1.3.1 Summary of Product Characteristics (SmPC)

Enclosed

1. Name of the medicinal product:

1.1 Name of the medicinal product :

KILLMAL TABLETS [Artemether and Lumefantrine Tablets]

1.2 Strength :
Artemether 80 mg
Lumefantrine USP 480 mg

1.3 Pharmaceutical form:

Film coated tablets for oral use

2. Qualitative and quantitative composition

Each film coated tablet contains:

Artemether	: 80 mg
Lumefantrine USP	: 480 mg
Excipients	: q.s.

Colour: Quinoline Yellow Lake

Qualitative declaration:
Artemether IH, Lumefantrine USP

Quantitative declaration:
Artemether 80 mg
Lumefantrine USP 480 mg

For Excipients see section 6.1

3. Pharmaceutical form

Film Coated Tablets for Oral use

4. Clinical particulars:

4.1 Therapeutic indications:

KILLMAL TABLETS are indicated for treatment of acute, uncomplicated malarial infections due to Plasmodium falciparum in patients of 35 kg bodyweight and above. KILLMAL TABLETS have been shown to be effective in geographical regions where resistance to chloroquine has been reported. Consideration should be given to official guidance regarding the appropriate use of antimalarial agents.

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4.2 Posology and method of administration

To increase absorption, KILLMAL TABLETS should be taken with food or a milky drink. If patient is unable to tolerate food, KILLMAL TABLETS should be administered, 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 tablet/s may be crushed.

Adults & over 35 kg: 2 B.I.D for 3 days

25kg to 34 kg: 1 $^{1/2}$ B.I.D for 3 days

15kg to 24 kg: 1 B.I.D for 3 days

- Recommended route of administration : oral use

4.3 Contraindications

KILLMAL TABLETS is contraindicated in patients with following cases:

- 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,
  - 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.
- 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

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4.4 Special warnings and precautions for use

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

KILLMAL TABLETS has not been evaluated for the treatment of severe malaria, including cases of cerebral malaria or other severe manifestations such as pulmonary oedema or renal failure. Due to limited data on safety and efficacy, KILLMAL TABLETS should not be given concurrently with other antimalarial agent unless there is no other treatment option.

If a patient deteriorates whilst taking KILLMAL 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 KILLMAL TABLETS.

If quinine is given after KILLMAL TABLETS, close monitoring of the ECG is advised.

If KILLMAL TABLETS is given after mefloquine, close monitoring of food intake is advised.

In patients previously treated with halofantrine, KILLMAL TABLETS should not be administered earlier than one month after the last halofantrine dose.

KILLMAL TABLETS is not indicated for, and has not been evaluated in, the treatment of malaria due to *P. vivax*, *P. malariae* or *P. ovale*, although some patients in clinical studies had co-infection with *P. falciparum* and *P. vivax* at baseline.

KILLMAL TABLETS is active against blood stages of *Plasmodium vivax*, but is not active against hypnozoites.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with other antimalarials

A drug interaction study with KILLMAL TABLETS 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 KILLMAL 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.

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 KILLMAL 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 KILLMAL 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 cardio toxicity of quinine. This effect was slightly, but significantly, greater when quinine was infused after KILLMAL 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 KILLMAL TABLETS

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 KILLMAL 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 KILLMAL TABLETS is considered unnecessary in falciparum malaria patients when administered in association with Ketoconazole or other potent CYP3A4 inhibitors.

Interaction with CYP450 enzymes

Studies in humans have demonstrated that artemisinin 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.

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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 KILLMAL TABLETS with drugs that are metabolised by this Iso-enzyme is contraindicated. *In vitro* studies indicated that Lumefantrine metabolism is inhibited by halofantrine and quinine.

Interaction with protease inhibitor anti-retroviral drugs

Due to variable patterns of inhibition, induction or competition for CYP3A4 with protease inhibitor anti-retroviral drugs, use of such drugs, especially combinations of them, concomitantly with KILLMAL TABLETS, requires clinical surveillance and monitoring of clinical response/undesirable effects.

Other interactions

Administration of KILLMAL TABLETS is contra-indicated in patients taking drugs that are known to prolong the QTc interval.

In patients previously treated with halofantrine, KILLMAL TABLETS should be dosed at least one month after the last halofantrine dose.

