1.3 PRODUCT INFORMATION

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the Medicinal Product

Artemether 80 mg and Lumefantrine 480 mg Tablets

2. Qualitative and Quantitative Composition Each

Uncoated tablet contains: Artemether 80 mg

Lumefantrine ..... 480 mg

Excipients ..... Q.S

3. Pharmaceutical Form

A yellow colour, round shapped uncoated tablet, having breakline on one side of the tablet and plain on the other side

4. Clinical Particulars

4.1 Therapeutic Indications

Artemether 80 mg and Lumefantrine 480 mg Tablets is indicated for the treatment of uncomplicated cases of malaria due to Plasmodium falciparum in adults and children of 35 kg and above. The most recent official guidelines on the appropriate use of antimalarial agents and local information on the prevalence of resistance to antimalarial drugs must be taken into consideration for deciding on the appropriateness of therapy with 80/480.

4.2 Posology and Method of Administration

Oral use Treatment should be administered at the time of initial diagnosis or at the onset of symptoms. It is preferable that the patient has a positive diagnostic test before administration. One tablet should be taken twice a day for three days (total six doses). The first dose should be followed by a second dose after 8 hours. The following two days the doses of Artemether 80 mg and Lumefantrine 480 mg Tablets should be given twice daily, morning and evening (i.e., 12 hours apart). To increase absorption, Artemether 80 mg and Lumefantrine 480 mg Tablets should be taken with food or a milky drink If a patient is unable to tolerate food, Artemether 80 mg and Lumefantrine 480 mg Tablets should still be administered, but the systemic exposure may be reduced. Patients who vomit within 1 hour of taking the medication should repeat the dose. If a dose is missed, it should be taken as soon as realized and then the recommended regimen continued until the full course of treatment has been completed.

Renal or hepatic impairment No dose adjustments are necessary in patients with renal or hepatic impairment. However, caution is advised when administering Artemether 80 mg and Lumefantrine 480 mg Tablets to patients with severe renal or hepatic problems. Pediatric patients weighing less than 35 kg: Appropriate dose adjustments cannot be achieved with this product. Other formulations containing lower amounts of artemether/lumefantrine are available for these patients. Elderly No special precautions or dosage adjustments are necessary in such patients.

4.3 Contraindications

Artemether 80 mg and Lumefantrine 480 mg Tablets is contraindicated in:

- Patients with known hypersensitivity to artemether, lumefantrine or to any of the excipients.
- Patients with severe malaria according to WHO definition.
- Patients with a personal or family history of congenital prolongation of the QTc interval or sudden death, or with any other clinical condition known to prolong the QTc interval, such as patients with a history of symptomatic cardiac arrhythmias, clinically relevant bradycardia or severe cardiac diseases.

- Patients taking drugs that are known to prolong QTc interval such as : antiarrhythmics of classes IA and III
- Neuroleptics and antidepressant agents
- Certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal agents
- Certain non-sedating antihistamines (terfenadine, astemizole)
- Cisapride
- Patients with known disturbances of electrolyte balance e.g., hypokalaemia or hypomagnesaemia
- Patients taking any drug which is metabolized by the cytochrome enzyme CYP2D6 (e.g., flecainide, metoprolol, imipramine, amitriptyline, clomipramine
  Patients taking drugs that are strong inducers of CYP3A4 such as rifampicin, carbamazepine, phenytoin, St John's wort.

4.4 Special Warnings and Precautions for Use

Artemether 80 mg and Lumefantrine 480 mg Tablets is not recommended during the first trimester of pregnancy in situations where other suitable and effective antimalarial are available.

Artemether 80 mg and Lumefantrine 480 mg Tablets has not been evaluated for the treatment of severe malaria, including cases of cerebral malaria or other severe manifestations such as pulmonary oedema or renal failure.

Due to limited data on safety and efficacy, Artemether 80 mg and Lumefantrine 480 mg Tablets should not be given concurrently with any other antimalarial agent unless there is no other treatment option.

