Summary of Product Characteristics (SPC)

1. Name of the medicinal product
Artemether and lumefantrine Tablets 80/480mg

1.1 International Non-Proprietary Name (INN)
Artemether and lumefantrine Tablets 80/480mg

1.2 Strength
80/480mg

1.3 Pharmaceutical form
Oral solid dosage form.

2. Qualitative and quantitative composition
Each Uncoated tablet contains:
Artemether 80mg
Lumefantrine 480mg

3. Pharmaceutical form
Oral solid dosage form.

4. Clinical particulars
4.1 Therapeutic indications
Artemether and lumefantrine Tablets 80/480mg 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.

4.2 Posology and method of administration
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.

Infants weighing less than 5 kg

The safety and efficacy of Artemether and lumefantrine Tablets 80/480mg tablets have not been established in infants weighing less than 5 kg and no dosing recommendations can be made. Currently available data are described

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 80/480mg should be taken with food or a milky drink. If patients are unable to tolerate food, Artemether and lumefantrine Tablets 80/480mg should be administered with water, 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

4.3 Contraindications

Artemether and lumefantrine Tablets 80/480mg is contraindicated in:

• patients with known hypersensitivity to the active substances or to any of the excipients listed.

• patients with severe malaria according to WHO definition*.

• patients who are taking any drug which is metabolised by the cytochrome enzyme CYP2D6 (e.g. 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 (proarrythmic). 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.
- flecainide

• patients with a history of symptomatic cardiac arrythmias 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.

• patients taking drugs that are strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's wort (*Hypericum perforatum*).

(*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 80/480mg is not recommended during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available.

Artemether and lumefantrine Tablets 80/480mg 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 80/480mg 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 80/480mg, 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 80/480mg.

If quinine is given after Artemether and lumefantrine Tablets 80/480mg, close monitoring of the ECG is advised.

If Artemether and lumefantrine Tablets 80/480mg is given after mefloquine, close monitoring of food intake is advised.

In patients previously treated with halofantrine, Artemether and lumefantrine Tablets 80/480mg should not be administered earlier than one month after the last halofantrine dose.

Artemether and lumefantrine Tablets 80/480mg is not indicated and has not been evaluated for prophylaxis of malaria.

Artemether and lumefantrine Tablets 80/480mg should be used cautiously in patients on anti-retroviral drugs (ARTs) since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of Artemether and lumefantrine Tablets 80/480mg.

Like other antimalarials (e.g. halofantrine, quinine and quinidine) Artemether and lumefantrine Tablets 80/480mg has the potential to cause QT prolongation.

Caution is recommended when combining Artemether and lumefantrine Tablets 80/480mg 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 nonnucleoside reverse transcriptase inhibitors should be used with caution in patients taking Artemether and lumefantrine Tablets 80/480mg .

Caution is recommended when combining Artemether and lumefantrine Tablets 80/480mg with hormonal contraceptives. Artemether and lumefantrine Tablets 80/480mg may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal

patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control for about one month.
Patients who remain averse to food during treatment should be closely monitored as the risk of recrudescence may be greater.

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 dose adjustment for the use of Artemether and lumefantrine Tablets 80/480mg in patients with renal impairment is recommended. Caution is advised when administering Artemether and lumefantrine Tablets 80/480mg 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. In patients with severe hepatic impairment, a clinically relevant increase of exposure to artemether and lumefantrine and/or their metabolites cannot be ruled out. Therefore caution should be exercised in dosing patients with severe hepatic impairment. In these patients, ECG and blood potassium monitoring is advised. No dose adjustment is recommended for patients with mild to moderate hepatic impairment

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 80/480mg. In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of Artemether and lumefantrine Tablets 80/480mg 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 80/480mg 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 triazole antifungal agents, certain non-sedating antihistamines (terfenadine, astemizole), cisapride, flecainide.

Interaction with drugs metabolized by CYP2D6

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 80/480mg with drugs that are metabolised by this iso-enzyme 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 80/480mg 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 Artemether and lumefantrine Tablets 80/480mg alone. Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's Wort is contraindicated with Artemether and lumefantrine Tablets 80/480mg. Inducers should not be administered at least one

month after Artemether and lumefantrine Tablets 80/480mg administration, unless critical 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 80/480mg should therefore not be given concurrently with other antimalarials unless there is no other treatment option.

If Artemether and lumefantrine Tablets 80/480mg is given following administration of mefloquine or quinine, close monitoring of food intake (for mefloquine) or of the ECG (for quinine) is advised. The long elimination half-life of lumefantrine must be taken into account when administering quinine in patients previously treated with Artemether and lumefantrine Tablets 80/480mg. In patients previously treated with halofantrine, Artemether and lumefantrine Tablets 80/480mg should not be administered earlier than one month after the last halofantrine dose.

