1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

FALCEE PLUS 80 / 480 MG
(Artemether and Lumefantrine Tablets)

2. Qualitative and quantitative composition

2.1 Label Claim

Each film coated tablet contains:

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

2.2 Quantitative Composition

S. No.	Ingredients	Label Claim	Property	Spec.	UOM	Overage (O.V.)	Qty. Per Mg /Tabs	Std Qty for (In Kg)
1	Artemether	80 mg	Active	IHS	Kg	Nil	80.00	8.000
2	Lumefantrine	480 mg	Active	USP	Kg	--	480.0	48.000
	Excipients							
3	Starch	--	Diluent	BP	Kg	--	100.00	10.000
4	Microcrystalline Cellulose	--	Diluent	BP	Kg	--	160.00	16.000
5	Croscarmellose Sodium	--	Disintegrate	BP	Kg	--	25.00	2.500
6	Povidone	--	Binder	BP	Kg	--	20.00	2.000
7	Isopropyl Alcohol	--	Solvent	BP	Kg	--	400.00	40.000
8	Colloidal Anhydrous Silica	--	Disintegrate	BP	Kg	--	5.00	0.500
9	Croscarmellose Sodium	--	Disintegrate	BP	Kg	--	30.00	3.000

10	Sodium Starch Glycolate	--	Disintegrate	BP	Kg	--	30.00	3.000
11	Purified Talc	--	Lubricant	BP	Kg	--	40.00	4.000
12	Magnesium Stearate	--	Lubricant	BP	Kg	--	30.00	3.000
Film coating								
1	H.P.M.C	--	Film former	BP	Kg	--	15.00	1.500
2	Polyethylene Glycol – 400	--	Plasticizer	BP	Kg	--	2.00	0.200
3	Titanium Dioxide	--	Colour/pigment	BP	Kg	--	5.00	0.500
4	Purified Talc	--	Anticaking agent	BP	Kg	--	4.70	0.470
5	Colour Tartrazine Yellow Lake	--	Colourant	IHS	Kg	--	0.30	0.030
6	Isopropyl Alcohol	--	solvent	BP	Kg	--	130.00	13.000
7	Dichloromethane	--	solvent	BP	Kg	--	400.00	40.000
	Average weight /weight of material in kg						**1025 mg**	**102.5 Kg**

Batch Size: 1.0 Lac

3. Pharmaceutical form

Yellow Coloured capsule shape biconvex, film coated tablet, break line on one side and plain on other side of each tablet.

4. Clinical particulars

4.1 Therapeutic indications

FALCEE PLUS 80 / 480 TABLETS is a combination of Artemether and Lumefantrine indicated for the treatment of acute uncomplicated Plasmodium falciparum malaria in adults, children and infants of 5 kg and above. As Artemether is effective against both drug sensitive and drug resistant P. Falciparum, it is also recommended for malaria infections acquired in areas where the parasites may be resistant to other antimalarials.

4.2 Posology and method of administration

Posology

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 FALCEE 80/480 should be given twice daily, morning and evening (i.e. 12 hours apart). To increase absorption, FALCEE 80/480 should be taken with food or a milky drink (see section 5.2). If a patient is unable to tolerate food, FALCEE 80/480 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 FALCEE 80/480 to patients with severe renal or hepatic problems (see section 4.4).

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.

Method of administration

Tablets for oral administration.

To increase absorption, FALCEE PLUS 80 / 480 MG should be taken with food or a milky drink. If patients are unable to tolerate food, FALCEE PLUS 80 / 480 MG 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

FALCEE PLUS 80 / 480 MG TABLETS is contraindicated in:

Patients with known hypersensitivity to the active substances or to any of the excipients

Patients with severe malaria according to WHO definition*.

Patients who are taking any drug which is metabolised by the cytochrome enzyme CYP2D6 (e.g. 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).

4.3 Special warnings and precautions for use

FALCEE PLUS 80 / 480 MG TABLETS must not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarials are available.

FALCEE PLUS 80 / 480 MG 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, FALCEE PLUS 80 / 480 MG TABLETS should not be given concurrently with any other antimalarial agent unless there is no other treatment option.

If a patient deteriorates whilst taking FALCEE PLUS 80 / 480 MG 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 FALCEE PLUS 80 / 480 MG TABLETS.