If a patient deteriorates whilst taking Artemether 80 mg and Lumefantrine 480 mg Tablets, alternative treatment for malaria should be started without delay. In such cases, monitoring of the ECG is recommended and steps should be taken to correct any electrolyte disturbances.

The long elimination half-life of lumefantrine must be taken into account when administering quinine in patients previously treated with Artemether 80 mg and Lumefantrine 480 mg Tablets.

If quinine is given after Artemether 80 mg and Lumefantrine 480 mg Tablets, close monitoring of the ECG is advised.

If Artemether 80 mg and Lumefantrine 480 mg Tablets is given after mefloquine, close monitoring of food intake is advised.

In patients previously treated with halofantrine, Artemether 80 mg and Lumefantrine 480 mg Tablets should not be administered earlier than one month after the last halofantrine dose.

Artemether 80 mg and Lumefantrine 480 mg Tablets is not indicated and has not been evaluated for prophylaxis of malaria.

Artemether 80 mg and Lumefantrine 480 mg Tablets should be used cautiously in patients on anti-retroviral drugs (ARTs) since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of Artemether 80 mg and Lumefantrine 480 mg Tablets.

Like other antimalarials (e.g. halofantrine, quinine and quinidine) Artemether 80 mg and Lumefantrine 480 mg Tablets has the potential to cause QT prolongation.

Caution is recommended when combining Artemether 80 mg and Lumefantrine 480 mg Tablets with drugs exhibiting variable patterns of inhibition, moderate induction or competition for CYP3A4 as the therapeutic effects of some drugs could be altered. Drugs that have a mixed inhibitory/induction effect on CYP3A4, especially anti-retroviral drugs such as HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors should be used with caution in patients taking Artemether 80 mg and Lumefantrine 480 mg Tablets.

Caution is recommended when combining Artemether 80 mg and Lumefantrine 480 mg Tablets with hormonal contraceptives. Artemether 80 mg and Lumefantrine 480 mg Tablets may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control for about one month. Patients who remain averse to food during treatment should be closely monitored as the risk of recrudescence may be greater.

Renal impairment

No specific studies have been carried out in this group of patients. There is no significant renal excretion of lumefantrine, artemether and dihydroartemisinin in studies conducted in healthy volunteers and clinical experience is limited. No dose adjustment for the use of Artemether 80 mg and Lumefantrine 480 mg Tablets in patients with renal impairment is recommended. Caution is advised when administering Artemether 80 mg and Lumefantrine 480 mg Tablets to patients with severe renal impairment. In these patients, ECG and blood potassium monitoring is advised.

Hepatic impairment

No specific studies have been carried out in this group of patients. In patients with severe hepatic impairment, a clinically relevant increase of exposure to artemether and lumefantrine and/or their metabolites cannot be ruled out. Therefore caution should be exercised in dosing patients with severe hepatic impairment. In these patients, ECG and blood potassium monitoring is advised. No dose adjustment is recommended for patients with mild to moderate hepatic impairment.

New infections

Data for a limited number of patients in a malaria endemic area show that new infections can be treated with a second course of Artemether 80 mg and Lumefantrine 480 mg Tablets. In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of Artemether 80 mg and Lumefantrine 480 mg Tablets cannot be recommended.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Artemether 80 mg and Lumefantrine 480 mg Tablets should not be used in patients taking drugs that are known to prolong the QTc interval as effects may be additive and increase the risk of cardiac arrhythmia.

Interaction with other antimalarials

Artemether 80 mg and Lumefantrine 480 mg Tablets should not be given concurrently with any other antimalarial agent. In addition, due to the propensity of some antimalarial agents to prolong the QTc interval, caution is advised when administering Artemether 80 mg and Lumefantrine 480 mg Tablets to patients in whom there may

still be detectable concentrations of these drugs in the plasma following prior treatments.

