BRAND NAME:	**OSYMAL FORTE TABLETS**
GENERIC NAME:	**ARTEMETHER AND LUMEFANTRINE TABLETS**

1.3 PRODUCT INFORMATION

1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

Enclosed

BRAND NAME:	**OSYMAL FORTE TABLETS**
GENERIC NAME:	**ARTEMETHER AND LUMEFANTRINE TABLETS**

1. Name of drug product

OSYMAL FORTE TABLETS

1.1 (Trade) name of product

OSYMAL FORTE TABLETS

(Artemether and Lumefantrine Tablets)

1.2 Strength

Artemether 80 mg

Lumefantrine 480 mg

1.3 Pharmaceutical Dosage Form

Oral dosage form **(**Tablets)

2. QUALITATIVE & QUANTITATIVE COMPOSITION

2.1 Qualitative Declaration

Each Film coated Tablet Contains:

Artemether……80 mg

Lumefantrine……480 mg

Excipients…….q.s.

Color: Tartrazine Yellow

BRAND NAME:	**OSYMAL FORTE TABLETS**
GENERIC NAME:	**ARTEMETHER AND LUMEFANTRINE TABLETS**

Batch Formula:

Batch Size: 4,00,000 Tablets

Sr. No.	Ingredients	Spec.	Unit Formula (mg)	Batch Formula (kg)
GRANULATION				
DRY MIXING				
1	Artemether	IH	80.000	32.000*
2	Lumefantrine	IH	480.000	192.000*
3	Maize Starch	BP	41.400	18.216**
4	Microcrystalline Cellulose	BP	18.000	7.200
5	Crospovidone	USP	8.000	3.200
BINDER				
6	PVP K-30	BP	10.000	4.000
7	Sodium Benzoate	BP	0.600	0.240
8	Isopropyl Alcohol	BP	q.s.	60.000
LUBRICATION				
9	Purified Talc	BP	10.000	4.000
10	Crospovidone	USP	10.000	4.000
11	Colloidal Anhydrous Silica (Aerosil)	BP	17.000	6.800
12	Magnesium Stearate	BP	25.000	10.000
Weigh of Compressed Tablet			**700.000**	**280.000**
COATING				
13	Spray tab Yellow	IH	5.000	2.800***
14	Methylene dichloride	BP	q.s.	34.573
15	Isopropyl Alcohol	BP	q.s.	18.200
Weigh of Coated Tablet			**705.000**	**282.000**

Remark:

* Quantity of Artemether and Lumefantrine change according to changes in quantity of Maize starch.

** 10% Extra Starch added in formulation to compensate loss of moisture from starch quantity during drying process

*** 40 % Extra Spray Tab yellow added in formulation to compensate loss during coating process.

3. PHARMACEUTICAL DOSAGE FORM

Tablets

Yellow coloured, circular, biconvex, film coated tablets debossed with “MAXHEAL” on one side & breakline on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Oral use

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

One tablet should be taken twice a day for three days (total six doses).The first dose should be followed by a second dose after 8 hours. The following two days the doses of OSYMAL FORTE TABLETS should be given twice daily, morning and evening (i.e. 12 hours apart).

To increase absorption, OSYMAL FORTE TABLETS should be taken with food or a milky drink. If a patient is unable to tolerate food, OSYMAL FORTE TABLETS should still be administered, but the systemic exposure may be reduced.

Patients who vomit within 1 hour of taking the medication should repeat the dose.

If a dose is missed, it should be taken as soon as realized and then the recommended regimen continued until the full course of treatment has been completed.

Renal or hepatic impairment

No dose adjustments are necessary in patients with renal or hepatic impairment. However, caution is advised when administering OSYMAL FORTE TABLETS to patients with severe renal or hepatic problems.

***Pediatric Patients Weighing less than 35 kg*:**

Appropriate dose adjustments cannot be achieved with this product. Other formulations containing lower amounts of artemether/lumefantrine are available for these patients.

Elderly

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

4.3 Contraindications

Artemether and Lumefantrine are 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 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. These drugs include:

- Antiarrhythmics of classes IA and III,
- Aeuroleptics, antidepressive agents,
- Aertain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole and triazole antifungal agents,
- Certain non-sedating antihistamines (terfenadine, astemizole),
- Cisapride.

• Patients with a history of symptomatic cardiac arythmias or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricle ejection fraction.

• Patients with disturbances of electrolyte balance e.g. hypokalemia or hypomagnesemia.

