Artemether & Lumefantrine Tablet 80/480 mg

SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

1- Name of the Medicinal Product:

1.1 Product Name

- **Generic Name or International Non-Proprietary Name (INN)**

  Artemether & Lumefantrine Tablet 80/480 mg

- **Brand Name**

  SUREM~~AT~~EM 80mg/480mg Tablet

1.2 Dosage Strength

Each Film coated Tablet Contains:
Artemether……..80 mg
Lumefantrine…….480 mg
Excipients……..q.s
Colour: - Tartrazine Yellow

1.3 Dosage Form

Film Coated Tablets

2- Quality and Quantitative Composition:

2.1 Qualitative Declaration

Each Film coated Tablet Contains:
Artemether……..80 mg
Lumefantrine…….480 mg
Excipients……..q.s
Colour: - Tartrazine Yellow

2.2 Quantitative Declaration

Description: Yellow Coloured, Round shape, Biconvex, Film coated tablets having break line at one side and plain at other side.

Artemether & Lumefantrine Tablet 80/480 mg

STD Batch Size: 162.400 kg / 2.00 Lac Tablets

Reference. MFR No: MFR/T-E390 Version No: 00

Sr No.	Ingredients	A.R No.	Specification	Overages	Quantity/ Tablet in mg	Standard Qty in kg
DRY MIXING						
1.	Artemether	RM210680	IH	Nil	81.000	16.200
2.	Lumefantrine	RM213082	IH	Nil	493.000	98.600
3.	Sodium Starch Glycolate	RM210013	BP	Nil	20.000	4.000
4.	Colloidal Silicon Dioxide	RM210962	BP	Nil	15.000	3.000
5.	Microcrystalline Cellulose	RM210010	BP	Nil	73.000	14.600
6.	Maize Starch	RM210930	BP	Nil	20.000	4.000
PASTE PREPARATION						
7.	PVPK-30	RM210121	BP	Nil	10.000	2.000
8.	Methyl Paraben	RM2101012	BP	Nil	0.700	0.140
9.	Propyl Paraben	RM210937	BP	Nil	0.140	0.028
10.	HPMC 15 CPS	RM210120	BP	Nil	16.000	3.200
11.	Purified Water	W220121	BP	Nil	q.s.	q.s.
LUBRICATION						
12.	Magnesium Stearate	RM210150	BP	Nil	19.000	3.800
13.	Talc	RM210933	BP	Nil	15.000	3.000
14.	Colloidal Silicon Dioxide	RM210792	BP	Nil	16.000	3.200
15.	Cross Carmellose Sodium	RM210158	BP	Nil	13.160	2.632
COATING						
16.	Methylene Chloride	RM210812	BP	Nil	q.s	q.s
17.	Isopropyl Alcohol	RM210020	BP	Nil	q.s	q.s
18.	Colour Tartrazine Yellow	RM210130	IH	Nil	20.000	4.000
Average wt. of Tablet (812.00 mg ± 5.0 %)						

Note:

Active material was calculated on assay or Potency Basis.

IH = In-house Specification

BP = British Pharmacopoeia

USP = United States Pharmacopoeia

Artemether & Lumefantrine Tablet 80/480 mg

- ***Justification for addition of Preservative***
  - Justification for addition of Preservative such as Methyl Paraben & Propyl Paraben in the preparation of Binder Salutation.
  - All the raw material are analyst as per Pharmacopeial Specification for chemical & Microbial Limit test.
  - Purified Water used for the manufacturing is under monitoring program for Microbial Limit test.
  - Manufacturing area monitored as per the predefined frequency for environmental monitoring.
  - As an additional precaution Methyl Paraben & Propyl Paraben added in the preparation binder solution to take care of Microbial Purity.

1. ***Quantity Adjusted to 100 % API assay (Artemether)***

Calculation:

*Assay for Artemether = 98.76 % as is basis

Qty required for Artemether per batch i.e. 2,00,000 tablets =

$$= \frac{\text{LA per tablet X Batch Size X 100}}{\text{Assay as is basis}}$$

$$= \frac{\text{80 mg X 2,00,000 X 100}}{98.76}$$

= **81.00 mg** of Artemether required.

