TOPMAL 80/480 Tablets –SmPC
(Artemether 80 mg and Lumefantrine 480 mg Tablets)

Summary of Product Characteristics

1. Name of the Finished Pharmaceutical product

TOPMAL 80/480 Tablets
(Artemether 80 mg and Lumefantrine 480 mg Tablets)

2. Qualitative and Quantitative composition

Label claim:
Each uncoated Tablet Contains:
Artemether..... 80 mg
Lumefantrine .....480 mg
Excipients .....q.s.

Batch Formula:

Batch size: 1, 50,000 Tablets

Sr. No.	Ingredients	Reference	Function	Qty. in mg Per tablet	Overages (%)	Std. Qty. In Kg
Raw Material for Dry Mixing						
1	Artemether	IH	Active Pharmaceutical Ingredient	80.00	----	12.00
2	Lumefantrine	IH	Active Pharmaceutical Ingredient	480.00	-----	72.00
3	Microcrystalline cellulose PH-101*	USP	Diluents	168.00	----	25.20
4	Croscarmellose Sodium	USP	Disintegrant	75.00	----	11.25
5	Colloidal silicon dioxide	USP	Glidant	4.00	----	0.60
Raw Materials for Binding						
6	Hydroxypropyl Methyl Cellulose E-3	BP	Binder	16.00	----	2.40
7	Polysorbate- 80	BP	Binder	2.00	----	0.30
8	Purified Water	BP	Solvent	q.s.	----	q.s.
Raw Material for Pre Blending						
9	Microcrystalline Cellulose (Avicel PH-102)	USP	Diluents	76.00	----	11.40
10	Croscarmellose	USP	Disintegrant	37.00		5.55
11	Colloidal Silicon dioxide	USP	Glidant	4.00	----	0.60
Raw Material for Blending & Lubrication						
12	Magnesium Stearate	USP	Lubricant	18.00		2.70
Uncoated Tablet Weight				**960.00**	**----**	**144.00**

***** Quantity of Microcrystalline cellulose PH-101 is to be adjusted to compensate the Extra quantity of API

TOPMAL 80/480 Tablets –SmPC
(Artemether 80 mg and Lumefantrine 480 mg Tablets)

3. Pharmaceutical Form

Solid Dosage form

Yellow coloured, capsule shaped, biconvex uncoated tablets having central break line on one side and plain on other side.

4. Clinical Particulars

4.1 Therapeutic indications

Artemether and Lumefantrine Tablets is indicated for the treatment of acute uncomplicated *Plasmodium falciparum* malaria in adults, children and infants of 5 kg and above. It is also considered in cases resistant to both chloroquine and sulfadoxine- pyrimethamine combination.

Consideration should be given to official guidance regarding the appropriate use of antimalarial agents.

It is not indicated as first line of treatment for malaria.

4.2 Posology and method of administration

Posology

Adults and children weighing 35 kg and above

For patients 12 years of age and above and 35 kg body weight and above, a course of treatment comprises six doses of four tablets i.e. total of 24 tablets, given over a period of 60 hours as follows: the first dose of four tablets, given at the time of initial diagnosis, should be followed by five further doses of four tablets given at 8, 24, 36, 48 and 60 hours thereafter.

Children and infants weighing 5 kg to less than 35 kg

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

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

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

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

Special populations

Infants weighing less than 5 kg

The safety and efficacy of Artemether and Lumefantrine Tablets have not been established in infants weighing less than 5 kg and no dosing recommendations can be made.

Older people

There is no information suggesting that the dosage in patients over 65 years of age should be different than in younger adults.

Method of administration

Tablets for oral administration.

To increase absorption, Artemether and Lumefantrine Tablets should be taken with food or a milky drink. If patients are unable to tolerate food, Artemether and Lumefantrine Tablets should be administered, but the systemic exposure may be reduced.

TOPMAL 80/480 Tablets –SmPC
(Artemether 80 mg and Lumefantrine 480 mg Tablets)

Artemether and Lumefantrine dispersible tablets should be thoroughly dispersed in at least 30 ml of water prior to consumption. To disperse tablets, stir until a uniform dispersion forms and drink the entire dispersion immediately.
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.

