MODULE 1	ADMINISTRATIVE INFORMATION AND PRODUCT INFORMATION	
BRAND NAME	ZULIMAL	
GENERIC NAME	Artemether 20mg and Lumefantrine 120mg Dispersible Tablets	

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the Medicinal Product

ZULIMAL
(Artemether 20mg and Lumefantrine 120mg Dispersible Tablets)

2. Qualitative and Quantitative Composition

Each uncoated tablet contains:
Artemether.....20mg
Lumefantrine 120mg
For Excipients see point 6.1.

3. Pharmaceutical Form

Uncoated Tablet

Yellow colour, oblong shape, biconvex, uncoated tablets having break line on one side & other plain.

4. Clinical Particulars

4.1 Therapeutic indications

Artemether + Lumefantrine tablet is indicated for the treatment of uncomplicated cases of malaria due to Plasmodium falciparum in adults, children and infants of 5 kg and above.

4.2 Posology and method of administration

Oral use

Table 1: Number of Artemether + Lumefantrine tablet for treatment according to weight bands

Weight range	1st day of treatment	2nd day of treatment	3rd day of treatment
≥ 5kg to < 15kg	1 tablet twice daily (2 x 20mg/120mg A/L)	1 tablet twice daily (2 x 20mg/120mg A/L)	1 tablet twice daily (2 x 20mg/120mg A/L)
15kg to < 25kg	2 tablets twice daily (2 x 40mg/240mg A/L)	2 tablets twice daily (2 x 40mg/240mg A/L)	2 tablets twice daily (2 x 40mg/240mg A/L)
25kg to <35kg	3 tablets twice daily (2 x 60mg/360mg A/L)	3 tablets twice daily (2 x 60mg/360mg A/L)	3 tablets twice daily (2 x 60mg/360mg A/L)
≥ 35kg (or ≥ 12 years of age	4 tablets twice daily (2 x 80mg/480mg A/L)	4 tablets twice daily (2 x 80mg/480mg A/L)	4 tablets twice daily (2 x 80mg/480mg A/L)

Treatment should be administered at the time of initial diagnosis or at the onset of symptoms. It is preferable that the patient has a positive diagnostic test before administration.

The first dose should be followed by a second dose after 8 hours. The following two days the doses of Artemether + Lumefantrine tablet should be given twice daily, morning and evening (i.e. 12 hours apart).

To increase absorption, Artemether + Lumefantrine tablet should be taken with food or a milky drink. If a patient is unable to tolerate food, Artemether + Lumefantrine tablet should still be administered, but the systemic exposure may be reduced. Patients who vomit within 1 hour of taking the medication should repeat the dose.

For very young children, the tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately.

Renal or hepatic impairment

No dose adjustments are necessary in patients with renal or hepatic impairment. However, caution is advised when administering Artemether + Lumefantrine tablet to patients with severe renal or hepatic problems.

Elderly

No special precautions or dosage adjustments are necessary in such patients.

The uncoated tablet(s) for one dose should be stirred in a small amount of water (approximately 10 ml per tablet) so that the active substance can be better dispersed before the suspension is drunk. Stir gently and administer immediately to the patient. Pour some more water (approximately 10 ml) into the glass and give immediately to the patient.

4.3 Contraindications

Hypersensitivity to artemether, lumefantrine or to any of the excipients.

4.4 Special warnings and precautions for use

Pregnancy: Artemether + Lumefantrine tablet should not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarials are available.

Prolongation of the QT-interval: Artemether + Lumefantrine tablet may prolong the QTc interval and increase the risk of cardiac arrhythmias. Therefore Artemether + Lumefantrine tablet should be avoided in 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, clinically relevant bradycardia or congestive heart failure.

. with known disturbances of electrolyte balance, e.g. hypokalaemia or hypomagnesaemia.

. taking drugs that prolong the QTc interval, such as class IA and III antiarrhythmics, certain neuroleptics and antidepressants, certain antibiotics (some macrolides and fluoroquinolones), certain non-sedating antihistamines (terfenadine, astemizole) and cisapride.

. taking drugs with narrow therapeutic index which are metabolized by cytochrome CYP2D6 (e.g. flecainide, metoprolol, imipramine, amitriptyline, clomipramine).

In these patients, ECG- and serum potassium-monitoring is advised.

Renal/hepatic dysfunction: Artemether + Lumefantrine tablet has not been studied in patients with severe renal or hepatic problems

Severe malaria: Artemether + Lumefantrine tablet 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. Use of Artemether + Lumefantrine tablet in such cases is also inadvisable on pharmacokinetic grounds, as it is uncertain if exposure of artemether and, in particular, oflumefantrine is adequate in these patients with high parasitaemia and little or no food intake.

Malaria prophylaxis: Artemether + Lumefantrine tablet has not been evaluated for malaria prophylaxis.

Malaria not caused by P. falciparum: Artemether + Lumefantrine tablet has not been evaluated for the treatment of malaria due to P. vivax, P. malariae, P. ovale or P. knowlesi.

Following treatment of mixed infections including P. vivax, follow-up treatment must be given in order to eradicate the exoerythrocytic forms of P. vivax.

