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Rx
Member of TGI Group of Companies

1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PRODUCT NAME : Artemether 80 mg + Lumefantrine 480 mg Tablets

BRAND NAME: CO-MAL FORTE 80/480 Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PRODUCT NAME: Artemether 80 mg + Lumefantrine 480 mg Tablets

Each uncoated tablet contains:
Artemether.....80 mg
Lumefantrine ..... 480 mg
Excipients..... q.s.

For complete list of excipients refer section 6.1.

3. PHARMACEUTICAL FORM:

Tablet

Yellow colored round biconvex tablet embossed with “breakline” on one side and plain on the other side

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication:

CO-MAL FORTE 80/480 is a fixed-dose combination of Artemether and Lumefantrine, which acts as a blood schizontocide. It is indicated for: Treatment, including stand-by emergency treatment of adults, children and infants (weighing 5 kg or more) with acute, uncomplicated infections due to Plasmodium falciparum or mixed infections including P. falciparum. Because CO-MAL FORTE 80/480 is effective against both drug-sensitive and drug-resistant P. falciparum it is also recommended for malaria infections acquired in areas where the parasites may be resistant to other antimalarial.

4.2 Posology and method of administration:

Treatment should start at the beginning of the high transmission period and is given in 3-day courses as follows: CO-MAL FORTE 80/480 Tablets should be taken with food. Patients with acute malaria are frequently averse to food. Patients should be encouraged to resume normal eating as soon as food can be tolerated since this improves absorption of artemether and lumefantrine.

For patients who are unable to swallow the tablets such as infants and children, Timal 80/480 Tablets may be crushed and mixed with a small amount of water (1 to 2 teaspoons) in a clean container for administration immediately prior to use. The container can be rinsed with more water and the contents swallowed by the patient. The crushed tablet preparation should be followed whenever possible by food/drink (e.g., milk, formula, pudding, broth, and porridge).

In the event of vomiting within 1 to 2 hours of administration, a repeat dose should be taken. If the repeat dose is vomited, the patient should be given an alternative antimalarial for treatment.

Dosage in Adult Patients (>16 Years of Age)

Sections or subsections omitted from the full prescribing information are not listed. A 3-day treatment schedule with a total of 6 doses is recommended for adult patients with a bodyweight of 35 kg and above:

single initial dose, again after 8 hours and then twice-daily (morning and evening)

for the following 2 days (total course of 6 tablets).

Body weight (kg)	Age (yrs)	Total Tablets	DOSAGE REGIMEN					
			Day1		Day 2		Day3	
			0 Hrs	8 Hrs	24 Hrs	36 Hrs	48 Hrs	60 Hrs
> 35	>14	6	1	1	1	1	1	1

4.3 Contraindications:

CO-MAL FORTE80/480 is contraindicated in: Known hypersensitivity to artemether, lumefantrine or to any of the excipients of CO-MAL FORTE 80/480

- Patients with severe malaria according to WHO definition*.
- First trimester of pregnancy in situations where other suitable and effective anti-malarial are available (see section WOMEN OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING AND FERTILITY).
- Patients with a 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, with clinically relevant bradycardia or with severe cardiac disease.
- Patients taking drugs that are known to prolong the 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 antihistaminics (terfenadine, astemizole),
  - cisapride.
- Patients with known disturbances of electrolyte balance e.g. hypokalemia 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 (Hypericumperforatum).

4.4 Special warning and precautions for use

Artemether 80 mg and Lumefantrine 480 mg Tablets must not be used in 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. 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 anyelectrolyte 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 480mg Tablets should not be administered earlier than one month after the last halofantrine dose. 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, induction or competition forCYP3A4 as the therapeutic effects of some drugs could be altered. Patients who remain averse to food during treatment should be closely monitored as the risk of recrudescence may be greater.

Caution is advised when administering Artemether 80 mg and Lumefantrine 480 mg Tablets to patients with severe renal, hepatic or cardiac problems.