…. (As 98.76 % Assay as is basis for Artemether)

Artemether & Lumefantrine Tablet 80/480 mg

2. *Quantity Adjusted to 100 % API assay (Lumefantrine)*

Calculation:

*Assay for Lumefantrine = 98.30 % as is basis

Qty required for Lumefantrine per batch i.e. 2, 00,000 tablets =

$$= \frac{\text{LA per tablet X Batch Size X 100}}{\text{Assay as is basis}}$$

$$= \frac{\text{480 mg X 2,00,000 X 100}}{98.30}$$

= **493.00 mg** of Lumefantrine required. ***(*Added API for 100 % API assay)***

…. (As 98.30 % Assay as is basis for Lumefantrine)

Artemether & Lumefantrine Tablet 80/480 mg

3. Pharmaceutical Form:

Yellow Coloured, Round shape, Biconvex, Film coated tablets having break line at one side and plain at other side.

4. Clinical particulars

4.1 Therapeutic indications

Artemether & Lumefantrine 80/480 Tablet 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 Artemether & Lumefantrine 80/480 Tablet.

4.2 Posology and method of administration

Posology

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 Artemether & Lumefantrine 80/480 Tablet should be given twice daily, morning and evening (i.e. 12 hours apart).
- To increase absorption, Artemether & Lumefantrine 80/480 Tablet should be taken with food or a milky drink.
- If a patient is unable to tolerate food, Artemether & Lumefantrine 80/480 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.
- 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 Artemether & Lumefantrine 80/480 Tablet to patients with severe renal or hepatic problems.

Paediatric 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 & Lumefantrine 80/480 Tablet is contraindicated in:

- Patients with known hypersensitivity to Artemether, Lumefantrine or to any of the excipients.
- Patients with severe malaria according to WHO definition.
- Patients with a personal or 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 severe cardiac diseases.
- Patients taking drugs that are known to prolong qtc interval such as :
- Antiarrhythmics of classes ia and iii
- Neuroleptics and antidepressant agents
- Certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal agents
- Certain non-sedating antihistamines (terfenadine, astemizole)
- Cisapride
- Patients with known disturbances of electrolyte balance e.g. hypokalaemia or hypomagnesaemia
- Patients taking any drug which is metabolized by the cytochrome enzyme CYP2D6 (e.g. flecainide, metoprolol, imipramine, amitriptyline, clomipramine

- Patients taking drugs that are strong inducers of CYP3A4 such as rifampicin, carbamazepine, phenytoin, St John's wort.

4.4 Special warnings and precautions for use :-

Artemether & Lumefantrine 80/480 Tablet is contraindicated in:

- Patients with known hypersensitivity to artemether, lumefantrine or to any of the excipients.
- Patients with severe malaria according to who definition.
- Patients with a personal or 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 severe cardiac diseases.
- Patients taking drugs that are known to prolong qtc interval such as :
- Antiarrhythmics of classes ia and iii
- Neuroleptics and antidepressant agents
- Certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal agents
- Certain non-sedating antihistamines (terfenadine, astemizole)
- Cisapride
- Patients with known disturbances of electrolyte balance e.g. Hypokalaemia or hypomagnesaemia
- Patients taking any drug which is metabolized by the cytochrome enzyme CYP2D6 (e.g. Flecainide, metoprolol, imipramine, amitriptyline, clomipramine
- Patients taking drugs that are strong inducers of CYP3A4 such as rifampicin, carbamazepine, phenytoin, St John's wort.

4.5 Interaction with other medicinal products and other forms of interaction

Artemether & Lumefantrine 80/480 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.

Artemether & Lumefantrine Tablet 80/480 mg

Interaction with other antimalarial

Artemether & Lumefantrine 80/480 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 80/480 Tablet 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, Artemether Lumefantrine 80/480 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.

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 80/480 Tablet 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. 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.

Artemether & Lumefantrine 80/480 Tablet 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 Artemether & Lumefantrine 80/480 Tablet) for malaria treatment.

Fertility

There is no information on the effects of Artemether & Lumefantrine 80/480 Tablet on fertility in humans.

4.3 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 80/480 Tablet should be warned that dizziness, fatigue or asthenia may occur, in which case their ability to drive or operate machines may be impaired.

4.4 Undesirable effects

The safety of Artemether/Lumefantrine has been evaluated in adults, adolescents and children in clinical trials with more than 3500 patients.

Adverse reactions reported from clinical studies and post-marketing experience are listed below according to system organ class.