If quinine is given after FALCEE PLUS 80 / 480 MG TABLETS, close monitoring of the ECG is advised.

If FALCEE PLUS 80 / 480 MG TABLETS is given after Mefloquine, close monitoring of food intake is advised.

In patients previously treated with halofantrine, FALCEE PLUS 80 / 480 MG TABLETS should not be administered earlier than one month after the last halofantrine dose.

FALCEE PLUS 80 / 480 MG TABLETS is not indicated and has not been evaluated for prophylaxis of malaria.

FALCEE PLUS 80 / 480 MG TABLETS 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 FALCEE PLUS 80 / 480 MG TABLETS.

Like other antimalarial (e.g. halofantrine, quinine and quinidine) FALCEE PLUS 80 / 480 MG TABLETS has the potential to cause QT prolongation.

Caution is recommended when combining FALCEE PLUS 80 / 480 MG 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 FALCEE PLUS 80 / 480 MG TABLETS.

Caution is recommended when combining FALCEE PLUS 80 / 480 MG TABLETS with hormonal contraceptives. FALCEE PLUS 80 / 480 MG 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 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 FALCEE PLUS 80 / 480 MG TABLETS in patients with renal impairment is recommended. Caution is advised when administering FALCEE PLUS 80 / 480 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. 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.

Older people

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 FALCEE PLUS 80 / 480 MG TABLETS. In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of FALCEE PLUS 80 / 480 MG TABLETS cannot be recommended.

4.4 Interaction with other medicinal products and other forms of interaction

Interaction with drugs that are known to prolong the QTc interval

FALCEE PLUS 80 / 480 MG 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 triazole antifungal agents, certain non-sedating antihistaminics (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 FALCEE PLUS 80 / 480 MG TABLETS 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 FALCEE PLUS 80 / 480 MG 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 FALCEE PLUS 80 / 480

MG TABLETS alone. Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's Wort is contraindicated with FALCEE PLUS 80 / 480 MG TABLETS.

Inducers should not be administered at least one month after FALCEE PLUS 80 / 480 MG TABLETS 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 FALCEE PLUS 80 / 480 MG TABLETS should therefore not be given concurrently with other antimalarials unless there is no other treatment option.

If FALCEE PLUS 80 / 480 MG TABLETS 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 FALCEE PLUS 80 / 480 MG TABLETS. In patients previously treated with halofantrine, FALCEE PLUS 80 / 480 MG TABLETS should not be administered earlier than one month after the last halofantrine dose.

Mefloquine

A drug interaction study with FALCEE PLUS 80 / 480 MG TABLETS in man involved administration of a 6-dose regimen over 60 hours in healthy volunteers which was commenced at 12 hours after completion of a 3-dose regimen of Mefloquine or placebo. Plasma Mefloquine concentrations from the time of addition of FALCEE PLUS 80 / 480 MG TABLETS were not affected compared with a group which received Mefloquine followed by placebo.

Pre-treatment with Mefloquine had no effect on plasma concentrations of Artemether or the Artemether/dihydroartemisinin ratio but there was a significant reduction in plasma levels of Lumefantrine, possibly due to lower absorption secondary to a Mefloquine-induced decrease in bile production. Patients should be encouraged to eat at dosing times to compensate for the decrease in bioavailability.

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 FALCEE PLUS 80 / 480 MG TABLETS (so as to produce concurrent plasma peak levels of Lumefantrine and quinine). Plasma

concentrations of Artemether and dihydroartemisinin (DHA) appeared to be lower. In this study, administration of FALCEE PLUS 80 / 480 MG TABLETS to 14 subjects had no effect on QTc interval. Infusion of quinine alone in 14 other subjects caused a transient prolongation of QTc interval, which was consistent with the known cardiotoxicity of quinine. This effect was slightly, but significantly, greater when quinine was infused after FALCEE PLUS 80 / 480 MG TABLETS in 14 additional subjects. It would thus appear that the inherent risk of QTc prolongation associated with i.v. quinine was enhanced by prior administration of FALCEE PLUS 80 / 480 MG TABLETS.

Concomitant use requiring caution

Interactions affecting the use of FALCEE PLUS 80 / 480TABLETS

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

FALCEE PLUS 80 / 480 MG 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.