4.5 Drug Interactions

Artemether and lumefantrine is contraindicated with concomitant use of drugs (they may cause prolonged QTc interval and Torsade de Pointes) such as: antiarrhythmic 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 no sedating antihistaminic (terfenadine, astemizole), cisapride, flecainide.

a) Interaction with drugs metabolized by CYP2D6:
Lumefantrine was found to inhibit CYP2D6 in vitro. This may be of particular clinical relevance for compounds with a low therapeutic index. Co-administration of Artemether and Lumefentrine with drugs that are metabolised by this iso-enzyme is contraindicated (e.g. neuroleptics, metoprolol, and tricyclic antidepressants such as imipramine, amitriptyline, clomipramine) is contraindicated.

b) Interaction with strong inducers of CYP3A4 such as rifampin:
Oral administration of rifampin (600 mg daily), a strong CYP3A4 inducer, with Artemether and Lumefentrine Tablets (6-dose regimen over 3 days) in six HIV-1 and tuberculosis co infected adults without malaria resulted in significant decreases in exposure to Artemether (89%), DHA(85%) and lumefantrine (68%) when compared to exposure values after Artemether and Lumefentrine alone. Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's Wort is contraindicated with Artemether and Lumefentrine
Inducers should not be administered at least one month after Artemether and Lumefentrineadministration, unless critical to use as judged by the prescriber.

c) Interaction with other antimalarial drugs:
Data on safety and efficacy are limited,Artemether and Lumefentrine should therefore not be given concurrently with other antimalarials unless there is no other treatment option. If Artemether and Lumefentrine is given following administration of mefloquine or quinine, close monitoring of food intake (for mefloquine) or of the ECG (for quinine) is advised. The long elimination half-life of lumefantrine must be taken into account when administering quinine inpatients previously treated with Artemether and Lumefentrine. In patients previously treated with halofantrine. Artemether and Lumefentrine should not be administered earlier than one month after the last halofantrine dose

Mefloquine:

A drug interaction study with Artemether and Lumefentrine in man involved administration of a 6-dose regimen over 60 hours in healthy volunteers which was commenced at 12 hours after completion of a 3-dose regimen of mefloquine or placebo. Plasma mefloquine concentrations from the time of addition of Artemether and Lumefentrine were not affected compared with a group which received mefloquine followed by placebo.

Pre-treatment with mefloquine had no effect on plasma concentrations of artemether or the artemether/dihydroartemisinin ratio but there was a significant reduction in plasma levels of lumefantrine, possibly due to lower absorption secondary to a mefloquine-induced decrease in bileproduction. Patients should be encouraged to eat at dosing times to compensate for the decrease inbioavailability.

Quinine:
A drug interaction study in healthy male volunteers showed that the plasma concentrations of lumefantrine and quinine were not affected when i.v. quinine (10 mg/kg BW over 2 hours) was given sequentially 2 hours after the last (sixth) dose of Artemether and Lumefentrine (so as to produce concurrent plasma peak levels of lumefantrine and quinine). Plasma concentrations of artemether and dihydroartemisinin (DHA) appeared to be lower. In this study, administration of Artemether and Lumefentrine to 14 subjects had no effect on QTc interval. Infusion of quininealone in 14 other subjects caused a transient prolongation of QTc interval, which was consistent with the known cardiotoxicity of quinine. This effect was slightly, but significantly, greater when quinine was infused after Artemether and Lumefentrine in 14 additional subjects. It would thus appear that the inherent risk of QTc prolongation associated with i.v. quinine was enhanced by prior administration of Artemether and Lumefentrine.

4.6 Pregnancy &Lactation

Pregnancy
There is insufficient data from the use of artemether and lumefantrine in pregnant women. In animal studies Artemether 80 mg and Lumefantrine 480 mg Tablets, as well as other artemisinin derivates, have been shown to cause post-implantation losses and serious birth defects when administered during the first trimester of pregnancy. Therefore, Artemether 80 mg and Lumefantrine 480 mg Tablets should not be used during the first trimester of pregnancy in situations where other suitable and effective anti-malarials are available. Nonetheless, it may be used when it is the only treatment immediately available.

Lactation
The amounts of artemether, dihydroartemisinin and lumefantrine in breast milk are small. Therefore, lactating women can receive artemisinin-based combination therapies for malaria treatment.

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 Adverse Effects

Cardiac disorders : Palpitations, Electrocardiogram QT prolonged
Nervous system disorders: Headache, Dizziness, Paraesthesia.
Respiratory, thoracic and mediastinal disorders: Cough.
Gastrointestinal disorders: Vomiting, Abdominal pain, Nausea, Diarrhoea.
Skin and subcutaneoustissue disorders: Rash, Pruritus, Myalgia.
Immune system disorders: Hypersensitivity.
Psychiatric disorders: Sleep disorders, Insomnia.