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

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

Table 1: Frequency of undesirable effects

	Adults and adolescents above 12 years of age	**Infants and children of 12 years of age and below (incidence estimates)**
Blood and lymphatic system disorders		
Delayed haemolytic anaemia[#]	Not known	Not known
Immune system disorders		
Hypersensitivity	Not known	Rare
Metabolism and nutrition disorders		
Decreased appetite	Very common	Very common (16.8 %)

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Psychiatric disorders		
Sleep disorders	Very common	Common (6.4 %)
Insomnia	Common	Uncommon
Nervous system disorders		
Headache	Very common	Very common (17.1 %)
Dizziness	Very common	Common (5.5 %)
Paraesthesia	Common	--
Ataxia, hypoaesthesia	Uncommon	--
Somnolence	Uncommon	Uncommon
Clonus	Common	Uncommon
Cardiac disorders		
Palpitations	Very common	Common (1.8 %)
Electrocardiogram QT prolonged	Common	Common (5.3 %)
Respiratory, thoracic and mediastinal disorders		
Cough	Common	Very common (22.7 %)
Gastrointestinal disorders		
Vomiting	Very common	Very common (20.2 %)
Abdominal pain	Very common	Very common (12.1 %)
Nausea	Very common	Common (6.5 %)
Diarrhoea	Common	Common (8.4 %)
Hepatobiliary disorders		
Liver function tests increased	Uncommon	Common (4.1 %)
Skin and subcutaneous tissue disorders		
Rash	Common	Common (2.7 %)
Pruritus	Common	Uncommon
Urticaria	Uncommon	Uncommon
Angioedema*	Not known	Not known
Musculoskeletal and connective tissue disorders		
Arthralgia	Very common	Common (2.1 %)
Myalgia	Very common	Common (2.2 %)
General disorders and administration site conditions		
Asthenia	Very common	Common (5.2 %)
Fatigue	Very common	Common (9.2 %)
Gait disturbance	Common	--

*: These adverse reactions were reported during post-marketing experience. Because these spontaneously reported events are from a population of uncertain size, it is difficult to estimate their frequency.
#: Has been reported up to a few weeks after treatment has been stopped.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via at:

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

Pharmacotherapeutic group: antimalarial, blood schizontocide,

ATC code: P01 BF01.

Pharmacodynamic effects

Artemether & Lumefantrine 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. Artemether & Lumefantrine has been reported to have potent activity in terms of clearing gametocytes.

By 2015, resistance to artemisinins emerged in Southeast Asia. Studies with Artemether & Lumefantrine in this region showed delayed parasite clearance (manifested as a higher proportion of patients with parasitemia on Day 3 after initiation of treatment), although overall efficacy as measured by cure rates after 28 days, remained high (WHO 2014). In Africa, only isolated reports on delayed parasite

clearance are available and a clear trend towards resistance development was not observed.

Treatment of Acute Uncomplicated P. falciparum Malaria

The efficacy of Artemether & Lumefantrine Tablets was evaluated for the treatment of acute, uncomplicated malaria (defined as symptomatic P. falciparum malaria without signs and symptoms of severe malaria or evidence of vital organ dysfunction) in five 6-dose regimen studies and one study comparing the 6-dose regimen with the 4-dose regimen. Baseline parasite density ranged from 500/µl - 200,000/µl (0.01% to 4% parasitemia) in the majority of patients. Studies were conducted in otherwise healthy, partially immune or non-immune adults and children (≥5kg body weight) with uncomplicated malaria in Thailand, sub-Saharan Africa, Europe, and South America.

Efficacy endpoints consisted of:

- 28-day cure rate, proportion of patients with clearance of asexual parasites within 7 days without recrudescence by day 28
- parasite clearance time (PCT), defined as time from first dose until first total and continued disappearance of asexual parasite which continues for a further 48 hours
- fever clearance time (FCT), defined as time from first dose until the first time body temperature fell below 37.5°C and remained below 37.5°C for at least a further 48 hours (only for patients with temperature >37.5°C at baseline)

The modified intent to treat (mITT) population includes all patients with malaria diagnosis confirmation who received at least one dose of study drug. Evaluable patients generally are all patients who had a day 7 and a day 28 parasitological assessment or experienced treatment failure by day 28. The results are presented in the table below:

Table 2 Clinical efficacy results

Study No.	**Age**	**Polymerase chain reaction (PCR)-corrected 28-day cure rate[1] n/N (%) in evaluable patients**	**Median FCT[2] [25th, 75th percentile]**	**Median PCT[2] [25th, 75th percentile]**	**Year/ Study location**