4.3 Contraindications

Artemether and Lumefantrine Tablets is contraindicated in:

i. Patients with known hypersensitivity to the active substances or to any of the excipients.
ii. Patients with severe malaria according to WHO definition. (Severe malaria by definition is associated with a high mortality. From a clinical perspective, there is a continuum from asymptomatic malaria to uncomplicated illness through to severe and lethal malaria)
iii. Patients who are taking any drug which is metabolised by the cytochrome enzyme CYP2D6 (e.g. metoprolol, flecainide, imipramine, amitryptyline, clomipramine).
iv. Patients with a family history of sudden death or of congenital prolongation of the QTc interval onelectrocardiograms, or with any other clinical condition known to prolong the QTc interval.

- Patients taking drugs that are known to prolong the QTc interval (proarrythmic). These drugs include:
  - antiarrhythmics of classes IA (quinidine, procainamide, disopyramide) and III (aminodaronesotalol)
  - neuroleptics, antidepressive agents,
  - certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole andtriazole antifungal agents,
  - certain non-sedating antihistamines (terfenadine, astemizole),
  - cisapride.
- Patients with a history of symptomatic cardiac arrythmias or with clinically relevant bradycardia or withcongestive cardiac failure accompanied by reduced left ventricle ejection fraction.
- Patients with disturbances of electrolyte balance e.g. hypokalemia or hypomagnesemia.
- Patients taking drugs that are strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St.John's wort (Hypericumperforatum).

('Presence of one or more of the following clinical or laboratory features:
Clinical manifestation: Prostration; impaired consciousness or unarousable coma; failure to feed; deep breathing, respiratory distress (acidotic breathing); multiple convulsions; circulatory collapse or shock; pulmonary edema(radiological); abnormal bleeding; clinical jaundice; hemoglobinuria

Laboratory test: Severe normocytic anemia; hemoglobuniuria; hypoglycemia; metabolic acidosis; renal impairment; hyperlactatemia; hyperparasitemia)

4.4 Special warnings and precautions for use

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

TOPMAL 80/480 Tablets –SmPC
(Artemether 80 mg and Lumefantrine 480 mg Tablets)

Artemether and Lumefantrine 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, Artemether and Lumefantrine Tablets 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 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 Artemether and Lumefantrine Tablets.

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

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

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

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

Artemether and Lumefantrine Tablets 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 Tablets.

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

Caution is recommended when combining Artemether and Lumefantrine Tablets 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 Tablets.

Caution is recommended when combining Artemether and Lumefantrine Tablets with hormonal contraceptives. Artemetherand Lumefantrine Tablets 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 methodof 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/ortheir metabolites cannot be ruled out. Therefore, caution should be exercised in dosing patients with severe hepaticimpairment.

Renal impairment

No specific studies have been carried out in this group of patients. There is no significant renal

excretion of lumefantrine,artemether and dihydroartemisinin in studies conducted in healthy volunteers and clinical experience is limited. No doseadjustment for the use of Artemether and Lumefantrine Tablets in patients with renal impairment is recommended. Caution isadvised when administering Artemether and Lumefantrine Tablets 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 mildto moderate hepatic impairment. Caution is advised when administering Artemether and Lumefantrine Tablets to patients withsevere 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 Tablets. In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of Artemetherand Lumefantrine Tablets cannot be recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindications of concomitant use

Interaction with drugs that are known to prolong the QTc interval

Artemether and Lumefantrine Tablets is contraindicated with concomitant use of drugs (they may cause prolonged QTc interval and Torsade de Pointes) such as: antiarrhythmics of classes IA and III, neuroleptics and antidepressant agents, certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and triazoleantifungal agents, certain non-sedating antihistaminics (terfenadine, astemizole), cisapride, flecainide.

Interaction with drugs metabolized byCYP2D6

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 Artemether and Lumefantrine Tablets with drugs that are metabolised by this isoenzyme is contraindicated (e.g. neuroleptics, metoprolol, and tricyclic antidepressants such as imipramine, amitriptyline, clomipramine) is contraindicated.

