1.5.1 PRESCRIBING INFORMATION (SUMMARY OF PRODUCT CHARATERISTICS)

1. NAME OF THE MEDICINAL PRODUCT

LAMITAR AM (Lumefantrine and Artemether Tablets 120mg + 20mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:

Lumefantrine	120 mg
Artemether	20 mg
Excipients	q.s.

For full list of Excipients, see Section 6.1

3. PHARMACEUTICAL FORM

Uncoated Tablets.
Yellow colored, round shaped, flat, beveled edged uncoated tablets with one side plain andbreakline on other side.

4. CLINICAL PARTICULARS

4.1.Therapeutic Indications

Lumefantrine and Artemether Tablets is indicated for the treatment of acute uncomplicated
Plasmodium falciparum malaria in adult, children and infants of 5kg and above.

4.2.Posology and Method of Administration

To increase absorption, Lumefantrine and Artemether Tablets should be taken with food or a milky drink. If patients are unable to tolerate food, Lumefantrine and Artemether Tablets should be administered with water, but the systemic exposure may be reduced. Patients who vomit within 1 hour of taking the medication should repeat the dose.

For administration to small children and infants, the tablets/s may be crushed.

Adults and children weighing 35kg and above

For patients of 12 years of age and above and of 35 kg body weight and above, a course of treatment comprises six doses of four tablets i.e., total of 24 tablets, given over a period of 60 hours as follows:

The first dose of four tablets, given at the time of initial diagnosis, should be followed by fivefurther doses of four tablets given at 8, 24, 36, 48 and 60 hours thereafter.

Children and infants weighing 5kg to less than 35kg

A six-dose regimen is recommended with 1 to 3 tablets per dose, depending on body weight:

5 to less than 15 kg body weight: The first dose of one tablet, given at the time of initialdiagnosis, should be followed by five further doses of one tablet given at 8, 24, 36, 48 and 60 hours thereafter.

15 to less than 25 kg bodyweight: The first dose of two tablets, given at the time of initial diagnosis, should be followed by five further doses of two tablets given at 8, 24, 36, 48 and 60 hours thereafter.

25 to less than 35 kg bodyweight: The first dose of three tablets, given at the time of initial diagnosis, should be followed by five further doses of three tablets given at 8, 24, 36, 48 and 60 hours thereafter.

4.3.Contra-indications

Lumefantrine and Artemether 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., flecainide, metoprolol, imipramine, amitryptyline, clomipramine).
• Patients with a family history of sudden death or of congenital prolongation of the QTc intervalon electrocardiograms, or with any other clinical condition known to prolong the QTc interval.
• Patients with a history of symptomatic cardiac arrhythmias or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricle ejection fraction.
• Patients with disturbances of electrolyte balance eg hypokalemia or hypomagnesemia
• Patients taking drugs that are strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's wort (Hypericum perforatum).
• Patients taking drugs that are known to prolong the QTc interval. 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, astemizole)
- Cisapride
- Flecainide

* 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; hemoglobuniuria; hypoglycemia; metabolic acidosis;renal impairment; hyperlactatemia; hyperparasitemia.

4.4.Special Warnings and Precautions for Use

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

Lumefantrine and Artemether 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, Lumefantrine and Artemether Tablets should not be given concurrently with any other anti-malarial agent unless there is no other treatment option.

If a patient deteriorates whilst taking Lumefantrine and Artemether 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 Lumefantrine and Artemether Tablets.

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

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

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

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

Lumefantrine and Artemether 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 Lumefantrine and Artemether.

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

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

Caution is recommended when combining Lumefantrine and Artemether with hormonal contraceptives. Lumefantrine and Artemether 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 Lumefantrine and Artemether in patients with renal impairment is recommended. Caution is advised when administering Lumefantrine and Artemether 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. Nodose adjustment is recommended for patients with mild to moderate hepatic impairment.

Elderly

There is no information suggesting that the dosage in patients over 65 years of age should bedifferent 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 Lumefantrine and Artemether. In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of Lumefantrine and Artemether cannot be recommended.

4.5.Interaction with Other Medicinal Products and Other Forms of Interaction
Contraindications of concomitant use

Interaction with drugs that are known to prolong the QTc interval
Lumefantrine and Artemether 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 antihistaminics (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 Lumefantrine and Artemether 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 Lumefantrine and Artemether 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 Lumefantrine and Artemether alone. Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's Wort is contraindicated with Lumefantrine and Artemether.

Inducers should not be administered at least one month after Lumefantrine and Artemether 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 Lumefantrine and Artemether should therefore not be given concurrently with other antimalarials unless there is no other treatment option.

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

Mefloquine

A drug interaction study with Lumefantrine and Artemether 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 Lumefantrine and Artemether 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 Lumefantrine and Artemether (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 Lumefantrine and Artemether 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 Lumefantrine and Artemether 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 Lumefantrine and Artemether.

Concomitant use requiring caution

Interactions affecting the use of Lumefantrine and Artemether

Interaction with CYP3A4 inhibitors

Both artemether and lumefantrine are metabolised predominantly by the cytochrome enzymeCYP3A4, but do not inhibit this enzyme at therapeutic concentrations.

Ketoconazole

The concurrent oral administration of ketoconazole with Lumefantrine and Artemether 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 Lumefantrine and Artemether is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors. Lumefantrine and Artemether 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.

Grape fruit 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 Lumefantrine and Artemether treatment.