Administration of a six-dose regimen of artemether/lumefantrine (over 60 hours) starting 12 hours after completion of a three-dose regimen of mefloquine or placebo in healthy volunteers showed no effect of mefloquine on plasma concentrations of artemether or the artemether/dihydroartemisinin ratio, but a 30-40% reduction in plasma levels of lumefantrine. These are possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production. Patients that have been pretreated with mefloquine should be encouraged to eat at dosing times to compensate for the decrease in bioavailability. Plasma mefloquine concentrations from the time of addition of artemether/lumefantrine were not affected compared with a group that received mefloquine followed by placebo.

In patients previously treated with halofantrine, Artemether 80 mg and Lumefantrine 480 mg Tablets should be dosed at least one month after the last halofantrine dose due to the long elimination half-life of halofantrine and the potential additive/synergistic effects on the QT-interval.

Interaction with CYP450 enzymes

Studies in humans have demonstrated that artemisinins have some capacity to induce CYP3A4 and CYP2C19 and inhibit CYP2D6 and CYP1A2. Although the magnitude of the changes was generally low it is possible that these effects could alter the therapeutic response or safety profile of drugs that are predominantly metabolised by these enzymes Lumefantrine was found to inhibit CYP2D6 in vitro. This may be of particular clinical relevance for compounds with a low therapeutic index.

Interaction with CYP450 3A4 inhibitors

Ketoconazole: Both artemether and lumefantrine are metabolised predominantly by the cytochrome enzyme CYP3A4, and do not inhibit this enzyme at therapeutic concentrations. The concurrent oral administration of ketoconazole with artemether/lumefantrine led to a modest increase (2-fold) in artemether, DHA, and lumefantrine exposure in healthy adult subjects. This increase in exposure to the

antimalarial combination was not associated with increased side effects or changes in electrocardiographic parameters. Dose adjustment of Artemether 80 mg and Lumefantrine 480 mg Tablets is not considered necessary when administered concomitantly with ketoconazole or other azole antifungals, but such combinations should be used with caution.

HIV Treatment Medications

HIV nucleoside and nucleotide reverse transcriptase inhibitors (NTRIs, e.g. abacavir, emtricitabine, lamivudine, tenofovir [TDF or TAF], zidovudine.

Co-administration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely.

HIV non-nucleoside reverse transcriptase inhibitors (NNRTIs):

Efavirenz: Co-administration of efavirenz and artemether/lumefantrine lead to decreases in Artemether exposure (51% and 79%), dihydroartemisinin exposure (46% and 75%) and lumefantrine exposure by (21% and 56%). Lumefantrine had no significant effect on efavirenz exposure in either study. Use with caution as decreased concentrations of artemether, dihydroartemisinin, or lumefantrine may result in a decrease of antimalarial efficacy.

Nevirapine: Lumefantrine is metabolised predominantly by CYP3A4. Upon co-administration with artemether/lumefantrine with nevirapine decreased the AUCs of artemether and dihydroartemisinin. In a crossover study lumefantrine exposure was decreased by 20% and lumefantrine reduced nevirapine exposure by 46%.

Use with caution.

Rilpivirine: Co-administration has not been studied but based on metabolism and clearance a pharmacokinetic interaction is unlikely. Rilpivirine should be used with caution when co-administered with a drug that has a potential risk to prolong the QT interval.

HIV Protease Inhibitors (PIs)

Atazanavir: Co-administration may increase plasma levels of artemisinins and lumefantrine. Both Lumefantrine and atazanavir have been shown to prolong the QT interval.

Darunavir: Co-administration may increase plasma levels of artemisinins and lumefantrine.

Lopinavir/ritonavir: Data from clinical studies and population modelling suggest that co-administration of lopinavir/ritonavir and artemether decreases exposure of dihydroartemisinin (the biologically active metabolite) by ~40-60%. Lumefantrine AUC was significantly increased by 2.3-fold and there was trend towards increased Cmax (1.4-fold). The clinical meaning of these opposite effects on artemether and lumefantrine is not clear. Both lumefantrine and lopinavir have been shown to prolong the QT interval.