Mefloquine

A drug interaction study with Artemether and lumefantrine Tablets 80/480mg 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 Artemether and lumefantrine Tablets 80/480mg 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.

Quinine

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 Artemether and lumefantrine Tablets 80/480mg (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 Artemether and lumefantrine Tablets 80/480mg 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 cardiotoxicity of quinine. This effect was slightly, but significantly, greater when quinine was infused after Artemether and lumefantrine Tablets 80/480mg 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 Artemether and lumefantrine Tablets 80/480mg.

Concomitant use requiring caution

Interactions affecting the use of Artemether and lumefantrine Tablets 80/480mg

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 80/480mg 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 80/480mg is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors.

Artemether and lumefantrine Tablets 80/480mg should be used cautiously with drugs that inhibit CYP3A4 and are contraindicated with drugs which additionally are known to prolong QTc Contraindications), due to potential for increased concentrations of lumefantrine which could lead to QT prolongation.

Interaction with weak to moderate inducers of CYP3A4

When Artemether and lumefantrine Tablets 80/480mg 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. ARTs, such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, are known to have variable patterns of inhibition, induction or competition for CYP3A4.

Artemether and lumefantrine Tablets 80/480mg 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 80/480mg, and increased lumefantrine concentrations may cause QT prolongation.

Lopinavir/ ritonavir

In a clinical study in healthy volunteers, lopinavir/ritonavir decreased the systemic exposures to artemether and DHA by approximately 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 80/480mg.

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 80/480mg. Interactions resulting in effects of Artemether and lumefantrine Tablets 80/480mg on other drugs

Interaction with drugs metabolized by CYP450 enzymes

When Artemether and lumefantrine Tablets 80/480mg 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 artemisinins have some capacity to induce CYP3A4 and CYP2C19 and inhibit CYP2D6 and CYP1A2. Although the magnitude of the changes was generally low it is possible that these effects could alter the therapeutic response of drugs that are predominantly metabolised 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

80/480mg 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 nonhormonal method of birth control for about one month.

Drug-food/drink interactions

Artemether and lumefantrine Tablets 80/480mg 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 80/480mg treatment. Administration of artemether with grapefruit juice in healthy adult subjects resulted in an approximately two fold increase in systemic exposure to the parent drug.

4.6 Pregnancy and lactation

Women of childbearing potential

Women 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.

Pregnancy

A meta-analysis of observational studies including over 500 artemether-lumefantrine exposed women in their first trimester of pregnancy assessed adverse pregnancy outcomes. The data showed that compared to quinine, artemisinin treatment, including artemether-lumefantrine, was not associated with an increased risk of miscarriage, stillbirth or congenital anomalies. However, due to the limitations of these studies, the risk of adverse pregnancy outcomes for artemether-lumefantrine exposed women in early pregnancy cannot be excluded. Safety data from pregnancy studies including over 1200 pregnant women who were exposed to Artemether lumefantrine during the second or third trimester did not show an increase in adverse pregnancy outcomes or teratogenic effects over background rates.

Studies in animals have shown reproductive toxicity.

Artemether and lumefantrine Tablets 80/480mg treatment is not recommended 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, Artemether and lumefantrine Tablets 80/480mg treatment should be considered if the expected benefit to the mother outweighs the risk to the foetus.

Breast-feeding

Animal data suggest excretion into breast milk but no data are available in humans. Women taking Artemether and lumefantrine Tablets 80/480mg 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 80/480mg unless potential benefits to the mother and child outweigh the risks of Artemether and lumefantrine Tablets 80/480mg treatment.

Fertility

There is no information on the effects of Artemether and lumefantrine Tablets 80/480mg on human fertility.

4.7 Effects on ability to drive and use machines

Patients receiving Artemether and lumefantrine Tablets 80/480mg should be warned that dizziness or fatigue/asthenia may occur in which case they should not drive or use machines.

4.8 Undesirable effects

The safety of Artemether and lumefantrine Tablets 80/480mg has been evaluated in 20 clinical trials with more than 3500 patients. A total of 1810 adults and adolescents above 12 years of age as well as 1788 infants and children of 12 years of age and below have received Artemether and lumefantrine Tablets 80/480mg in clinical trials.

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 %)
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	--

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: antimalarials, blood schizontocide,

ATC code: P01 BF01.

Artemether and lumefantrine Tablets 80/480mg 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 and lumefantrine Tablets 80/480mg has been reported to have potent activity in terms of clearing gametocytes.

