National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

1. NAME OF THE MEDICINAL PRODUCT

MALQUIT 40/240 (Artemether and Lumefantrine Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Artemether 40 mg

Lumefantrine 240 mg Excipients Q.S.

3. PHARMACEUTICAL FORM

Film coated Tablets

4. Clinical particulars

4.1 Therapeutic indications

- Artemether and Lumefantrine Tablets are indicated for the treatment of acute uncomplicated Plasmodium falciparum malaria in adults, children and infants of 5 kg and above.
- Consideration should be given to official guidance regarding the appropriate use of antimalarial agents.

Posology and method of administration

For oral administration

Body Weight (Kg)	**Age (Yrs)**	**Total Tablets**	**DOSAGE REGIMEN**					
			Day 1		**Day 2**		**Day 3**	
			0hrs	8hrs	24hrs	36hrs	48hrs	60hrs
5-14	<3	6	1	1	1	1	1	1
15-24	>3- 9	12	2	2	2	2	2	2
25-34	>9-14	18	3	3	3	3	3	3
>35	>14	24	4	4	4	4	4	4

4.2 Contraindications

Artemether and Lumefantrine Tablets is contraindicated in:

- patients with known hypersensitivity to the active substances or to any of the excipients.
- patients with severe malaria according to WHO definition*.
- patients who are taking any drug which is metabolised by the cytochrome enzyme CYP2D6 (e.g. metoprolol, imipramine, amitriptyline, clomipramine).

- patients with a family history of sudden death or of congenital prolongation of the QTc interval on electrocardiograms, or with any other clinical condition known to prolong the QTc interval.
- patients taking drugs that are known to prolong the QTc interval (proarrhythmic). These drugs include:
- antiarrhythmics of classes IA and III,
- neuroleptics, antidepressive agents,
- certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole and triazole antifungal agents, certain non-sedating antihistamines (terfenadine, artemizole)
- cisapride.
- flecainide

- patients with a history of symptomatic cardiac arrhythmias or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricular ejection fraction.
- patients with disturbances of electrolyte balance e.g. hypokalemia or hypomagnesemia.
- patients taking drugs that are strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's wort (Hypericum perforatum).

*Presence of one or more of the following clinical or laboratory features:

Clinical manifestation: Prostration; impaired consciousness or unarousable coma; failure to feed; deep breathing, respiratory distress (acidotic breathing); multiple convulsions; circulatory collapse or shock; pulmonary edema (radiological); abnormal bleeding; clinical jaundice; hemoglobinuria

Laboratory test: Severe normocytic anemia; hemoglobinuria; hypoglycemia; metabolic acidosis; renal impairment; hyperlactatemia; hyperparasitemia).

4.3 Special warnings and precautions for use

Artemether and Lumefantrine Tablets must not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarials are available .

Artemether and Lumefantrine Tablets have 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 and Lumefantrine 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 and Lumefantrine 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 and Lumefantrine Tablets.

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

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

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

Artemether and Lumefantrine Tablets are not indicated and have not been evaluated for prophylaxis.

Artemether and Lumefantrine Tablets should be used cautiously in patients on ARTs since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of Artemether and Lumefantrine Tablets,.

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

Caution is recommended when combining Artemether and Lumefantrine 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 and Lumefantrine Tablets.

Caution is recommended when combining Artemether and Lumefantrine Tablets with hormonal contraceptives. Artemether and Lumefantrine 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.

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.

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 and Lumefantrine Tablets in patients with renal impairment is recommended. Caution is advised when administering Artemether and Lumefantrine 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. No dose adjustment is recommended for patients with mild to moderate hepatic impairment. Caution is advised when administering Artemether and Lumefantrine Tablets to patients with severe hepatic impairment. In these patients, ECG and blood potassium monitoring is advised.

Elderly

There is no information suggesting that the dosage in patients over 65 years of age should be different than in younger adults.