Ritonavir: Co-administration may increase plasma levels of artemisinins and lumefantrine, as both are metabolised by CYP3A4. Caution is recommended. HIV Integrase Strand-Transfer Inhibitors (INSTIs)

Dolutegravir, Raltegravir: Co-administration has not been studied but based on metabolism/elimination and toxicity profiles there is little potential for interaction.

Elvitegravir/cobicistat: Co-administration has not been studied. Artemether and lumefantrine are metabolized by CYP3A4. Elvitegravir/cobicistat may increase concentrations of artemisinins and lumefantrine.

Pharmacokinetic Enhancer

Cobicistat: Co-administration has not been studied. Cobicistat may increase concentrations of artemisinins and lumefantrine by inhibition of CYP3A4.

Antivirals against Hepatitis B or C

Co-administration has not been studied. In many instances a clinically significant interaction appears unlikely. However, consult the summary of product characteristics of the desired medication.

4.6 Pregnancy and Lactation

Pregnancy

A moderate amount of data on pregnant women in their first trimester (more than 500 pregnancy outcomes) is available for artemether/lumefantrine. Data from a recent meta-analysis have shown that compared to quinine, artemether/lumefantrine treatment in the first trimester was not associated with an increased risk of miscarriage or stillbirth. While the data are limited, they indicate no difference in the prevalence of major congenital anomalies between treatment groups.

A large amount of data on pregnant women in their second and third trimester (more than 4000 documented pregnancy outcomes) is available for artemisinin derivatives including artemether/lumefantrine. They indicate no fetal or neonatal toxicity. Medither can be used during pregnancy.

Lactation

The amounts of artemether, dihydroartemisinin and lumefantrine in breast milk are small. Therefore, breastfeeding women can receive artemisinin-based combination therapies (including Artemether 80 mg and Lumefantrine 480 mg Tablets) for malaria treatment.

Female fertility

There is no information on the effects of Artemether 80 mg and Lumefantrine 480 mg Tablets on fertility in humans.

4.7 Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed. Patients receiving Artemether 80 mg and Lumefantrine 480 mg Tablets should be warned that dizziness, fatigue or asthenia may occur, in which case their ability to drive or operate machines may be impaired.

4.8 Undesirable Effects

The safety of artemether/lumefantrine has been evaluated in adults, adolescents and children in clinical trials with more than 3500 patients. Adverse reactions reported from

clinical studies and post-marketing experience are listed below according to system organ class. Adverse reactions are ranked under headings of frequency using the Med DRA frequency 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 available data).

These adverse reactions were reported during post-marketing experience. Because these spontaneously reported events are from a population of uncertain size, it is difficult to estimate their frequency.

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 to the marketing authorisation holder, or, if available, via the national reporting system.

Table 1: Frequency of undesirable effects

	Adults and adolescents above 12 years of age	Infants and children of 12 years of age and below (incidence estimates*)
Cardiac disorders		
Palpitations	Very common	Uncommon
Electrocardiogram QT prolonged	Uncommon	rare
Nervous system disorders		
Headache	Very common	Common
Dizziness	Very common	Common
Gait disturbance	uncommon	--
Ataxia, hypoaesthesia	Uncommon	--
Clonic movements	Common	Uncommon
Somnolence	uncommon	uncommon
Respiratory, thoracic and mediastinal disorders		
Cough	Common	Very common
Gastrointestinal disorders		
Vomiting	Very common	Very common
Abdominal pain	Very common	common
Nausea	Very common	Common
Decreased appetite	Very common	Very common
Diarrhoea	Common	Common
Skin and subcutaneous tissue disorders		
Rash	Common	Common
Pruritus	Common	Uncommon
Urticaria	Uncommon	Uncommon
Arthralgia	Very common	Common
Myalgia	Very common	Common
General disorders and administration site conditions		
Asthenia	Very common	Common
Fatigue	Very common	Common
Immune system disorders		
Hypersensitivity	Not known	Rare
Blood and lymphatic system disorders		
Delayed haemolytic anaemia*	Not known	Not known
Hepatobiliary disorders		
Liver function tests abnormal	Uncommon	Common
Psychiatric disorders		
Sleep disorders	Very common	uncommon