Due to the limited data on safety and efficacy, KILLMAL 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 KILLMAL TABLETS to patients in whom there may still be detectable concentrations of these drugs in the plasma following prior treatments.

4.6 Pregnancy and lactation

Pregnancy

There is insufficient data from the use of Artemether and Lumefantrine in pregnant women. Based on animal data, KILLMAL TABLETS 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 during early gestation. KILLMAL TABLETS treatment must not be used during the first trimester of pregnancy in situations where other suitable and effective antimalarials are

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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 KILLMAL TABLETS should not breast-feed during their treatment. Due to the long elimination half-life of Lumefantrine (4 to 6 days), it is recommended that breast-feeding should not resume until at least one week after the last dose of KILLMAL TABLETS unless potential benefits to the mother and child outweigh the risks of KILLMAL TABLETS treatment.

4.7 Effects on ability to drive and use machines:

Not Stated.

4.8 Undesirable effects:

Headache, dizziness, weakness, muscle or joint pain, tiredness, difficulty falling asleep or staying asleep, vomiting, loss of appetite, some side effects can be serious.

If you experience any of these symptoms, call your doctor immediately:

abnormal or fast heartbeat, fainting, rash, hives, difficulty breathing or swallowing, swelling of the lips, tongue, face, or throat, hoarseness, difficulty speaking

4.9 Overdose:

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

5. Pharmacological properties:

5.1 Pharmacodynamic properties:

Pharmacodynamic effects

KILLMAL 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 hemoglobin breakdown, to the nontoxic haemozoin, malaria

pigment. Lumefantrine is thought to interfere with the polymerisation process, while Artemether generates reactive metabolites as a result of the interaction between its peroxide bridge and haem iron. Both Artemether and Lumefantrine have a secondary action involving inhibition of nucleic acid- and protein synthesis within the malarial parasite.

The antimalarial activity of the combination of Lumefantrine and Artemether in KILLMAL TABLETS is greater than that of either substance alone. In a double-blind comparative study in adults in China (n=157), the 28-day cure rate of KILLMAL TABLETS when given at 4 doses was 94 % compared with 90 % for Lumefantrine and 46 % for Artemether based on intent-to-treat (ITT) population, when given as monotherapy. For the evaluable population, 28-day cure rates were 100 % for KILLMAL TABLETS, compared with 92 % for Lumefantrine and 55 % for Artemether when given as monotherapy.

5.2 Pharmacokinetic Properties

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 KILLMAL 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 µng·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 KILLMAL 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*.

Elimination

Artemether and dihydroartemisinin are rapidly cleared from plasma with a terminal half-life 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 KILLMAL TABLETS.

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 was 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. Artemisinin (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 stably expressed in HEK293 cells, Lumefantrine 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 IC_{50} values, the order of potency of HERG current block was halofantrine (IC_{50} = 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 KILLMAL TABLETS TABLETS.

6. Pharmaceutical particulars

6.1 List of excipients

Sr. No.	Ingredient	Specification
1.	Lactose	BP
2.	Microcrystalline Cellulose	BP
3.	Sodium Starch Glycolate	BP
4.	Starch	BP
5.	Sodium Methyl Hydroxybenzoate	BP
6.	Sodium Propyl Hydroxybenzoate	BP
7.	Purified Talc	BP
8.	Magnesium Stearate	BP
9.	Polacrilin Potassium (kyron T314)	USP
10.	Sodium Lauryl Sulfate	BP
11.	Hydrophobic Colloidal Anhydrous Silica	BP
12.	Hydroxypropylmethylcellulose 15 CPS.	BP
13.	Titanium Dioxide	BP
14.	Purified talc	BP
15.	Quinoline yellow lake	IH
16.	Isopropyl Alcohol	BP
17.	Dichloromethane	BP

6.2 Incompatibilities

None

6.3 Shelf life

36 months (3 Years) from date of manufacturing

6.4 Special precautions for storage

Store below 30°C in a dry place.

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Keep medicines out of reach of children.

6.5 Nature and contents of container

1 X 6 tablets Alu-Amber PVC blister, Such 1 blister to be packed in a carton along with pack insert

6.6 Special precautions for disposal :

None

7. Registrant :

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9. Date of revision of the text: NA

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