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 and Lumefantrine Tablets. In the absence of

carcinogenicity study data, and due to lack of clinical experience, more than two courses of Artemether and Lumefantrine Tablets cannot be recommended.

4.4 Interaction with other medicinal products and other forms of interaction

Interaction with drugs that are known to prolong the QTc interval

Artemether and Lumefantrine Tablets is contraindicated with concomitant use of drugs (they may cause prolonged QTc interval and Torsade de Pointes) 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, flecainide

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 Lumefantrine Tablets 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.

Interaction with strong inducers of CYP3A4 such as rifampin

Oral administration of rifampin (600 mg daily), a strong CYP3A4 inducer, with Artemether and Lumefantrine Tablets Tablets (6-dose regimen over 3 days) in six HIV-1 and tuberculosis coinfected 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 Lumefantrine Tablets alone. Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's Wort is contraindicated with Artemether and Lumefantrine Tablets.

Inducers should not be administered at least one month after Artemether and Lumefantrine Tablets administration, unless critical to use as judged by the prescriber.

Concomitant use not recommended

Interaction with other antimalarial drugs

Data on safety and efficacy are limited, and Artemether and Lumefantrine Tablets should therefore not be given concurrently with other antimalarials unless there is no other treatment option.

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

Mefloquine

A drug interaction study with Artemether and Lumefantrine Tablets in man involved administration of a 6-dose regimen over 60 hours in healthy volunteers which 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 Lumefantrine Tablets 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 bile production. Patients should be encouraged to eat at dosing times to compensate for the decrease in bioavailability.

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 Lumefantrine Tablets (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 Lumefantrine Tablets to 14 subjects had no effect on QTc interval. Infusion of quinine alone 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 Lumefantrine Tablets 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 Lumefantrine Tablets.

Concomitant use requiring caution

Interactions affecting the use of Artemether and Lumefantrine Tablets

Interaction with CYP3A4 inhibitors

Both artemether and lumefantrine are metabolised predominantly by the cytochrome enzyme CYP3A4, but do not inhibit this enzyme at therapeutic concentrations.

Ketoconazole

The concurrent oral administration of ketoconazole with Artemether and Lumefantrine Tablets 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. Based on this study, dose adjustment of Artemether and Lumefantrine Tablets is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors.

Artemether and Lumefantrine Tablets should be used cautiously with drugs that inhibit CYP3A4 and are contraindicated with drugs which additionally are known to prolong QTc, due to potential for increased concentrations of lumefantrine which could lead to QT prolongation.

Grapefruit juice

Administration of artemether with grapefruit juice in healthy adult subjects resulted in an approximately two-fold increase in systemic exposure to the parent drug. Grapefruit juice should be used cautiously during Artemether and Lumefantrine Tablets treatment.

Interaction with weak to moderate inducers of CYP3A4

When Artemether and Lumefantrine Tablets are co-administered with moderate inducers of CYP3A4, it may result in decreased concentrations of artemether and/or lumefantrine and loss of antimalarial efficacy .

Interaction with antiretroviral drugs such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors

Both artemether and lumefantrine are metabolized by CYP3A4. Anti-retroviral drugs (ARTs), such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, are known to have variable patterns of inhibition, induction or competition for CYP3A4. Artemether and Lumefantrine Tablets should be used cautiously in patients on ARTs since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of Artemether and Lumefantrine Tablets, and increased lumefantrine concentrations may cause QT prolongation.

Lopinavir/ ritonavir

In a clinical study in healthy volunteers, lopinavir/ritonavir decreased the systemic exposures to artemether and DHA by approximately 40% but increased the exposure to

lumefantrine by approximately 2.3- fold. Exposures to lopinavir/ritonavir were not significantly affected by concomitant use of Artemether and Lumefantrine Tablets.

Nevirapine

In a clinical study in HIV-infected adults, nevirapine significantly reduced the median Cmax and AUC of artemether by approximately 61% and 72%, respectively and reduced the median Cmax and AUC of dihydroartemisinin by approximately 45% and 37%, respectively. Lumefantrine Cmax and AUC were non-significantly reduced by nevirapine. Artemether/lumefantrine reduced the median Cmax and AUC of nevirapine by approximately 43% and 46% respectively.