4.9 Overdose

Experience of over dosage with artemether and lumefantrine is limited. In cases of suspected over dosage symptomatic and supportive therapy should be given as appropriate, which should include monitoring of ECG and serum electrolytes.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antimalarials, Artemisinin and derivatives, combinations.
ATC code: P01BF01

Pharmacodynamic effects

Artemether 80 mg and Lumefantrine 480 mg Tablets comprises a fixed ratio of 1:6 parts of artemether and lumefantrine, respectively. The site of antiparasitic action of both components is the food vacuole of the malarial parasite, where they are thought to interfere with the conversion of haem, a toxic intermediate produced during haemoglobin breakdown, to the nontoxic haemozoin, malaria pigment. Lumefantrine is thought to interfere with the polymerisation process, while artemether generates reactive metabolites as a result of the interaction between its peroxide bridge and haem iron. Both artemether and lumefantrine have a secondary action involving inhibition of nucleic acid- and protein synthesis within the malarial parasite.

Clinical efficacy

The efficacy of artemether/lumefantrine was evaluated for the treatment of acute, uncomplicated malaria (defined as symptomatic P. falciparum malaria without signs and symptoms of severe malaria or evidence of vital organ dysfunction) in five 6-dose regimen studies and one study comparing the 6-dose regimen with the 4-dose regimen. Baseline parasite density ranged from 500/µL - 200,000/µL (0.01% to 4% parasitaemia) in the majority of patients.

Studies were conducted in otherwise healthy, partially immune or non-immune adults and children (=5kg body weight) with uncomplicated malaria in Thailand, sub-Saharan Africa, Europe, and South America. Efficacy endpoints consisted of:

- 28-day cure rate, proportion of patients with clearance of asexual parasites within 7 days without recrudescence by day 28
- Parasite clearance time (PCT), defined as time from first dose until first total and continued disappearance of asexual parasite which continues for a further 48 hours
- Fever clearance time (FCT), defined as time from first dose until the first time body temperature fell below 37.5°C and remained below 37.5°C for at least a further 48 hours (only for patients with temperature >37.5°C at baseline) .

- The modified intent to treat (mITT) population includes all patients with malaria diagnosis confirmation who received at least one dose of study drug. Evaluable patients generally are all patients who had a day 7 and a day 28 parasitological assessment or experienced treatment failure by day 28. The results are presented in the table below:

Clinical efficacy results

Study No.	Age	Polymerase chain reaction (PCR)-corrected 28-day cure rate[1] n/N (%) in evaluable patients	Median FCT[2] [25th, 75th percentile]	Median PCT[2] [25th, 75th percentile]	Year/ Study location
A025[3]	3-62 years	93/96 (96.9)	n[3]=59 35 hours [20, 46]	n=118 44 hours [22, 47]	1996-97 Thailand
A026	2-63 years	130/133 (97.7)	n[3]=87 22 hours [19, 44]	NA	1997-98 Thailand
A028	12-71 years	148/154 (96.1)	n[3]=76 29 hours [8, 51]	n=164 29 hours [18, 40]	1998-99 Thailand
A2401	16-66 years	119/124 (96.0)	n[3]=100 37 hours [18, 44]	n=162 42 hours [34, 63]	2001-05 Europe, Columbia
A2403	2 months-9 years	289/299 (96.7)	n[3]=309 8 hours [8, 24]	n=310 24 hours [24, 36]	2002-03 3 countries in Africa
B2303[CT]	3 months-12 years	403/419 (96.2)	n[3]=323 8 hours [8, 23]	n=452 35 hours [24, 36]	2006-07 5 countries in Africa
B2303[DT]	3 months-12 years	394/416 (94.7)	n[3]=311 8 hours [8, 24]	n=446 34 hours [24, 36]	2006-07 5 countries in Africa

Efficacy cure rate based on blood smear microscopy mITT population

For patients who had a body temperature >37.5°C at baseline only

Only the 6-dose regimen over 60 hour's group data is presented.