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A025[4]	3-62 years	93/96 (96.9)	n[3]=59 35 hours [20, 46]	n=118 44 hours [22, 47]	1996-97 Thailand
A026	2-63 years	130/133 (97.7)	n[3]=87 22 hours [19, 44]	NA	1997-98 Thailand
A028	12-71 years	148/154 (96.1)	n[3]=76 29 hours [8, 51]	n=164 29 hours [18, 40]	1998-99 Thailand
A2401	16-66 years	119/124 (96.0)	n[3]=100 37 hours [18, 44]	n=162 42 hours [34, 63]	2001-05 Europe, Columbia
A2403	2 months-9 years	289/299 (96.7)	n[3]=309 8 hours [8, 24]	n=310 24 hours [24, 36]	2002-03 3 countries in Africa
B2303[CT]	3 months-12 years	403/419 (96.2)	n[3]=323 8 hours [8, 23]	n=452 35 hours [24, 36]	2006-07 5 countries in Africa
B2303[DT]	3 months-12 years	394/416 (94.7)	n[3]=311 8 hours [8, 24]	n=446 34 hours [24, 36]	2006-07 5 countries in Africa

[1] Efficacy cure rate based on blood smear microscopy
[2] mITT population
[3] For patients who had a body temperature >37.5°C at baseline only
[4]Only the 6-dose regimen over 60 hour's group data is presented
[CT] –Artemether & Lumefantrine tablets administered as crushed tablets
[DT] –Artemether & Lumefantrine Dispersible tablets

Artemether & Lumefantrine 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. In 319 adult patients in whom gametocytes were present, the median time to gametocyte clearance with Artemether & Lumefantrine was 96 hours. Artemether & Lumefantrine is active against blood stages of *Plasmodium vivax*, but is not active against hypnozoites.

Paediatric population

Three studies have been conducted

Study A2403 was conducted in Africa in 310 infants and children aged 2 months to 9 years, weighing 5 kg to 25 kg, with an axillary temperature ≥37.5°C. Results of 28-day cure rate (PCR-corrected), median parasite clearance time (PCT), and fever clearance time (FCT) are reported in table 3 below.

Study B2303 was conducted in Africa in 452 infants and children, aged 3 months to 12 years, weighing 5 kg to <35 kg, with fever (≥37.5°C axillary or ≥38°C rectally) or history of fever in the preceding 24 hours. This study compared crushed tablets and dispersible tablets. Results of 28-day cure rate (PCR-corrected), median parasite clearance time (PCT), and fever clearance time (FCT) for crushed tablets are reported in table 3 below.

Table 3 Clinical efficacy by weight for pediatric studies

Study No. **Weight category**	**Median PCT[1]** **[25th, 75th percentile]**	**PCR-corrected 28-day cure rate[2] n/N (%) in evaluable patients**
Study A2403		
5 - <10 kg	24 hours [24, 36]	145/149 (97.3)
10 - <15 kg	35 hours [24, 36]	103/107 (96.3)
15 -25 kg	24 hours [24, 36]	41/43 (95.3)
Study B2303[CT]		
5 - <10 kg	36 hours [24, 36]	65/69 (94.2)
10 - <15 kg	35 hours [24, 36]	174/179 (97.2)
15 -<25 kg	35 hours [24, 36]	134/140 (95.7)
25-35 kg	26 hours [24, 36]	30/31 (96.8)

[1] mITT population

[2] Efficacy cure rate based on blood smear microscopy

[CT] Artemether & Lumefantrine tablets administered as crushed tablets

Study B2306, was a multi-centre, open-label, single-arm study conducted in 20 infants in Africa,

Benin and Burkina Faso to evaluate the efficacy, safety and pharmacokinetics of dispersible tablets in infants aged >28 days and <5 kg of body weight, who were treated with one dispersible tablet (20 mg artemether/120 mg lumefantrine) given twice-daily for three days and followed up for six weeks (core follow-up) and at the age of 12 months (long-term follow-up).

Dispersible tablets were well tolerated with reported adverse events of mild to moderate severity. In the per protocol population, PCR-corrected cure rate at days 28 and 42 was 100% (95% CI: 79.4, 100). For important exposure results. Although neurotoxicity was not observed in the patients in Study B2306, artemether has been associated with neurotoxicity in studies in rats and dogs.