4.9 Overdose

In cases of suspected overdosage symptomatic and supportive therapy should be given asappropriate, which should include ECG and blood potassium monitoring.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties

Mechanism of action

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 malaria parasite, where they are thought to interfere with the conversion of haem, a toxic intermediate produced during hemoglobin 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 malaria parasite.

Pharmacodynamic effects:

Clinical Efficacy and Safety:

Artemether 80 mg and Lumefantrine 480 mg Tablets 80/480 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 malaria 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 malaria parasite. Artemether 80 mg and Lumefantrine 480 mg Tablets has been reported to have potent activity in terms of clearing gametocytes.

Resistance

By 2015, resistance to artemisinins emerged in Southeast Asia. Studies with Artemether 80 mg and Lumefantrine 480 mg Tablets in this region showed delayed parasite clearance (manifested as a higher proportion of patients with parasitemia on Day 3 after initiation of treatment), although overall efficacy as measured by cure rates after 28 days, remained high (WHO 2014). In Africa, only isolated reports on delayed parasite clearance are available and a clear trend towards resistance development was not observed.

<u>Treatment of Acute Uncomplicated P. falciparum Malaria</u>

The efficacy of Artemether 80 mg and Lumefantrine 480 mg Tablets 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% parasitemia) 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:

Table 2 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, 75thpercentile]**	**Year/ Study location**
A025[4]	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

[1] Efficacy cure rate based on blood smear microscopy

[2] mITT population

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

[4]Only the 6-dose regimen over 60 hours group data is presented

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. In 319 adult patients in whom gametocytes were present, the median time to gametocyte clearance with Artemether 80 mg and Lumefantrine 480 mg Tablets was 96 hours. Artemether 80 mg and Lumefantrine 480 mg Tablets is active against blood stages of *Plasmodium vivax*, but is not active against hypnozoites.

Paediatric population

Three studies have been conducted

Study A2403 was conducted in Africa in 310 infants and children aged 2 months to 9 years, weighing 5 kg to 25 kg, with an auxiliary temperature ≥37.5°C. Results of 28-day cure rate (PCR-corrected), median parasite clearance time (PCT), and fever clearance time (FCT) are reported in table 3 below.

Study B2303 was conducted in Africa in 452 infants and children, aged 3 months to 12 years, weighing 5 kg to <35 kg, with fever (≥37.5°C auxiliary or ≥38°C rectally) or history of fever in the

preceding 24 hours. This study compared crushed tablets and dispersible tablets. Results of 28-day cure rate (PCR-corrected), median parasite clearance time (PCT), and fever clearance time (FCT) for crushed tablets are reported in table 3 below.

Table 3 Clinical efficacy by weight for pediatric studies

Study No. **Weight category**	**Median PCT[1]** **[25th, 75th percentile]**	**PCR-corrected 28-day cure rate[2]n/N (%) in evaluable patients**
Study A2403		
5 - <10 kg	24 hours [24, 36]	145/149 (97.3)
10 - <15 kg	35 hours [24, 36]	103/107 (96.3)
15 -25 kg	24 hours [24, 36]	41/43 (95.3)
Study B2303[CT]		
5 - <10 kg	36 hours [24, 36]	65/69 (94.2)
10 - <15 kg	35 hours [24, 36]	174/179 (97.2)
15 -<25 kg	35 hours [24, 36]	134/140 (95.7)
25-35 kg	26 hours [24, 36]	30/31 (96.8)

[1] mITT population

[2] Efficacy cure rate based on blood smear microscopy

[CT] Artemether 80 mg and Lumefantrine 480 mg Tablets administered as crushed tablets

Study B2306, was a multi-centre, open-label, single-arm study conducted in 20 infants in Africa, Benin and Burkina Faso to evaluate the efficacy, safety and pharmacokinetics of dispersible tablets in infants aged >28 days and <5 kg of body weight, who were treated with one dispersible tablet (20 mg artemether/120 mg lumefantrine) given twice-daily for three days and followed up for six weeks (core follow-up) and at the age of 12 months (long-term follow-up).

Dispersible tablets were well tolerated with reported adverse events of mild to moderate severity. In the per protocol population, PCR-corrected cure rate at days 28 and 42 was 100% (95% CI: 79.4, 100). For important exposure results, see section 5.2. Although neurotoxicity was not observed in the patients in Study B2306, artemether has been associated with neurotoxicity in studies in rats and dogs, see section 5.3.

QT/QTc Prolongation:

Adults and children with malaria

For information on the risk of QT/QTc prolongation in patients see section 4.4

Healthy adults

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 was associated with prolongation of QTcF. 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.