By 2015, resistance to artemisinins emerged in Southeast Asia. Studies with Artemether and lumefantrine Tablets 80/480mg 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 and lumefantrine Tablets 80/480mg 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.

Table 2 Clinical efficacy results

Study No.	Age	Polymerase chain reaction (PCR)-corrected 28-day cure rate1 n/N (%) in evaluable patients	Median FCT2 [25th, 75th percentile]	Median PCT2 [25th, 75th percentile]	Year/ Study location
A0254	3-62 years	93/96 (96.9)	n3=59 35 hours [20, 46]	n=118 44 hours [22, 47]	1996-97 Thailand
A026	2-63 years	130/133 (97.7)	n3=87 22 hours [19, 44]	NA	1997-98 Thailand
A028	12-71 years	148/154 (96.1)	n3=76 29 hours [8, 51]	n=164 29 hours [18, 40]	1998-99 Thailand
A2401	16-66 years	119/124 (96.0)	n3=100 37 hours [18, 44]	n=162 42 hours [34, 63]	2001-05 Europe, Columbia
A2403	2 months-9 years	289/299 (96.7)	n3=309 8 hours [8, 24]	n=310 24 hours [24, 36]	2002-03 3 countries in Africa
B2303CT	3 months-12 years	403/419 (96.2)	n3=323 8 hours [8, 23]	n=452 35 hours [24, 36]	2006-07 5 countries in Africa
B2303DT	3 months-12 years	394/416 (94.7)	n3=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
4Only the 6-dose regimen over 60 hours group data is presented
CT – Artemether and lumefantrine Tablets 80/480mg tablets administered as crushed tablets
DT – Artemether and lumefantrine Tablets 80/480mg Dispersible tablets
Artemether and lumefantrine Tablets 80/480mg 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 and lumefantrine Tablets 80/480mg was 96 hours. Artemether and

lumefantrine Tablets 80/480mg 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 PCT1 [25th, 75th percentile]	PCR-corrected 28-day cure rate2 n/N (%) in evaluable patients	
Study A2403 5 - <10 kg 10 - <15 kg 15 -25 kg	24 hours [24, 36] 35 hours [24, 36] 24 hours [24, 36]	145/149 (97.3) 103/107 (96.3) 41/43 (95.3)	
Study B2303CT 5 - <10 kg 10 - <15 kg 15 -<25 kg	36 hours [24, 36] 35 hours [24, 36] 35 hours [24, 36] 26 hours [24, 36]	65/69 (94.2) 174/179 (97.2) 134/140 (95.7) 30/31 (96.8)	

1 mITT population

2 Efficacy cure rate based on blood smear microscopy

CT Artemether and lumefantrine Tablets 80/480mg 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 and lumefantrine Tablets 80/480mg 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 and lumefantrine Tablets 80/480mg 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

Absorption	
Oral bioavailability	49.7– 104 ng/mL and 169-308 ng· h/ml in adult
Food effect	Food has also been shown to increase the absorption
Distribution	
Volume of distribution (mean)	---
Plasma protein binding in vitro	95.4% and 99.7%,
Tissue distribution	---
Metabolism	
	predominantly through the isoenzyme CYP3A4/5.
Active metabolite(s)	Human liver microsomes metabolise artemether to the biologically active main metabolite
Elimination	
Elimination half life	2 hours
Mean systemic clearance (Cl/F)	---
% of dose excreted in urine	NA*
% of dose excreted in faeces	NA*

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 >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 IC50 was 8.1 μ M for lumefantrine and 5.5 μ M for its desbutyl metabolite.

6. Pharmaceutical particulars

6.1 List of excipients

Povidone
Hypromellose
Microcrystalline Cellulose
Tartrazine Lake
Isopropyl Alcohol
Colloidal silicon Dioxide
Crosscarmellose Sodium
Magnesium Stearate

6.2 Incompatibilities

None Known.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C in a dry place.

6.5 Nature and contents of container

1 PVC Blister of 6 tablets are packed in mono carton along with insert.

6.6 Special precautions for disposal and other handling

None Known.

7. Manufactured By
Scott-Edil Pharmacia Limited,
56, EPIP, Phase-I, Jharmajri,
Baddi, Distt. Solan- 173205 (H.P)
INDIA

8. Marketed By
Scott-Edil Pharmacia Limited,
56, EPIP, Phase-I, Jharmajri,
Baddi, Distt. Solan- 173205 (H.P)
INDIA

9. Date of revision of the text
JUNE 2022

10. DOSIMETRY (IF APPLICABLE)
Not applicable

11. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)
Not Applicable