Interaction with weak to moderate inducers of CYP3A4

When Lumefantrine and Artemether is 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 anti-retroviral 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. Lumefantrine and Artemether 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 Lumefantrine and Artemether, 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 Lumefantrine and Artemether.

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 Lumefantrine and Artemether.

Interactions resulting in effects of Lumefantrine and Artemether on other drugs

Interaction with drugs metabolized by CYP450 enzymes
When Lumefantrine and Artemether is 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 wasgenerally 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, Lumefantrine and Artemether 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 nonhormonal method of birth control for about one month.

Drug-food/drink interactions
Lumefantrine and Artemether 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 Lumefantrine and Artemether treatment.

4.6.Fertility, Pregnancy and Lactation

Pregnancy

Based on animal data, Lumefantrine and Artemether is 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 duringearly gestation.

Safety data from an observational pregnancy study of approximately 500 pregnant

women who were exposed to Lumefantrine and Artemether (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.

Lumefantrine and Artemether treatment must not be used during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available. However, it should notbe 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 benefitto the mother outweighs the risk to the foetus.

Women of childbearing potential

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.

Lactation

Animal data suggest excretion into breast milk but no data are available in humans. Women taking Lumefantrine and Artemether 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 breastfeeding should not resume until at least one week after the last dose of Lumefantrine and Artemether Tablets unless potential benefits to the mother and child outweigh the risks of Lumefantrine and Artemether Tablets treatment.

Fertility

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

4.7.Effects on Ability to Drive and Use Machines

Patients receivingLumefantrine and Artemether shouldbe warned that dizziness or fatigue/asthenia may occur in which case they should not drive or use machines.

4.8.Undesirable Effects

Adverse reactions are ranked under headings of frequency, the most frequent first, using thefollowing convention:
Very common (≥1/10)
common (≥1/100, <1/10)
uncommon (≥1/1,000,
<1/100) rare (≥1/10,000,

<1/1,000)
very rare (<1/10,000)

Immune system disorders
Rare: Hypersensitivity

Metabolism and nutrition disorders
Very common: Decreased appetite

Psychiatric disorders
Very common: Sleep disorders Common: Insomnia

Nervous system disorders
Very common: Headache, dizziness Common: Paraesthesia, clonus
Uncommon: Ataxia, hypoaesthesia, somnolence

Cardiac disorders
Common: Electrocardiogram QT prolongedVery Common: Palpitations

Respiratory, thoracic and mediastinal disorders
Common: Cough

Gastrointestinal disorders
Very common: Vomiting, Abdominal pain, NauseaCommon: Diarrhoea

Hepatobiliary disorders
Uncommon: Liver function tests increased

Skin and subcutaneous tissue disorders
Common: Pruritus, rash
Uncommon: Urticaria
Not known: Angioedema

Musculoskeletal and connective tissue disorders
Very common: Arthralgia, myalgia

General disorders and administration site conditions

Very common: Asthenia, fatigue Common: Gait disturbance

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

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.Pharmacodynamics Properties:

Pharmacotherapeutic group: antimalarials, blood schizontocide, ATC code: P01 BF01.

Pharmacodynamic effects

Lumefantrine and Artemether 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.

5.2.Pharmacokinetics Properties

Pharmacokinetic characterisation of Lumefantrine and Artemether 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 Lumefantrine and Artemether, 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 Lumefantrine and Artemether 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), 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 artemether/dihydroartemisinin AUC ratio is 1.2 after a single dose and 0.3 after 6 doses given over 3 days. In-vivo data indicate that artemisinins have some capacity to induce cytochrome isoenzymes CYP2C19 and CYP3A4.

Lumefantrine is N-debutylated, mainly by CYP3A4, in human liver microsomes; the N-debutylated metabolite of lumefantrine is active. 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 Lumefantrine and Artemether Tablets.

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

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 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 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

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 7mg/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 (characterized 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 and25 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 andin 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 ≥ 300mg/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 post-partum days 7 to 13, and at doses of 30 or 120 mg/kg/day on post-partum days14 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 usingcalculated 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 cardiacrepolarization. The potency was lower than the other antimalarial drugs tested. From the estimated IC values, the order of potency of HERG current block was halofantrine (IC =0.04 μM) >chloroquine (2.5 μM) >mefloquine 2.6 μM) >desbutyllumefantrine (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.

6. PHARMACEUTICAL PARTICULARS

6.1.List of Excipients

Lumefantrine Granules

Croscarmellose sodium, Gelatin, Polysorbate 80 and Purified Water.

Artemether Granules

Mannitol, Sodium Sulphite, Ethyl Cellulose 10cp, Shellac Bleach (Regular), Isopropyl Alcohol,Sodium Hydroxide and Purified water.

Lumefantrine and Artemether Tablet

Sodium Carbonate anhydrous, Sodium Lauryl Sulphate, Croscarmellose Sodium, Purified Talcand Magnesium Stearate.

6.2.Incompatibilities

Not applicable.

6.3.Shelf Life

30 Months

6.4.Special Precautions for Storage

Store below 30°C. Protect form moisture.

6.5. Nature and Contents of Container

Alu Alu Blister pack of 8 tablets using Cold form laminate for Alu Alu blister and PrintedAluminium Foil.

6.6. Special precautions for disposal and other handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

Ind-Swift Limited

8. MARKETING AUTHORISATION NUMBER

TAN 21 HM 0122

9. DATE OF FIRST REGISTRATION /RENEWAL OF THE REGISTRATION

29th March 2021

10. DATE OF REVISION OF THE TEXT