Other antimalarials:

Unless there is no other treatment option, Artemether + Lumefantrine tablet should not be given concurrently with any other antimalarial agent due to limited data on safety and efficacy.

If a patient deteriorates while taking Artemether + Lumefantrine tablet, 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. Due to the potential of additive/synergistic QT-prolongation, close ECG-monitoring is advised when quinine is given after Artemether + Lumefantrine tablet.

If Artemether + Lumefantrine tablet is given after mefloquine, close monitoring of food intake is advised.

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

Hormonal contraceptives: Artemether + Lumefantrine tablet may reduce the effectiveness of hormonal contraceptives. Patients should be advised to use an additional non-hormonal method of birth control.

Intake with food and drinks: Patients who remain averse to food during treatment should be closely monitored, as the risk of recrudescence may be greater.

4.5 Interaction with other medicinal products and other forms of interaction

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

Interaction with other antimalarials

Artemether + Lumefantrine tablet should not be given concurrently with any other antimalarial agent. In addition, due to the propensity of some antimalarial agents to prolong the QTc interval, caution is advised when administering Artemether + Lumefantrine tablet to patients in who there may still be detectable concentrations of these drugs in the plasma following prior treatments.

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

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

<u>Interaction with CYP450 enzymes</u>

Studies in humans have demonstrated that artemisinins have some capacity to induce CYP3A4 and CYP2C19 and inhibit CYP2D6 and CYP1A2. Although the magnitude of the changes was generally low it is possible that these effects could alter the therapeutic response or safety profile of drugs that are predominantly metabolised by these enzymes.

Lumefantrine was found to inhibit CYP2D6 in vitro. This may be of particular clinical relevance for compounds with a low therapeutic index.

Interaction with CYP450 3A4 inhibitors

Ketoconazole: both artemether and lumefantrine are metabolised predominantly by the cytochrome enzyme CYP3A4, and do not inhibit this enzyme at therapeutic concentrations. The concurrent oral administration of ketoconazole with artemether/lumefantrine led to a modest increase (2 fold) in artemether, DHA, and lumefantrine exposure in healthy adult subjects. This increase in exposure to the antimalarial combination was not associated with increased side effects or changes in electrocardiographic parameters. Dose adjustment of Artemether + Lumefantrine tablet is not considered necessary when administered concomitantly with ketoconazole or other azole antifungals, but such combinations should be used with caution.

HIV protease inhibitors: When co-administered with lopinavir and ritonavir, the AUC of lumefantrine increased by 193% and the Cmax by 82%. Artemether and lumefantrine did not significantly affect lopinavir exposure. Data for other protease inhibitors are not available. Artemether + Lumefantrine tablet and HIV protease inhibitors should be coadministered with caution.

4.6 Pregnancy and Lactation

Pregnancy: There is insufficient data from the use of artemether and lumefantrine in pregnant women. In animal studies Artemether + Lumefantrine tablet, 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 + Lumefantrine tablet 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 (including Artemether + Lumefantrine tablet) 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 + Lumefantrine tablet should be warned that dizziness, fatigue or asthenia may occur, in which case their ability to drive or operate machines may be impaired.

4.8 Undesirable effects

Adverse reactions are ranked under headings of frequency using the MedDRA frequency convention:

Very common (≥1/10), Common (≥1/100 to Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1000), Very rare (<1/10,000), Not known (cannot be estimated from available data).

Table 2: Frequency of undesirable effects

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

4.9 Overdose

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

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimalarials, Artemisinin and derivatives, combinations,

ATC code: P01BF01

Pharmacodynamic effects:

Artemether + Lumefantrine tablet 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 Pharmacokinetic properties

Artemether

Absorption

Artemether is absorbed fairly rapidly and dihydroartemisinin (DHA), the active metabolite of artemether, appears rapidly in the systemic circulation with peak plasma concentrations of both compounds reached about 2 hours after dosing. The absolute bioavailability is unknown.

Following single dose administration of 4 tablets of Artemether + Lumefantrine tablet in healthy volunteers, the mean (± SD) artemether C max value was 81 (±41) ng/ml, the corresponding value for AUC was 238 (±125) ng.h/ml, and the mean artemether tmax value was 2.83 (± 0.94) hours. The pharmacokinetic data for dihydroartemisinin were supportive and indicated a comparable bioavailability between Test and Reference.

In healthy volunteers the relative bioavailability of artemether was increased more than two-fold when taken with food.

Distribution

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

Metabolism

Artemether is rapidly and extensively metabolised with substantial first-pass metabolism. Artemether is metabolised in the liver to the biologically active main metabolite DHA (demethylation), predominantly through the isoenzyme CYP3A4/5. The pharmacokinetics of artemether in adults is time-dependent. During repeated administration of arthemeter/lumefantrine, plasma artemether levels decreased significantly, while levels of the active metabolite (dihydroartemisinin) increased, although not to a statistically significant degree. The ratio of day 3/day 1 AUC for artemether was between 0.19 and 0.44, and was between 1.06 and 2.50 for dihydroartemisinin. This suggests that there was induction of the enzyme responsible for the metabolism of artemether. DHA is further converted to inactive metabolites, primarily by glucuronidation. In vivo data indicate that artemisinins have some capacity to induce cytochrome isoenzymes CYP2C19 and CYP3A4.