Interaction with strong inducers of CYP3A4 such as rifampin

Oral administration of rifampin (600 mg daily), a strong CYP3A4 inducer, with Artemether and Lumefantrine Tablets (6-dose regimen over 3 days) in six HIV-1 and tuberculosis coinfected adults without malaria resulted in significant decreases in exposure to artemether (89%), DHA (85%) and lumefantrine (68%) when compared to exposure values after Artemetherand Lumefantrine Tablets

alone. Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin,St. John's Wort is contraindicated with Artemether and Lumefantrine Tablets.
Inducers should not be administered at least one month after Artemether and Lumefantrine Tablets administration, unlesscritical to use as judged by the prescriber.
Concomitant use not recommended
Interaction with other antimalarial drugs
Data on safety and efficacy are limited, and Artemether and Lumefantrine Tablets should therefore not be given concurrentlywith other antimalarials unless there is no other treatment option.
If Artemether and Lumefantrine Tablets is given following administration of mefloquine or quinine, close monitoring of foodintake (for mefloquine) or of the ECG (for quinine) is advised. The long elimination half-life of lumefantrine must be taken intoaccount when administering quinine in patients previously treated with Artemether and Lumefantrine Tablets. In patientspreviously treated with halofantrine, Artemether and LumefantrineTablets should not be administered earlier than one monthafter the last halofantrine dose.

Mefloquine

A drug interaction study with Artemether and Lumefantrine Tablets in man involved administration of a 6-dose regimen over60 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 Artemether and Lumefantrine Tablets were notaffected 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/dihydroartemisin in ratio but there was a significant reduction in plasma levels of lumefantrine, possibly due tolower absorption secondary to a mefloquine-induced decrease in bile production. Patients should be encouraged to eat atdosing times to compensate for the decrease in bioavailability.

Quinine

A drug interaction study in healthy male volunteers showed that the plasma concentrations of lumefantrine and quinine werenot affected when i.v. quinine (10 mg/kg BW over 2 hours) was given sequentially 2 hours after the last (sixth) dose ofArtemether and Lumefantrine Tablets (so as to produce concurrent plasma peak levels of lumefantrine and quinine). Plasmaconcentrations of artemether and dihydroartemisinin (DHA) appeared to be lower. In this study, administration of Artemetherand Lumefantrine Tablets to 14 subjects had no effect on QTc interval. Infusion of quinine alone in 14 other subjects caused atransient prolongation of QTc interval, which was consistent with the known cardiotoxicity of quinine. This effect was slightly, but significantly, greater when quinine was infused after Artemether and Lumefantrine Tablets in 14 additional subjects. Itwould thus appear that the inherent risk of QTc prolongation associated with i.v. quinine was enhanced by prior administrationof Artemether and Lumefantrine Tablets.

TOPMAL 80/480 Tablets –SmPC
(Artemether 80 mg and Lumefantrine 480 mg Tablets)

Concomitant use requiring caution Interactions affecting the use of Artemether and Lumefantrine Tablets

Interaction with CYP3A4 inhibitors

Both artemether and lumefantrine are metabolised predominantly by the cytochrome enzyme CYP3A4, but do not inhibit this enzyme at therapeutic concentrations.

Ketoconazole

The concurrent oral administration of ketoconazole with Artemether and Lumefantrine 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 Artemether and Lumefantrine Tablets is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors. Artemether and Lumefantrine Tablets should be used cautiously with drugs that inhibit CYP3A4 and are contraindicated with drugs which additionally are known to prolong QTc, due to potential for increased concentrations of lumefantrine which could lead to QT prolongation.

Grapefruit juice

Administration of artemether with grapefruit juice in healthy adult subjects resulted in an approximately two-fold increase in systemic exposure to the parent drug. Grapefruit juice should be used cautiously during Artemether and Lumefantrine Tablets treatment.

Interaction with weak to moderate inducers of CYP3A4

When Artemether and Lumefantrine Tablets is co-administered with moderate inducers of CYP3A4, it may result in decreased concentrations of artemether and/or lumefantrine and loss of antimalarial efficacy.

Interaction with anti-retroviral drugs such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors

Both artemether and lumefantrine are metabolized by CYP3A4. Anti-retroviral drugs (ARTs), such as protease inhibitors andnon-nucleoside reverse transcriptase inhibitors, are known to have variable patterns of inhibition, induction or competition forCYP3A4. Artemether and Lumefantrine Tablets 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 LumefantrineTablets, and increased lumefantrine concentrations may cause QT prolongation.

Looinavir/ ritonavir

In a clinical study in healthy volunteers, lopinavir/ritonavir decreased the systemic exposures to artemether and DHA byapproximately 40% but increased the exposure to lumefantrine by approximately 2.3- fold. Exposures to lopinavir/ritonavir were not significantly affected by concomitant use of Artemether and Lumefantrine Tablets.