Efavirenz

Efavirenz decreased the exposures to artemether, DHA, and lumefantrine by approximately 50%, 45%, and 20%, respectively. Exposures to efavirenz were not significantly affected by concomitant use of Artemether and Lumefantrine Tablets.

Interactions resulting in effects of Artemether and Lumefantrine Tablets on other drugs

Interaction with drugs metabolized by CYP450 enzymes

When Artemether and Lumefantrine Tablets are co-administered with substrates of CYP3A4 it may result in decreased concentrations of the substrate and potential loss of substrate efficacy. 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 of drugs that are predominantly metabolised by these enzymes.

Interaction with hormonal contraceptives

In vitro, the metabolism of ethinyl estradiol and levonorgestrel was not induced by artemether, DHA, or lumefantrine. However, artemether has been reported to weakly induce, in humans, the activity of CYP2C19, CYP2B6, and CYP3A. Therefore, Artemether and Lumefantrine Tablets

may potentially reduce the effectiveness of hormonal contraceptives. 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 .

Drug-food/drink interactions

Artemether and Lumefantrine Tablets should be taken with food or drinks rich in fat such as milk as the absorption of both artemether and lumefantrine is increased.

Grapefruit juice should be used cautiously during Artemether and Lumefantrine Tablets treatment.

4.5 Pregnancy and Lactation

Women 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

Pregnancy

There is insufficient data from the use of artemether and lumefantrine in pregnant women. Based on animal data, Artemether and Lumefantrine Tablets are suspected to cause serious birth defects when administered during the first trimester of pregnancy Reproductive studies with artemether have shown evidence of post-implantation losses and teratogenicity in rats and rabbits. Other artemisinin derivatives have also demonstrated teratogenic potential with an increased risk during early gestation.

Safety data from an observational pregnancy study of approximately 500 pregnant women who were exposed to Artemether and Lumefantrine Tablets (including a third of patients who were exposed in the first trimester), and published data of another over 500 pregnant women who were exposed to artemether- lumefantrine (including over 50 patients who were exposed in the first trimester), as well as published data of over 1,000 pregnant women who were exposed to artemisinin derivatives, did not show an increase in adverse pregnancy outcomes or teratogenic effects over background rates.

Artemether and Lumefantrine Tablets treatment must not be used during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available. However, it should not be withheld in life-threatening situations, where no other effective antimalarials are available. During the second and third trimester, treatment should only be considered if the expected benefit to the mother outweighs the risk to the foetus.

Lactation

Animal data suggest excretion into breast milk but no data are available in humans. Women taking Artemether and Lumefantrine Tablets should not breast-feed during their treatment. Due to the long elimination half-life of lumefantrine (2 to 6 days), it is recommended that breast-feeding should not resume until at least one week after the last dose of Artemether and Lumefantrine Tablets unless potential benefits to the mother and child outweigh the risks of Artemether and Lumefantrine Tablets treatment.

Fertility

There is no information on the effects of Artemether and Lumefantrine Tablets on human fertility.

4.6 Effects on ability to drive and use machines

Patients receiving Artemether and Lumefantrine Tablets should be warned that dizziness or fatigue/asthenia may occur in which case they should not drive or use machines.

4.7 Undesirable effects

The safety of Artemether and Lumefantrine Tablets has been evaluated in 20 clinical trials with more than 3500 patients. A total of 1810 adults and adolescents above 12 years of age as well as 1788 infants and children of 12 years of age and below have received Artemether and Lumefantrine Tablets in clinical trials.

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 MedDRA 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).

