight decrease in CYP1A2 activity. Caution is therefore, advised when Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules 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 DHA.

Effect of co-administered medicinal products on Artemisinin with Piperaquine Phosphate

Soft Gelatin Capsules

Piperaquine is metabolised by CYP3A4 in vitro. The contribution of CYP3A4 to elimination of piperaquine in vivo is unknown. Concomitant treatment with medicinal products which inhibit CYP3A4 may lead to a marked increase of piperaquine plasma concentration resulting in an exacerbation of the effect on QTc Therefore, particular caution is required if Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules is administered to patients taking such medicinal products (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.

All these potential interactions should be kept in mind for patients who require Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules treatment and, due to the long half-life of piperaquine, for up to 3 months after the treatment.

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 DHA may also be reduced.
Concomitant treatment with such medicinal products is not recommended.

Food interaction

Absorption of piperaquine is increased in the presence of fatty food which may increase its effect on QTc interval. Therefore, Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules should be taken with water only as described in section 4.2. Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules 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 DHA and piperaquine in pregnant women. Based on animal data, Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules is suspected to cause serious birth defects when administered during the first trimester of pregnancy Reproductive studies with artemisinin derivatives have demonstrated teratogenic potential with an increased risk during early gestation 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.

Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules should not be used during pregnancy in situations where other suitable and effective anti- malarials are available.

Lactation

Animal data suggest excretion of piperaquine into breast milk but no data are available in humans. Women taking Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules 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 DHA in both females and males.

4.7 Effects on ability to drive and use machines

Adverse event data collected in clinical trials suggest that Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules 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 Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules 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 Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules.

In a randomized trial in which 767 adults and children with uncomplicated P. falciparum malaria were exposed to Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules, 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 Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules 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, the most frequent first, 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 Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules

SOC	Very Common	Common	Uncommon
Infections and infestations		P falciparum infection	Influenza Respiratory tract infection
Blood and lymphatic system disorders		Anaemia	
Metabolism and nutrition disorders			Anorexia
Nervous system disorders		Headache	Dizziness Convulsion

Cardiac disorders		QTc prolonged Tachycardia	Cardiac conduction disorders Sinus arrhythmias
			Bradycardia
Respiratory, thoracic and mediastinal disorders			Cough
Gastrointestinal disorders			Vomiting Abdominal pain Diarrhoea Nausea
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 Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules 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 Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules:

SOC	Very Common	Common	Uncommon
Infections and infestations	Influenza P. falciparum infection	Respiratory tract infection Ear infection	
Blood and lymphatic system disorders		Anaemia Leuckocytoses NEC Leukopenias/neutropenia Thrombocytopenia	Hypochromasia Lymphadenopathy Splenomegaly Thrombocythaemia
Metabolism and nutrition disorders		Anorexia	
Nervous system disorders			Convulsion Headache
Eye disorders		Conjunctivitis	
Cardiac disorders		Heart rate irregular QT/QTc prolonged	Cardiac murmur Cardiac conduction disorders
Respiratory, thoracic and mediastinal disorders	Cough		Epistaxis Rhinorrhoea
Gastrointestinal disorders		Abdominal pain Vomiting Diarrhoea	Nausea Stomatitis
Hepatobiliary disorders			Hepatitis Hepatomegaly Jaundice Abnormal liver function tests
Skin and subcutaneous Tissue disorders		Dermatitis Rash	Pruritis Acanthosis

Musculoskeletal and connective tissue disorders			Arthralgia
General disorders and administration site conditions	Pyrexia	Asthenia	

4.9 Overdose

In clinical trials, nine patients received double the cumulative intended dose of Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules. 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 Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules 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. Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules 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. Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules 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)			
	Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules	AS + MQ	A + L	95 % two-sided CI on the treatment difference (ARTEMISININ WITH PIPERAQUINE PHOSPHATE SOFT GELATIN CAPSULES - 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 Artemisinin with Piperaquine Phosphate Soft

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

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

5.2 Pharmacokinetic properties

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

Absorption

DHA is very rapidly absorbed, Tmax being approximately 1-2 hrs after single and multiple dosing. In patients, mean Cmax (CV %) and AUCINF of DHA (observed after the first dose of Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules) were 752 (47 %) ng/ml and 2,002 (45 %) ng/ml*h, respectively.

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

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

In healthy volunteers, DHA 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 Tmax of approximately 5 hours following a single and repeated dose. In patients mean (CV %) Cmax and AUC0-24 (observed after the first dose of Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules 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, Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules 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

Distribution

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

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

The metabolism of piperaquine in humans has not been studied in vivo. 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. As a consequence, there is the potential for increasing plasma concentrations of

CYP3A4 substrates, and also for the increase of piperaquine plasma concentrations when Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules is concomitantly administered with CYP3A4 substrates, and CYP3A4 inhibitors, respectively (see section 4.5).

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

Elimination

The elimination half-life of DHA 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 %). DHA is eliminated by metabolism (mainly glucuroconjugation). Its clearance was found to be slightly lower in female than in male healthy volunteers. Data regarding DHA 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 patients.

In a paediatric pharmacokinetic study, and based on very limited sampling, minor differences were observed for DHA 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.
DHA and piperaquine were not genotoxic/clastogenic based on in vitro and in vivo testing.
No carcinogenicity studies have been performed.

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

Phototoxicity

There are no phototoxicity concerns with DHA, 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

Refined Soya Oil
Lecithin
Gelatin
Glycerin
Sorbitol 70% Non crystallising
Sodium methyl Paraben
Sodium propyl Paraben
Purified water
FD & C Bue # 1 Titanium
Dioxide

6.2 Incompatibilities

No compatibilities have been observed.

6.3 Shelf life

30 months from the date of manufacturing

6.4 Special precautions for storage

Store in a dry place below 30^0 C. Protect from light.

Keep out of reach of children

6.5 Nature and contents of container

Artemisinin with Piperaquine Phosphate Soft Gelatin Capsules is available as blister pack of 4's Capsules.

1 such blister is packed in a unit carton, along with package insert.

6.6 Special precautions for disposal and other handling

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

7. APPLICANT:

Comfort Care Pharmaceuticals Ltd, No 1 The Penthouse Comfort Mall, Gwarinpa, Abuja.

MANUFACTURER:

Olive Health Care, 197/2, Athiyawad, Dabhel Village, Daman-396210, India.