4.4 Special warnings and precautions for use

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

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

Due to limited data on safety and efficacy, Artemether and Lumefantrine 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, 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 considered when administering quinine in patients previously treated with Artemether and Lumefantrine. If quinine is given after Artemether and Lumefantrine, close monitoring of the ECG is advised If Artemether and Lumefantrine is given after mefloquine, close monitoring of food intake is advised. In patients previously treated with halofantrine, Artemether and Lumefantrine should not be administered earlier than one month after the last halofantrine dose. Artemether and Lumefantrine is not indicated and has not been evaluated for prophylaxis. Artemether and Lumefantrine 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. Like other antimalarials (e.g. halofantrine, quinine and quinidine) Artemether and Lumefantrine has the potential to cause QT prolongation.

Caution is recommended when combining Artemether and Lumefantrine 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. Caution is recommended when combining Artemether and Lumefantrine with hormonal contraceptives. Artemether and Lumefantrine 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 dihydroartemisinic in studies conducted in healthy volunteers and clinical experience is limited. No dose adjustment for the use of Artemether and Lumefantrine in patients with renal impairment is recommended. Caution is advised when administering Artemether and Lumefantrine 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 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. In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of Artemether and Lumefantrine cannot be recommended.

4.5 Interaction with other medicinal products and other forms of interaction

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

Interaction with other antimalarials

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

Administration of a six-dose regimen of artemether/lumefantrine (over 60 hours) starting 12 hours after completion of a three-dose regimen of mefloquine or placebo in healthy volunteers showed no effect of mefloquine on plasma concentrations of artemether or the artemether/dihydroartemisinin ratio, but a 30-

40% reduction in plasma levels of lumefantrine. These are possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production. Patients that have been pretreated with mefloquine should be encouraged to eat at dosing times to compensate for the decrease in bioavailability. Plasma mefloquine concentrations from the time of addition of artemether/lumefantrine were not affected compared with a group that received mefloquine followed by placebo.

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

Interaction with CYP450 enzymes

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

Interaction with CYP450 3A4 inhibitors

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

HIV Treatment Medications

HIV nucleoside and nucleotide reverse transcriptase inhibitors (NTRIs, e.g. abacavir, emtricitabine, lamivudine, tenofovir [TDF or TAF], zidovudine.) Co-administration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely.

HIV non-nucleoside reverse transcriptase inhibitors (NNRTIs):

Efavirenz: Co-administration of efavirenz and artemether/lumefantrine lead to decreases in artemether exposure (51% and 79%), dihydroartemisinin exposure (46% and 75%) and lumefantrine exposure by

(21% and 56%). Lumefantrine had no significant effect on efavirenz exposure in either study. Use with caution as decreased concentrations of artemether, dihydroartemisinin, or lumefantrine may result in a decrease of antimalarial efficacy.

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

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

HIV Protease Inhibitors (PIs)

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

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

Ritonavir: Co-administration may increase plasma levels of artemisinins and lumefantrine, as both are metabolised by CYP3A4. Caution is recommended.

HIV Integrase Strand-Transfer Inhibitors (INSTIs)

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

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

Pharmacokinetic Enhancer

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

Antivirals against Hepatitis B or C

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

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data on pregnant women in their first trimester (more than 500 pregnancy outcomes) is available for artemether/lumefantrine. Data from a recent meta-analysis have shown that compared to quinine, artemether/lumefantrine treatment in the first trimester was not associated with an increased risk of miscarriage or stillbirth. While the data are limited, they indicate no difference in the prevalence of major congenital anomalies between treatment groups (for animal data see section 5.3). A large amount of data on pregnant women in their second and third trimester (more than 4000 documented pregnancy outcomes) is available for artemisinin derivatives including artemether/lumefantrine. They indicate no fetal or neonatal toxicity. OSYMAL FORTE TABLETS can be used during pregnancy.

Breast-feeding

The amounts of artemether, dihydroartemisinin and lumefantrine in breast milk are small. Therefore, breastfeeding women can receive artemisinin-based combination therapies (including OSYMAL FORTE TABLETS) for malaria treatment. Fertility There is no information on the effects of OSYMAL FORTE TABLETS on fertility in humans.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients receiving OSYMAL FORTE TABLETS should be warned that dizziness, fatigue or asthenia may occur, in which case their ability to drive or operate machines may be impaired.

4.8 Undesirable effects

The safety of OSYMAL FORTE 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 OSYMAL FORTE TABLETS in clinical trials. Adverse reactions reported from clinical studies and post-marketing experience are listed below according to system organ class.

BRAND NAME:	**OSYMAL FORTE TABLETS**
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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, hypaesthesia	Uncommon	--
Somnolence	Uncommon	Uncommon
Clonus	Common	Uncommon
Cardiac disorders		
Palpitations	Very common	Common (1.8 %)
Electrocardiogram 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.

4.9 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.