Nevirapine
In a clinical study in HIV-infected adults, nevirapine significantly reduced the median Cmax and AUC of artemether by approximately 61% and 72%, respectively and reduced the median Cmax and AUC of dihydroartemisinin by approximately 45% and 37%, respectively. Lumefantrine Cmax and AUC were non-significantly reduced by nevirapine.
Artemether/lumefantrine reduced the median Cmax and AUC of nevirapine by approximately 43% and 46% respectively.

Efavirenz
Efavirenz decreased the exposures to Artemether, DHA, and Lumefantrine by approximately 50%, 45%, and 20%, respectively.
Exposures to efavirenz were not significantly affected by concomitant use of Artemether and Lumefantrine Tablets.

Interactions resulting in effects of Artemether and Lumefantrine Tablets on other drugs
Interaction with drugs metabolized by CYP45Q enzymes
When Artemether and Lumefantrine Tablets is co-administered with substrates of CYP3A4 it may result in decreased concentrations of the substrate and potential loss of substrate efficacy. Studies in humans have demonstrated that artemisinin's 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 metabolized by these enzymes.

Interaction with hormonal contraceptives
In vitro, the metabolism of ethinyl estradiol and Levonorgestrel was not induced by Artemether, DHA, or Lumefantrine. However, Artemether has been reported to weakly induce, in humans, the activity of CYP2C19, CYP2B6, and CYP3A. Therefore, Artemether and Lumefantrine Tablets may potentially reduce the effectiveness of hormonal contraceptives. Patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non hormonal method of birth control for about one month.

Drug-food/drink interactions
Artemether and Lumefantrine Tablets should be taken with food or drinks rich in fat such as milk as the absorption of both Artemether and Lumefantrine is increased.
Grapefruit juice should be used cautiously during Artemether and Lumefantrine Tablets treatment.

4.6 Fertility, pregnancy and lactation
Pregnancy
There is insufficient data from the use of artemether and lumefantrine in pregnant women. Based on

animal data, Artemether and Lumefantrine 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. Safety data from an observational pregnancy study of approximately 500 pregnant women who were exposed to Artemether and Lumefantrine Tablets (including a third of patients who were exposed in the first trimester), and published data of another over 500 pregnant women who were exposed to artemether- lumefantrine (including over 50 patients who were exposed inthe first trimester), as well as published data of over 1,000 pregnant women who were exposed to artemisinin derivatives, didnot show an increase in adverse pregnancy outcomes or teratogenic effects over background rates.
Artemether and Lumefantrine Tablets treatment must not be used during the first trimester of pregnancy in situations where other suitable and effective antimalarials are 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.

Women of childbearing potential
Women using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional nonhormonal method of birth control for about one month.

Lactation
Animal data suggest excretion into breast milk but no data are available in humans. Women taking Artemether and Lumefantrine Tablets should not breast-feed during their treatment. Due to the long elimination half-life of lumefantrine (2 to 6 days), it is recommended that breast-feeding should not resume until at least one week after the last dose of Artemether and Lumefantrine Tablets unless potential benefits to the mother and child outweigh the risks of Artemether and Lumefantrine Tablets treatment.

4.7 Effects on ability to drive and use machines
Patients receiving Artemether and Lumefantrine Tablets should be warned that dizziness or fatigue/asthenia may occur in which case they should not drive or use machines.

4.8 Undesirable effects
Adverse reactions reported from clinical studies and post-marketing experience are listed below according to system organ class.
Metabolism and nutrition disorders: Decreased appetite
Psychiatric disorders: Sleep disorders, Insomnia
Nervous system disorders: Headache, Dizziness, Paraesthesia, Clonus
Cardiac disorders: Palpitations, Electrocardiogram QT prolonged
Respiratory, thoracic and mediastinal disorders: Cough

Gastrointestinal disorders: Vomiting, Abdominal pain, Nausea, Diarrhoea
Hepatobiliary disorders: Liver function tests increased
Skin and subcutaneous tissue disorders: Rash, Pruritus
Musculoskeletal and connective tissue disorders: Arthralgia, Myalgia
General disorders and administration site conditions: Asthenia, Fatigue
Delayed haemolytic anaemia: Frequency unknown