In the adult/adolescent population included in clinical trials, 8 patients (0.8%) receiving experienced a QTcB >500 msec and 3 patients (0.4%) a QTcF>500 msec. Prolongation of QTcF interval >30 msec was observed in 36% of patients.

In clinical trials conducted in children with the 6-dose regimen, no patient had post-baseline QTcF>500 msec whereas 29.4% had QTcF increase from baseline >30 msec and 5.1% >60 msec. In clinical trials conducted in adults and adolescents with the 6-dose regimen, post-baseline QTcF

prolongation of >500 msec was reported in 0.2% of patients, whereas QTcF increase from baseline >30 msec was reported in 33.9% and >60 msec in 6.2% of patients.

In the infant/children population included in clinical trials, 3 patients (0.2%) experienced a QTcB >500 msec. No patient had QTcF>500 msec. Prolongation of QTcF intervals >30 msec was observed in 34% of children weighing 5-10 kg, 31% of children weighing 10-15 kg and 24% of children weighing 15-25 kg, and 32% of children weighing 25-35 kg.

5.2 Pharmacokinetic properties

Pharmacokinetic characterization of Artemether and lumefantrine is limited by the lackof an intravenous formulation, and the very high inter-and intra-subject variability ofartemether and lumefantrine plasma concentrations and derived pharmacokinetic parameters (AUC, Cmax).

i) Absorption:

During acute P. falciparum malaria infection, there is marked intra- and inter-patient variability with regard to Lumefantrine absorption, probably because of differences in food intake. Food enhances the absorption of both artemether and lumefantrine. In healthy volunteers when it was taken after a high-fat meal the relative bioavailability of artemether was more than doubled, and that of lumefantrine increased sixteen-fold compared with fasted conditions. Likewise, in patients with malaria, food increases the absorption of lumefantrine, although to a lesser extent (approximately two-fold), most probably due to the lower fat content of the food eaten by acutely ill patients. Acutely illpatients are reluctant to eat and tend to avoid high-fat foods. In order to improve bioavailability, patients should be encouraged to take it with a normal diet as soon as food can be tolerated.

ii) Distribution:

Artemether and lumefantrine are both highly bound to human serum proteins *in vitro* (95.4% and 99.7%, respectively). Dihydroartemisinin is also bound to human serumproteins (47-76%).

Metabolism

Artemether is rapidly and extensively metabolised (substantial first-pass metabolism) both *in vitro* and in humans. Human liver microsomes metabolise artemether to the biologically active main metabolite dihydroartemisinin (demethylation), predominantly through the isoenzyme CYP3A4/5. This metabolite has also been detected in humans *in vivo*.

Dihydroartemisinin is further converted to inactive metabolites. The pharmacokinetics of artemether in adults is time-dependent. During repeated administration of artemether plasma 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. Artemether and dihydroartemisinin were reported to have a mild inducing effect on CYP3A4 activity.The clinical evidence of induction is consistent with the *in vitro* data. Lumefantrine is N-debutylated, mainly by CYP3A4, in human liver microsomes. *In vivo* in animals (dogs and rats), glucuronidation of lumefantrine takes place directly and after oxidative biotransformation. In humans, the exposure to lumefantrine increases with repeated administration of Lumefantrine over the 3-day treatment period, consistent with the slow elimination of the compound (see section 5.2 Elimination). Systemic exposure to the metabolite desbutyl-lumefantrine, for which the *in vitro* antiparasitic effect is 5 to 8fold higher than that for 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

Elimination

Artemether and dihydroartemisinin are rapidly cleared from plasma with a terminal half-life of about 2 hours. Lumefantrine is eliminated very slowly with an elimination half-life of 2 to 6 days. Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of Artemether and Lumefentrine .

Limited urinary excretion data are available for humans. In 16 healthy volunteers, neither lumefantrine nor artemether was found in urine after administration of Artemether and Lumefentrine, and only traces of dihydroartemisinin were detected (urinary excretion of dihydroartemisinin amounted to less than 0.01% of the artemether dose).

In animals (rats and dogs), no unchanged artemether was detected in faeces and urine due to its rapid and extensive first-pass metabolism, but numerous metabolites (partly identified) have been detected in faeces, bile and urine. Lumefantrine was excreted unchanged in faeces and with traces only in urine. Metabolites of lumefantrine were eliminated in bile/faeces.

Special population: not done

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.