QT/QTc Prolongation:

Adults and children with malaria
For information on the risk of QT/QTc prolongation in patients.
Healthy adults

In a healthy adult volunteer parallel group study including a placebo and moxifloxacin control group (n=42 per group), the administration of the six dose regimen of Artemether & Lumefantrine was associated with prolongation of QTcF. The mean changes from baseline at 68, 72, 96, and 108 hours post first dose were 7.45, 7.29, 6.12 and 6.84 msec, respectively. At 156 and 168 hours after first dose, the changes from baseline for QTcF had no difference from zero. No subject had a >30 msec increase from baseline nor an absolute increase to >500 msec. Moxifloxacin control was associated with a QTcF increase as compared to placebo for 12 hours after the single dose with a maximal change at 1 hour after dose of 14.1 msec.

In the adult/adolescent population included in clinical trials, 8 patients (0.8%) receiving Artemether & Lumefantrine experienced a QTcB >500 msec and 3 patients (0.4%) a QTcF >500 msec. Prolongation of QTcF interval >30 msec was observed in 36% of patients.

In clinical trials conducted in children with the 6-dose regimen, no patient had post-baseline QTcF >500 msec whereas 29.4% had QTcF increase from baseline >30 msec and 5.1% >60 msec. In clinical trials conducted in adults and adolescents with the 6-dose regimen, post-baseline QTcF prolongation of >500 msec was reported in 0.2% of patients, whereas QTcF increase from baseline >30 msec was reported in 33.9% and >60 msec in 6.2% of patients.

In the infant/children population included in clinical trials, 3 patients (0.2%) experienced a QTcB >500 msec. No patient had QTcF >500 msec. Prolongation of QTcF intervals >30 msec was observed in 34% of children weighing 5-10 kg, 31%

of children weighing 10-15 kg and 24% of children weighing 15-25 kg, and 32% of children weighing 25-35 kg.

5.2 Pharmacokinetic properties

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

Absorption

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

Biotransformation

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*.

Glucuronidation of dihydroartemisinin is predominately catalysed by UGT1A9 and UGT2B7.

Dihydroartemisinin is further converted to inactive metabolites.

The pharmacokinetics of artemether in adults is time-dependent. During repeated administration of Artemether & 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. Artemether and dihydroartemisinin were reported to have a mild inducing effect on CYP3A4 activity. The clinical evidence of induction is consistent with the *in vitro* data described.

Lumefantrine is N-debutylated, mainly by CYP3A4, in human liver microsomes. *In vivo* in animals (dogs and rats), glucuronidation of lumefantrine takes place directly and after oxidative biotransformation. In humans, the exposure to lumefantrine increases with repeated administration of Artemether & Lumefantrine over the 3-day treatment period, consistent with the slow elimination of the compound.ystemic exposure to the metabolite desbutyl-lumefantrine, for which the *in vitro* antiparasitic effect is 5 to 8 fold higher than that for lumefantrine, was less than 1% of the exposure to the parent drug. Desbutyl-lumefantrine data is not available specifically for an African population. *In vitro,* lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations.

Elimination

Artemether and dihydroartemisinin are rapidly cleared from plasma with a terminal half-life of about 2 hours. Lumefantrine is eliminated very slowly with an elimination half-life of 2 to 6 days. Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of Artemether & Lumefantrine.

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

In animals (rats and dogs), no unchanged artemether was detected in faeces and urine due to its rapid and extensive first-pass metabolism, but numerous metabolites (partly identified) have been detected in faeces, bile and urine. Lumefantrine was excreted unchanged in faeces and with traces only in urine. Metabolites of lumefantrine were eliminated in bile/faeces.

Dose proportionality

No specific dose proportionality studies were performed. Limited data suggest a dose-proportional increase of systemic exposure to lumefantrine when doubling the Artemether & Lumefantrine dose. No conclusive data is available for artemether.

Bioavailability/bioequivalence studies

Systemic exposure to lumefantrine, artemether and dihydroartemisinin was similar following administration of Artemether & Lumefantrine as dispersible tablets and crushed tablets in healthy adults.

Systemic exposure to lumefantrine was similar following administration of Artemether & Lumefantrine dispersible tablets and intact tablets in healthy adults. However, exposure to artemether and dihydroartemisinin was significantly lower (by 20-35%) for the dispersible than for the intact tablet. These findings are not considered to be clinically relevant for the use of the dispersible tablets in the paediatric population since adequate efficacy of Artemether & Lumefantrine dispersible tablets was demonstrated in this population. The dispersible tablet is not recommended for use in adults.

Older people

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.

Paediatric population

In paediatric malaria patients, mean Cmax (CV%) of artemether (observed after first dose of Artemether & Lumefantrine) 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 Artemether & Lumefantrine) 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.