4.9 Overdose

There is no information on overdose of Artemether and Lumefantrine Tablets higher than the doses recommended for treatment.
In case of suspected over dosage symptomatic and supportive therapy should be given as appropriate ECG and blood electrolyte levels should be monitored.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group*:* Antimalarials, blood Schizontocide
ATC code P01 BF01

Mechanism of Action:
Artemether and Lumefantrine Tablets is indicated for the treatment of acute uncomplicated Plasmodium falciparum malaria in adults, children and infants of 5 kg and above.
Consideration should be given to official guidance regarding the appropriate use of antimalarial agents

5.2 Pharmacokinetic properties

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

Absorption

Artemether is absorbed fairly rapidly and dihydroartemisinin, the active metabolite of artemether, appears rapidly in the systemic circulation with peak plasma concentrations of both compounds reached about 2 hours after dosing. Mean Cmaxand 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 and Lumefantrine Tablets. 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 5.109.80 pg/mL) about 6-8hours after dosing. Mean AUC values of lumefantrine ranged between 108 and 243 pgh/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 and Lumefantrine 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 microsomesmetaboliseartemether to the biologically active main metabolite dihydroartemisinin (demethylation), predominantly through the isoenzyme CYP3A4/5. This metabolite has also been detected in humans in vivo.
Dihydroartemisinin is further converted to inactive metabolites.
The pharmacokinetics of artemether in adults is time-dependent. During repeated administration of Artemether and Lumefantrine Tablets, 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 dihydroartemisininwere reported to have a mild inducing effect on CYP3A4 activity
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 and Lumefantrine Tablets over the 3-day treatment period, consistent with the slow elimination of the compound. Systemic 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 elevant effects on the

pharmacokinetics of Artemether and Lumefantrine Tablets.
Limited urinary excretion data are available for humans. In 16 healthy volunteers, neither lumefantrine nor artemether was found in urine after administration of Artemether and Lumefantrine Tablets, and only traces of dihydroartemisinin weredetected (urinary excretionof 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 firstpass 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

5.3 Preclinical safety data

General toxicity

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

Neurotoxicity

Studies in dogs and rats have shown that intramuscular injections of artemether resulted in brain lesions. Changes observed mainly in brainstem nuclei included chromatolysis, eosinophilic cytoplasmic granulation, spheroids, apoptosis and dark neurons. Lesions were observed in rats dosed for at least 7 days and dogs for at least 8 days, but lesions were not observed after shorter intramuscular treatment courses or after oral dosing. The estimated artemether 24 h AUC after 7 days of dosing at the no observed effect level is approximately 7-fold greater or more than the estimated artemether 24 h AUC in humans. The hearing threshold was affected at 20 dB by oral artemether administration to dogs at a dose of about 29 times the highest artemether clinical dose (160 mg/day) based on body surface area comparisons. Most nervous system disorder adverse events in the studies of the 6-dose regimen were mild in intensity and resolved by the end of the study.

Mutagenicity

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 embryotoxicartemether 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 ≥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.

Based on the available non-clinical data, a potential for QTc prolongation in the human cannot be discounted. For effects in the human see sections 4.3, 4.4 and 5.1.

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline Cellulose PH-101-USP
Crosscarmellose Sodium-USP
Colloidal Silicon dioxide-USP
Hydroxypropyl Methyl Cellulose E-3-BP
Polysorbate 80-BP
Purified Water-BP
Microcrystalline Cellulose-USP
Magnesium Stearate-USP

6.2 Incompatibilities

Not applicable.

TOPMAL 80/480 Tablets –SmPC
(Artemether 80 mg and Lumefantrine 480 mg Tablets)

TOPMAL 80/480 Tablets –SmPC
(Artemether 80 mg and Lumefantrine 480 mg Tablets)

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store below 30ºC. Protect from light and moisture.

6.5 Nature and contents of container
Alu- PVDC Blister pack of 06 tablets and such 10 Alu- PVC blisters are packed in a carton alongwith package inserts.

6.6 Special precautions for disposal and other handling
No special requirements.

7. Applicant/Holder of Certificate of Product Registration
Society for Family Health
Block IV Plot 24-28, Ogun State
Housing Corporation Estate
Off Idiroko Road, Ota, Ogun State.

8. Drug Product Manufacturer
Acme Formulation Pvt. Ltd.
Ropar Road, Nalagarh, Dist. Solan,
Himachal Pradesh-174 101 (India)

9. NAFDAC Registration number
B4-8975