5.0 Pharmacological properties

5.1 Pharmacodynamics properties

Pharmacotherapeutic group : Antimalarials, blood schizonticide **ATC Code :** P01BF01

Pharmacodynamic effects

OSYMAL FORTE 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 Pharmacokinetic properties

Absorption:

Artemether is absorbed fairly rapidly with peak plasma concentrations reached about 2 hours after

dosing. Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentration about 6-8 hours after dosing. 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 OSYMAL FORTE 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). Dihydroartimisinin 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 dihydroartemisinic (demethylation), predominantly through the isoenzyme CYP3A4/5. This metabolite has also been detected in humans in vivo. The artemether/dihydroartemisinic AUC ratio is 1.2 after a single dose and 0.3 after 6 doses given over 3 days. In-vivo data indicate that artemisinin's have some capacity to induce cytochrome isoenzymes CYP2C19 and CYP3A4. Dihydroartimisinin is further converted to inactive metabolites. 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 kinetic profile of the metabolite desbutyllumefantrine, for which the in-vitro antiparasitic effect is 5 to 8-fold higher than lumefantrine, has not been documented. In vitro, lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations.

Elimination:

Artemether and Dihydroartimisinin are rapidly cleared from plasma with an elimination halflife of about 2 hours. Lumefantrine is eliminated very slowly with a terminal half-life of 2 3 days in healthy

volunteers and 4 - 6 days in patients with falciparum malaria. Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of Lumefantrine and artemether.

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 (unidentified) have been detected in both faeces and urine. 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.

Dose proportionality

No specific dose proportionality studies were performed. Limited data suggest a doseproportional increase of systemic exposure to lumefantrine when doubling the OSYMAL FORTE TABLETS dose. No conclusive data is available for artemether.

Bioavailability/bioequivalence studies

Systemic exposure to lumefantrine, artemether and Dihydroartimisinin was similar following administration of OSYMAL FORTE TABLETS as Film coated tablets and crushed tablets in healthy adults.

Systemic exposure to lumefantrine was similar following administration of OSYMAL FORTE TABLETS Film coated tablets and intact tablets in healthy adults. However, exposure to artemether and Dihydroartimisinin was significantly lower (by 20-35%) for the Film coated than for the intact tablet. These findings are not considered to be clinically relevant for the use of the Film coated tablets in the paediatric population since adequate efficacy of OSYMAL FORTE TABLETS Film coated tablets was demonstrated in this population.

Special populations

No specific pharmacokinetic studies have been performed in elderly patients. However, there is no information suggesting that the dosage in patients over 65 years of age should be different than in younger adults.

In paediatric malaria patients, mean Cmax (CV%) of artemether (observed after first dose of were 223 (139%), 198 (90%) and 174 ng/mL (83%) for body weight groups 5-<15, 15-<25 and 25-<35 kg, respectively, compared to 186 ng/mL (67%) in adult malaria patients. The associated mean Cmax of

DHA were 54.7 (108%), 79.8 (101%) and 65.3 ng/mL (36%), respectively compared to 101 ng/mL (57%) in adult malaria patients. AUC of lumefantrine (population mean, covering the six doses of OSYMAL FORTE TABLETS were 577, 699 and 1150 µg•h/mL for paediatric malaria patients in body weight groups 5-<15, 15-<25 and 25- <35 kg, respectively, compared to a mean AUC of 758 µg•h/mL (87%) in adult malaria patients. The elimination half- lives of artemether and lumefantrine in children are unknown. No specific pharmacokinetic studies have been performed either in patients with hepatic or renal insufficiency or elderly patients. The primary clearance mechanism of both artemether and lumefantrine may be affected in patients with hepatic impairment. In patients with severe hepatic impairment, a clinically significant 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. Based on the pharmacokinetic data in 16 healthy subjects showing no or

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction and development.

6. Pharmaceutical Particulars

6.1. List of excipients

Maize Starch
Microcrystalline Cellulose
Sodium Benzoate
Colloidal anhydrous silica (Aerosil)
Purified Talc
PVP K-30
Sodium Saccharine
Crospovidone
Colloidal anhydrous silica
Magnesium Stearate
Methylene dichloride

Isopropyl Alcohol

Spray tab Yellow

6.2. Incompatibilities

None

6.3. Shelf life

36 Months.

6.4. Special precautions for storage

Store below 30^0C, protect from light.

6.5. Nature and contents of container

10 X 1 X 6 Tablets packed in Alu-PVC Blister.

6.6. Instruction for use and handling

No special requirement

7. Marketing Authorization Holder

MAXHEAL LABORATORIES PVT LTD

PLOT NO. - 2-7/80-85, SURSEZ,

G.I.D.C SACHIN, SURAT GUJARAT-

394230. INDIA

8. Marketing Authorization Number

Not Applicable.

9. Date of First Authorization /Renewal of the Authorization

Not Applicable.

10. Date of Revision of the

Not Applicable.