–Artemether/lumefantrine tablets administered as crushed tablets

– Artemether/lumefantrine Dispersible tablets

Artemether/lumefantrine is not indicated for, and has not been evaluated in, the treatment of malaria due to *P. vivax*, *P. malariae* or *P. ovale*, although some patients in clinical studies had co-infection with *P. falciparum* and *P. vivax* at baseline. Artemether/lumefantrine is active against blood stages of *Plasmodium vivax*, but is not active against hypnozoites.

Resistance

Strains of P. falciparum with a moderate decrease in susceptibility to artemether or lumefantrine alone can be selected in vitro or in vivo, but not maintained in the case of artemether. Alterations in some genetic regions of P. falciparum [multidrug resistant 1 (pfmdr1), chloroquine resistance transporter (pfcrt), and kelch 13 (K13)] based on in vitro testing and/or identification of isolates in endemic areas where artemether/lumefantrine treatment was administered, have been reported. The clinical relevance of these findings is not known.

QT/QTc Prolongation:

For information on the risk of QT/QTc prolongation in patients see Contraindications. In a healthy adult volunteer parallel group study including a placebo and moxifloxacin control group (n = 42 per group), the administration of the six dose regimen of artemether/lumefantrine with food was associated with a moderate prolongation of QTcF (QT interval corrected by Fridericias formula). The mean changes from baseline at 68, 72, 96, and 108 hours post first dose were 7.45, 7.29, 6.12 and 6.84 msec, respectively. At 156 and 168 hours after first dose, the changes from baseline for QTcF had no difference from zero. No subject had a > 30 msec increase from baseline nor an absolute increase to > 500 msec. Moxifloxacin control was associated with a QTcF

increase as compared to placebo for 12 hours after the single dose with a maximal change at 1 hour after dose of 14.1 msec.

5.2 Pharmacokinetic Properties

No pharmacokinetic data are available for Artemether 80 mg and Lumefantrine 480 mg Tablets. A bioequivalence study was conducted with Artemether & Lumefantrine Tablets 80/480, which is proportionally similar to Artemether 80 mg and Lumefantrine 480 mg Tablets in composition.

ARTEMETHER

Absorption

Artemether is absorbed fairly rapidly and dihydroartemisinin (DHA), the active metabolite of artemether, appears rapidly in the systemic circulation with peak plasma concentrations of both compounds reached about 2 hours after dosing. The absolute bioavailability is unknown. Following single dose administration of 1 tablets of Artemether 80 mg and Lumefantrine 480 mg Tablets in healthy volunteers, the mean (± SD) artemether Cmax value was 81 (±41) ng/ml, the corresponding value for AUC was 238 (±125) ng.h/ml, and the mean artemether tmax value was 2.83 (± 0.94) hours. The pharmacokinetic data for dihydroartemisinin were supportive and indicated a comparable bioavailability between Test and Reference. In healthy volunteers the relative bioavailability of artemether was increased more than two-fold when taken with food.

Distribution

Artemether is 95.4% bound to human serum proteins in vitro. The active metabolite dihydroartemisinin (DHA) is also bound to human serum proteins (47-76%).