	Adults and adolescents above 12 years of age	**Infants and children of 12 years of age and below (incidence estimates)**
Immune system disorders		
Hypersensitivity	Not known	Rare
Metabolism and nutrition disorders		
Decreased appetite	Very common	Very common (16.8 %)
Psychiatric disorders		
Sleep disorders	Very common	Common (6.4 %)
Insomnia	Common	Uncommon
Nervous system disorders		
Headache	Very common	Very common (17.1 %)
Dizziness	Very common	Common (5.5 %)
Paraesthesia	Common	--
Ataxia, hypoaesthesia	Uncommon	--
Somnolence	Uncommon	Uncommon
Clonus	Common	Uncommon
Cardiac disorders		
Palpitations	Very common	Common (1.8 %)
Electrocardiogram QT prolonged	Common	Common (5.3 %)
Respiratory, thoracic and mediastinal disorders		
Cough	Common	Very common (22.7 %)
Gastrointestinal disorders		

Vomiting	Very common	Very common (20.2 %)
Abdominal pain	Very common	Very common (12.1 %)
Nausea	Very common	Common (6.5 %)
Diarrhoea	Common	Common (8.4 %)
Hepatobiliary disorders		
Liver function tests increased	Uncommon	Common (4.1 %)
Skin and subcutaneous tissue disorders		
Rash	Common	Common (2.7 %)
Pruritus	Common	Uncommon
Urticaria	Uncommon	Uncommon
Angioedema*	Not known	Not known
Musculoskeletal and connective tissue disorders		
Arthralgia	Very common	Common (2.1 %)
Myalgia	Very common	Common (2.2 %)
General disorders and administration site conditions		
Asthenia	Very common	Common (5.2 %)
Fatigue	Very common	Common (9.2 %)
Gait disturbance	Common	--

*: 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.

4.8 Overdose

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

PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: antimalarials, blood schizonticide, ATC code: P01 BF01.
Pharmacodynamic effects

Artemether and Lumefantrine Tablets comprise 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 hemozoin, 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

5.2 Pharmacokinetic properties

Pharmacokinetic characterisation of Artemether and Lumefantrine Tablets is limited by the lack of an intravenous formulation, and the very high inter-and intra-subject variability of artemether and lumefantrine plasma concentrations and derived pharmacokinetic parameters (AUC, Cmax).

Absorption

Artemether is absorbed fairly rapidly and dihydroartemisinin, the active metabolite of artemether, appears rapidly in the systemic circulation with peak plasma concentrations of both compounds reached about 2 hours after dosing. Mean Cmax and AUC values of artemether ranged between 60.0-104 ng/mL and 146-338 ng·h/mL, respectively, in fed healthy adults after a single dose of Artemether and Lumefantrine Tablets, 80 mg artemether/480 mg lumefantrine. Mean Cmax and AUC values of dihydroartemisinin ranged between 49.7-104 ng/mL and 169-308 ng·h/mL, respectively. Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentration (mean between 5.10-9.80 µg/mL) about 6-8 hours after dosing. Mean AUC values of lumefantrine ranged between 108 and 243 µg·h/mL. Food enhances the absorption of both artemether and lumefantrine: in healthy volunteers the relative bioavailability of artemether was increased more than two-fold, and that of lumefantrine sixteen-fold compared with fasted conditions when Artemether and Lumefantrine Tablets was taken after a high-fat meal.

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 (assuming 100% absorption after a high-fat meal, the amount absorbed under fasted conditions

would be <10% of the dose). Patients should therefore be encouraged to take the medication with a normal diet as soon as food can be tolerated.

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 serum proteins (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 and Lumefantrine Tablets, 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. 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 described in section 4.5

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 Artemether and Lumefantrine Tablets over the 3-day treatment period, consistent with the slow elimination of the compound . Systemic exposure to the metabolite desbutyl-lumefantrine, for which the in vitro antiparasitic effect is 5 to 8 fold 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 Lumefantrine Tablets.