Elimination

Artemether and dihydroartemisinin are rapidly cleared from plasma with an elimination half-life of about 2 hours. No urinary excretion data are available for humans. In rats and dogs unchanged artemether has not been detected in faeces and urine due to its rapid and high-first-pass metabolism, but several metabolites (unindentified) have been detected in both faeces and urine.

Lumefantrine

Absorption Absorption of lumefantrine, a highly lipophilic compound, starts after a lagtime of up to 2 hours, with peak plasma concentration about 6-8 hours after dosing. The absolute bioavailability is unknown. Following single dose administration of 4 tablets of Artemether + Lumefantrine tablet in healthy volunteers, the mean (±SD) lumefantrine Cmax value was 6136 (±2880) ng/ml, the corresponding value for AUC was 99070 (±48130)ng.h/ml and the mean lumefantrine tmax value was 5.93 (± 0.73) hours. In healthy volunteers the relative bioavailability of lumefantrine, when was taken after a high-fat meal, was increased sixteen-fold compared with fasted conditions. Food has also been shown to increase the absorption of lumefantrine in patients with malaria, although to a lesser extent (approximately two-fold), most probably due to the lower fat content of the food ingested by acutely ill patients. The food interaction data indicate that absorption oflumefantrine under fasted conditions is very poor. Patients should therefore be encouraged to take the medication with a normal diet as soon as food can be tolerated.

Distribution

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

Metabolism

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

Elimination

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

5.3 Preclinical safety data

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

Mutagenicity: No evidence of mutagenicity was detected in in vitro or in vivo tests with an artemether:lumefantrine combination (consisting of 1 part artemether: 6 parts lumefantrine). In the micronucleus test myelotoxicity was seen at all dose levels (500, 1,000 and 2,000 mg/kg), but recovery was almost complete 48 hours after dosing. Carcinogenicity: Carcinogenicity studies with the artemether/lumefantrine combination were not conducted.

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

Embryotoxicity has been observed in rat and rabbit reproductive toxicity studies conducted with artemether, a derivative of artemisinin. Artemisinins (e.g. artesunate) are known to be embryotoxic.

Artemether caused increases in post-implantation loss and teratogenicity (characterised as a low incidence of cardiovascular and skeletal malformations) in rats at 19.4 mg/kg, and in rabbits at 30 mg/kg. Maternal toxicity was also observed in rabbits at 30 mg/kg/day. No other adverse effects were observed at lower doses in rabbits. The no observed effect dose was 3 mg/kg/day in rats and 25 mg/kg/day in rabbits.

The embryotoxic artemether dose, 20 mg/kg/day in the rat, yields artemether and dihydroartemisinin exposures similar to those achieved in humans. Artesunate, a structurally related compound, also caused increases in post-implantation loss and teratogenicity (low incidence of cardiovascular and skeletal malformations) in rats at 6 mg/kg and in the lowest dose tested in the rabbits, 5 mg/kg/day.

Cardiovascular Pharmacology: In toxicity studies in dogs at doses > 600 mg/kg/day only, there was some evidence of prolongation of the QTc interval, at higher doses than intended for use in man. In an in vitro assay of HERG channels, lumefantrine and the main metabolite desbutyl-lumefantrine showed some inhibitory potential in one of the currents responsible for cardiac repolarization. From the estimated IC50 values, the order of potency of HERG current block was halofantrine (IC50 = 0.04 μM) > chloroquine (2.5 μM) > mefloquine 2.6 μM) > desbutyl-lumefantrine (5.5 μM) > lumefantrine (8. 1 μM). Clinical studies show, that prolongation of QTcF can occur with standard dosing of artemether/lumefantrine.

6. Pharmaceutical Particulars

6.1 List of Excipients

Microcrystalline Cellulose, Hypromellose, Mannitol, Croscarmellose Sodium, Crospovidone, Doshion (544 DS), Purified Talc, Magnesium Stearate, Colloidal Anhydrous Silica, Aspartame, Flavour Mango, Flavour Mint, Colour Lake Quinoline yellow

6.2 Incompatibilities

None

6.3 Shelf life

24 months from the manufacturing date.

6.4 Special precautions for storage

Store below 30° C. Protect from light and moisture.

6.5 Nature and contents of container

Alu/PVC pack. Each carton contains 1 blister of 6 tablets along with pack insert.

6.6 Special Precaution for disposal

None

7. Manufacturer

ZAHIDI PHARMACEUTICALS PVT. LTD.
J-1601/10, 3rd PHASE, ROAD NO. 17, G.I.D.C.,
UMBERGAON – 396171, DIST. VALSAD,
(GUJARAT) INDIA

8. Marketing Authorization Holder

MASAN PHARMACEUTICAL LTD
300, Rijiyar Zaki Quarters,
Kano, Kano State

9. Marketing Authorization Number

Not Applicable.

10. Date of First Authorization /Renewal of the Authorization

Not Applicable.

11. Date of Revision of the Text

Not Applicable.