Metabolism

Artemether is rapidly and extensively metabolised with substantial first-pass metabolism. Artemether is metabolised in the liver to the biologically active main metabolite DHA (demethylation), predominantly through the isoenzyme CYP3A4/5. The pharmacokinetics of artemether in adults is time dependent. During repeated administration of artemether/lumefantrine, plasma artemether levels decreased significantly, while levels of the active metabolite (dihydroartemisinin) increased,

although not to a statistically significant degree. The ratio of day 3/day 1 AUC for artemether was between 0.19 and 0.44, and was between 1.06 and 2.50 for dihydroartemisinin. This suggests that there was induction of the enzyme responsible for the metabolism of artemether. DHA is further converted to inactive metabolites, primarily by glucuronidation. In vivo data indicate that artemisinins have some capacity to induce cytochrome isoenzymes CYP2C19 and CYP3A4.

Elimination

Artemether and dihydroartemisinin are rapidly cleared from plasma with an elimination half-life of about 2 hours.

No urinary excretion data are available for humans. In rats and dogs unchanged artemether has not been detected in faeces and urine due to its rapid and high-first-pass metabolism, but several metabolites (unindentified) have been detected in both faeces and urine.

LUMEFANTRINE

Absorption

Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentration about 6-8 hours after dosing. The absolute bioavailability is unknown.

Following single dose administration of 1 tablets of 80/480 in healthy volunteers, the mean (± SD) lumefantrine Cmax value was 6136 (±2880) mg/ml, the corresponding value for AUC was 99070 (±48130) mg.h/ml, and the mean lumefantrine tmax value was 5.93 (± 0.73) hours. Lumefantrine exposure from one 80 mg/480 mg tablet is equivalent to four 20 mg/120 mg tablets.

In healthy volunteers the relative bioavailability of lumefantrine, when was taken after a high-fat meal, was increased sixteen-fold compared with fasted conditions. Food has also been shown to increase the absorption of lumefantrine in patients with malaria, although to a lesser extent (approximately two-fold), most probably due to the lower fat content of the food ingested by acutely ill patients. The food interaction data indicate that absorption of lumefantrine under fasted conditions is very poor. Patients should

therefore be encouraged to take the medication with a normal diet as soon as food can be tolerated.

Distribution

Lumefantrine is 99.7% bound to human serum proteins in vitro.

Metabolism

Lumefantrine is N-debutylated, mainly by CYP3A4, in human liver microsomes. The systemic exposure to the metabolite desbutyl-lumefantrine, for which the in vitro antiparasitic effect is 5 to 8 fold higher than lumefantrine, was less than 1% of the exposure to the parent drug. Desbutyl-lumefantrine data is not available specifically for an African population. In vitro, lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations. In humans, the exposure to lumefantrine increases with repeated administration of artemether/lumefantrine over the 3-day treatment period, consistent with the slow elimination of the compound.

Elimination

Lumefantrine is eliminated very slowly with a terminal half-life of approximately 3 days. No urinary excretion data are available for humans. Lumefantrine is eliminated via the bile in rats and dogs, with excretion primarily in the faeces. After oral dosing in rats and dogs qualitative and quantitative recovery of metabolites in bile and faeces was relatively low, most of the dose being recovered as parent drug.

Pharmacokinetics in special patient populations

Specific pharmacokinetic studies have not been performed in patients with hepatic or renal insufficiency. No pharmacokinetic studies are available in elderly patients.

Pediatric population

In pediatric malaria patients, mean Cmax (CV%) of artemether (observed after first dose) were 223 (139%), 198 (90%) and 174 mg/ml (83%) for body weight groups 5-<15, 15-<25 and 25-<35 kg, respectively, compared to 186 mg/ml (67%) in adult malaria patients. The associated mean Cmax of DHA were 54.7 (108%), 79.8 (101%) and 65.3 mg/ml (36%), respectively compared to 101 mg/ml (57%) in adult malaria patients. AUC of lumefantrine (population mean, covering the six doses of artemether/lumefantrine) were 577, 699 and 1150 µgh/ml for pediatric malaria patients in body weight groups 5-<15, 15-<25 and 25-<35 kg, respectively, compared to a mean

AUC of 758 µg•h/ml (87%) in adult malaria patients. The elimination half-lives of artemether and lumefantrine in children are unknown.