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 Lumefantrine Tablets, 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

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. Changes observed mainly in brainstem nuclei included chromatolysis, eosinophilic cytoplasmic granulation, spheroids, apoptosis and dark neurons. Lesions were observed in rats dosed with artemether at 25 mg/kg for 7 or 14 days and dogs dosed at 20 mg/kg for 8 days or longer, but lesions were not observed after shorter courses of drug or after oral dosing. The estimated artemether 24 h AUC after 7 days of dosing at the no observed effect level (10 mg/kg/day given intramuscularly) is approximately 7- fold greater than the estimated artemether 24 h AUC in humans on day 1 of the standard 3-day oral treatment regimen; oral exposure in humans decreases on subsequent days, thus the exposure margin increases. Dogs dosed orally with 143 mg/kg artemether showed a statistically measureable effect on the hearing threshold at 20 dB. This dose is equivalent

to 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
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. 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.

Fertility

After artemether-lumefantrine administration for 10 weeks in males and 2 weeks in females, reduced fertility occurred at 1000 mg/kg/day where altered sperm motility, abnormal sperm, reduced epididymal

sperm count, increased testes weight, and embryotoxicity and other reproductive effects (decreased implants and viable embryos, increased preimplantation loss) were also observed. General toxicity was observed in males and females at doses ≥ 300 mg/kg/day. 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 specific study to investigate the neurotoxicity of artemether in juvenile rats involved oral administration of artemether during four different dosing intervals, at doses of 30 or 80 mg/kg/day on postpartum days 7 to 13, and at doses of 30 or 120 mg/kg/day on postpartum days 14 to 21, 22 to 28, or 29 to 36. Mortality, clinical signs and reductions in body weight parameters occurred most notably during the first two dosing intervals. 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 of orally administered artemether on the brain of juvenile rats.
Juvenile studies in the rat indicate that very young animals (aged 7-21 days) are more sensitive to artemether than adult animals. There is no difference in sensitivity in slightly older (3-5 weeks of age) animals following 13 weeks of artemether/lumefantrine administration. Consistent with the later data, 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 only, 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 an in vitro assay of HERG channels stably expressed in HEK293 cells, lumefrantrine and the main metabolite desbutyl-lumefantrine showed some inhibitory potential in one of the currents responsible for cardiac repolarization. The potency was lower than the other antimalarial drugs tested. 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).
Additional studies were performed to evaluate the in vitro effects of artemether and its active metabolite, dihydroartemisinin, on the HERG current. At concentrations that produced significant inhibition, the safety margins for artemether and dihydroartemisinin are greater than 100 if they are estimated using the total therapeutic concentration at Cmax or greater than 1000 if they are estimated using the calculated free Cmax. Based on the available non-clinical data, a potential for QTc prolongation in the human cannot be discounted. For effects in the human.

6.0 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose	BP
Lactose	BP
Sodium Starch Glycolate	BP
Idacol Tartrazine supra	In-House
Povidone	BP
Methylparaben	BP
Propylparaben	BP
Maize Starch	BP
Magnesium Stearate	BP
Croscarmellose Sodium	BP
Colloidal Anhydrous Silica	BP
Hydroxypropylmethyl Cellulose	BP
Purified Talc	BP
Polyethylene Glycol - 4000	BP
Titanium Dioxide	BP
Methylene Chloride	BP
Isopropyl Alcohol	BP

6.2 Incompatibilities

None

6.3 Shelf life

36months

7.1 Special precautions for storage

Store in a dark, dry place, Not exceeding 30℃ temp.

7.2 Nature and contents of container

2 x 6 Tablets Alu-PVC Blister Pack

7.3 Special precautions for disposal

Not applicable

8.1 APPLICANT

JAWA INTERNATIONAL LTD.

Jawa House Compound,

Plot 6 Abimbola Way,

Isolo Industrial Estate,

Isolo, Lagos, Nigeria

E-mail: spjawasil@gmail.com

8.2 MANUFACTURER:

SWISS PHARMA PVT. LTD.

3709, G.I.D.C. Phase IV,

Vatva, Ahmedabad –382445,

Gujarat,India

www.swisspharma.in