Infants weighing <5 kg

Study B2306 showed that the C_{max} of artemether and DHA in infants with uncomplicated *P. falciparum* malaria weighing <5 kg and older than 28 days of age who were treated with artemether/lumefantrine dispersible tablets, was on average 2- to 3-fold higher than that in pediatric patients with a body weight ≥5 kg and children up to 12 years of age treated with the same dose of Artemether & Lumefantrine tablets. The mean C_{max} of lumefantrine was similar to that observed in pediatric patients with a body weight ≥5 kg.

Race/Ethnicity

Pharmacokinetics of artemether, DHA and lumefantrine in the Japanese population was found to be consistent with other populations.

Hepatic and Renal impairment

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 insignificant renal excretion of lumefantrine, artemether and dihydroartemisinin, no dose adjustment for the use of Artemether & Lumefantrine in patients with renal impairment is advised.

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 adult 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

Artemether and lumefantrine were not genotoxic/clastogenic based on *in vitro* and *in vivo* testing.

Carcinogenicity

Carcinogenicity studies were not conducted.

Reproductive toxicity studies

Embryotoxicity was observed in rat and rabbit reproductive toxicity studies conducted with artemether, a derivative of artemisinin. Artemisinins are known to be embryotoxic. Lumefantrine alone caused no sign of reproductive or development toxicity at doses up to 1,000 mg/kg/day in rats and rabbits, doses which are at least

10 times higher than the daily human dose based on body surface area comparisons.

Reproductive toxicity studies performed with the artemether-lumefantrine combination caused maternal toxicity and increased post-implantation loss in rats and rabbits.

Artemether caused increases in post-implantation loss and teratogenicity (characterised as a low incidence of cardiovascular and skeletal malformations) in rats and rabbits. The embryotoxic artemether dose in the rat yields artemether and dihydroartemisinin exposures similar to those achieved in humans based on AUC.

Fertility

Artemether-lumefantrine administration yielded altered sperm motility, abnormal sperm, reduced epididymal sperm count, increased testes weight, and embryotoxicity; other reproductive effects (decreased implants and viable embryos, increased preimplantation loss) were also observed. 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 study investigated the neurotoxicity of oral Artemether in juvenile rats. Mortality, clinical signs and reductions in body weight parameters occurred most notably in younger rats. 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 in juvenile rats.

Very young animals are more sensitive to the toxic effect of artemether than adult animals. There is no difference in sensitivity in slightly older animals compared to adult animals. 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 $\geq$600 mg/kg/day, there was some evidence of prolongation of the QTc interval (safety margin of 1.3-fold to 2.2-fold for Artemether using calculated free Cmax), at higher doses than intended for use in man. In vitro hERG assays showed a safety margin of >100 for artemether and dihydroartemisinin. The hERG IC_{50} was 8.1 µM for lumefantrine and 5.5 µM for its desbutyl metabolite.

6. Pharmaceutical Particulars:

Artemether & Lumefantrine Tablet 80/480 mg

6.1 List of excipients

- Sodium starch Glycolate
- Colloidal silicon dioxide
- Microcrystalline cellulose
- Maize starch
- PVPK-30
- Methyl Paraben
- Propyl Paraben
- HPMC 15 CPS
- Purified Water
- Magnesium Stearate
- Talc
- Cross Carmellose sodium
- Methylene chloride
- Isopropyl alcohol
- Colour Tartrazine yellow

6.2 Incompatibilities

None stated

6.3 Shelf life

3 Years from the date of manufacture.

6.4 Special precautions for storage

Store below 30°C.

Protect from light and moisture.

6.5 Nature and contents of container

Pack 6 Tablets in a Blister with the help of aluminum foil and Golden Yellow PVDC in the arrangement of 1x6.Pack such 1 Blister in a printed Inner carton along with its package insert in the arrangement of 1x6's. Pack Such 10 Inner Cartons in an Outer Carton in the arrangement of 10x1x6's.

6.6- Special precautions for disposal <and other handling>

No special requirements

7- Manufacturer Name:

SURMOUNT LABORATORIES PVT. LTD.
Plot No A-2/4003, GIDC Ind. Estate,
Ankleshwar-393002, Gujarat, India
Email: surmountlaborat@gmail.com

SALOM DRUGS AND CHEMICAL COMPANY LTD,
AKINSOJI STREET OSHODI LAGOS

8.0 Marketing authorization number (s)

To be allocated

9.0 Date of first authorization / renewal of authorization

To be allocated

10.0 Date of revision of the text

To be allocated