5.3 Preclinical Safety Data

General toxicity

The main changes observed in repeat-dose toxicity studies were associated with the expected pharmacological action on erythrocytes, accompanied by responsive secondary haematopoiesis.

Mutagenicity

No evidence of mutagenicity was detected in in vitro or in vivo tests with an Artemether: Lumefantrine combination (consisting of 1 part artemether: 6 parts lumefantrine). In the micronucleus test myelotoxicity was seen at all dose levels (500, 1,000 and 2,000 mg/kg), but recovery was almost complete 48 hours after dosing.

Carcinogenicity

Carcinogenicity studies with the artemether/lumefantrine combination were not conducted.

Reproductive toxicity studies

Reproductive toxicity studies performed with the artemether/lumefantrine combination caused maternal toxicity and increased post-implantation loss in rats and rabbits at doses 50 mg/kg/day (corresponding to approximately 7 mg/kg/day artemether) and 175 mg/kg/day (corresponding to 25 mg/kg/day artemether)respectively. These effects were not observed at lower doses. Lumefantrine alone caused no sign of reproductive or development toxicity at doses up to 1,000 mg/kg/day in rats and rabbits.

Embryotoxicity has been observed in rat and rabbit reproductive toxicity studies conducted with artemether, a derivative of artemisinin. Artemisinins (e.g. artesunate) are known to be embryotoxic in animals. Artemether caused increases in post-implantation loss and teratogenicity (characterised as a low incidence of cardiovascular and skeletal malformations) in rats at 19.4 mg/kg, and in rabbits at 30 mg/kg. Maternal toxicity was also observed in rabbits at 30 mg/kg/day. No other adverse effects were observed at lower doses in rabbits.

The no observed effect dose was 3 mg/kg/day in rats and 25 mg/kg/day in rabbits.

The embryotoxic artemether dose, 20 mg/kg/day in the rat, yields artemether and dihydroartemisinin exposures similar to those achieved in humans.

Artesunate, a structurally related compound, also caused increases in post-implantation loss and teratogenicity (low incidence of cardiovascular and skeletal malformations) in rats at 6 mg/kg and in the lowest dose tested in the rabbits, 5 mg/kg/day.

Cardiovascular Pharmacology

In toxicity studies in dogs at doses > 600 mg/kg/day only, there was some evidence of prolongation of the QTc interval, at higher doses than intended for use in man. In an in vitro assay of HERG channels, Lumefantrine and the main metabolite desbutyl-lumefantrine showed some inhibitory potential in one of the currents responsible for cardiac repolarization. From the estimated IC50 values, the order of potency of HERG current block was halofantrine (IC50 = 0.04 μM) > chloroquine (2.5 μM) > mefloquine (2.6 μM) > desbutyl-lumefantrine (5.5 μM) > lumefantrine (8.1 μM). Clinical studies show, that prolongation of QTcF can occur with standard dosing of artemether/Lumefantrine.

6. Pharmaceutical Particulars

6.1 List of Excipients

Dibasic calcium Phosphate, Maize Starch Powder, Micro Crystalline Cellulose, Sodium Starch Glycolate, P. V. P. K-30, Croscarmellose Sodium, Colloidal Anhydrous Silica, Purified Talc, Magnesium Stearate, Brilliant Blue FCF (Rapid Coat) & Purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

36 months

6.4 Special Precautions for Storage

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

6.5 Nature and Contents of Container

6 Tablet pack in PVC/Alu Blister, Such 1 Blister in one inner carton with a packing insert. Such 10 inner carton pack in one outer carton.

6.6 Special Precautions for Disposal and Other Handling

Not applicable.

7.0 Manufacturer/Applicant

CLARIOD PHARMACEUTICALS PVT LTD

217/P, OPP. GURUKUL ENGLISH MEDIUM, KANOD PIRANA ROAD, TAL-DASKROI DIST-AHMEDABAD 382425 INDIA