Neurotoxicity

Studies in dogs and rats have shown that intramuscular injections of artemether resulted in brain lesions mainly in brainstem nuclei. Changes observed mainly in brainstem nuclei included chromatolysis, eosinophilic cytoplasmic granulation, spheroids, apoptosis and dark neurons. Lesions were observed in rats dosed for at least 7 days and dogs for at least 8 days, but lesions were not observed after shorter intramuscular treatment courses or after oral dosing. The estimated artemether 24 h AUC after 7 days of dosing at the no observed effect level is approximately 7-fold greater or more than the estimated artemether 24 h AUC in adult humans. The hearing threshold was affected at 20 dB by oral artemether administration to dogs at a dose of about 29 times the highest artemether clinical dose (160 mg/day) based on body surface area comparisons. Most nervous system disorder adverse events in the studies of the 6-dose regimen were mild in intensity and resolved by the end of the study.

Mutagenicity

Artemether and lumefantrine were not genotoxic/clastogenic based on *in vitro* and *in vivo* testing.

Carcinogenicity

Carcinogenicity studies were not conducted.

Reproductive toxicity studies

Embryotoxicity was observed in rat and rabbit reproductive toxicity studies conducted with artemether, a derivative of artemisinin. Artemisinins are known to be embryotoxic. Lumefantrine alone caused no sign of reproductive or development toxicity at doses up to 1,000 mg/kg/day in rats and rabbits, doses which are at least 10 times higher than the daily human dose based on body surface area comparisons.

Reproductive toxicity studies performed with the artemether-lumefantrine combination caused maternal toxicity and increased post-implantation loss in rats and rabbits.

Artemether caused increases in post-implantation loss and teratogenicity (characterised as a low incidence of cardiovascular and skeletal malformations) in rats and rabbits. The embryotoxicartemether dose in the rat yields artemether and dihydroartemisinin exposures similar to those achieved in humans based on AUC.

Fertility

Artemether-lumefantrine administration yielded altered sperm motility, abnormal sperm, reduced epididymal sperm count, increased testes weight, and embryotoxicity; other reproductive effects (decreased implants and viable embryos, increased preimplantation loss) were also observed. The no

adverse effect level for fertility was 300 mg/kg/day. The relevance to this finding in humans is unknown.

Juvenile toxicity studies

A study investigated the neurotoxicity of oral artemether in juvenile rats. Mortality, clinical signs and reductions in body weight parameters occurred most notably in younger rats. Despite the systemic toxicity noted, there were no effects of artemether on any of the functional tests performed and there was no evidence of a direct neurotoxic effect in juvenile rats.

Very young animals are more sensitive to the toxic effect of artemether than adult animals. There is no difference in sensitivity in slightly older animals compared to adult animals. Clinical studies have established the safety of artemether and lumefantrine administration in patients weighing 5 kg and above.

Cardiovascular Safety Pharmacology

In toxicity studies in dogs at doses ≥600 mg/kg/day, there was some evidence of prolongation of the QTc interval (safety margin of 1.3-fold to 2.2-fold for artemether using calculated free Cmax), at higher doses than intended for use in man. In vitro hERG assays showed a safety margin of >100 for artemether and dihydroartemisinin. The hERG IC_{50} was 8.1 µM for lumefantrine and 5.5 µM for its desbutyl metabolite.

Based on the available non-clinical data, a potential for QTc prolongation in the human cannot be discounted. For effects in the human see sections 4.3, 4.4 and 5.1.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

List of Excipients:

Micro crystalline cellulose powder 101
Cross Carmellos Sodium
Iso Propyl Alcohol
Polysorbate 80
Aerosil
Cross Carmellos Sodium
Magnesium Stearate
HPMC

6.2 Incompatibilities

Not Applicable

6.3 Shelf Life

36 Months.

6.4 Special precautions for storage:

Do not store above 30°C. Protect from light.
Keep the medicine out of reach of children.

6.5 Nature and contents of container

6 tablets packed in an ALU-PVC Blister pack along with leaflet

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

Manufactured for:
CHI PHARMACEUTICAL LIMITED
No 14 CHIVITA AVENUE, AJAO ESTATE,
ISOLO, LAGOS
NIGERIA.

Manufactured on contract by:

SAGAR VITACEUTICALS NIGERIA LIMITED.
COMMERCIAL DISTRICT B BLOCK, PLOT 6,
NEW MAKUN CITYKM 53/55, LAGOS-IBADAN
EXPRESSWAY.SAGAMU, OGUN STATE
NIGERIA.