Interaction with weak to moderate inducers of CYP3A4

When FALCEE PLUS 80 / 480 MG 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. ARTs, such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, are known to have variable patterns

of inhibition, induction or competition for CYP3A4. FALCEE PLUS 80 / 480 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 FALCEE PLUS 80 / 480 TABLETS, 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 FALCEE PLUS 80 / 480 MG 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 FALCEE PLUS 80 / 480 MG TABLETS.

Interactions resulting in effects of FALCEE PLUS 80 / 480 MG TABLETS on other drugs

Interaction with drugs metabolized by CYP450 enzymes

When FALCEE PLUS 80 / 480 MG 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 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, FALCEE PLUS 80 / 480 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

FALCEE PLUS 80 / 480 MG 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 FALCEE PLUS 80 / 480 MG TABLETS 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.

4.5 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

Based on animal data, FALCEE PLUS 80 / 480 MG 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 FALCEE PLUS 80 / 480 MG 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 in the first trimester), as well as published data of over 1,000 pregnant women who were exposed to Artemisinin derivatives, did not show an increase in adverse pregnancy outcomes or teratogenic effects over background rates.

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 FALCEE PLUS 80 / 480 MG TABLETS the second and third trimester, treatment should only 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 FALCEE PLUS 80 / 480 MG 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 FALCEE PLUS 80 / 480 MG TABLETS unless potential benefits to the mother and child outweigh the risks of FALCEE PLUS 80 / 480 MG TABLETS

Fertility

There is no information on the effects of FALCEE PLUS 80 / 480 MG TABLETS on human fertility.

4.6 Effects on ability to drive and use machines

Patients receiving FALCEE PLUS 80 / 480 MG TABLETS should be warned that dizziness or fatigue/asthenia may occur in which case they should not drive or use machines.

4.7 Undesirable effects

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

They include:

Type of Disorder	Adults and adolescents above 12 years of age	Infants and children of 12 years of age and below

Immune system disorders Hypersensitivity	Not known	Rare
Metabolism and nutrition disorders Decreased appetite	Very common	Very common
Psychiatric disorders Sleep disorders Insomnia	Very common Common	Common Uncommon
Nervous system disorders Headache Dizziness Paraesthesia Ataxia, hypoaesthesia Somnolence	Very common Very common Very common Common	Very common Very common Common Common
Hepatobiliary disorders Liver function tests increased	Uncommon	Common

4.8 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.

Pharmacodynamic effects

FALCEE PLUS 80 / 480 MG TABLETS comprises a fixed ratio of 1:6 parts of Artemether and Lumefantrine, respectively. The site of antiparasitic action of both components is the food vacuole of the malarial parasite, where they are thought to interfere with the conversion of haem, a toxic intermediate produced during haemoglobin breakdown, to the nontoxic haemozoin, malaria pigment. Lumefantrine is thought to interfere with the polymerisation process, while Artemether generates reactive metabolites as a result of the interaction between its peroxide

bridge and haem iron. Both Artemether and Lumefantrine have a secondary action involving inhibition of nucleic acid- and protein synthesis within the malarial parasite.

Treatment of Acute Uncomplicated P. falciparum Malaria

The efficacy of FALCEE PLUS 80 / 480 MG 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.

5.3Pharmacokinetic properties

Pharmacokinetic characterisation of FALCEE PLUS 80 / 480 MG 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 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 FALCEE PLUS 80 / 480 MG TABLETS, 80 mg Artemether/480 mg Lumefantrine. Mean Cmax and AUC values of dihydroartemisinin ranged between 49.7-104 ng/mL and 169-308 ng·h/mL, respectively. Absorption of Lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentration (mean between 5.10-9.80 µg/mL) about 6-8 hours after dosing. Mean AUC values of Lumefantrine ranged between 108 and 243 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 FALCEE PLUS 80 / 480 MG 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%).

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.

Dihydroartemisinin is further converted to inactive metabolites.

The pharmacokinetics of Artemether in adults is time-dependent. During repeated administration of FALCEE PLUS 80 / 480 MG 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 dihydroartemisinin were reported to have a mild inducing effect on CYP3A4 activity. The clinical evidence of induction is consistent with the in vitro data.

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 FALCEE PLUS 80 / 480 MG 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 relevant effects on the pharmacokinetics of FALCEE PLUS 80 / 480 MG TABLETS.

Limited urinary excretion data are available for humans. In 16 healthy volunteers, neither Lumefantrine nor Artemether was found in urine after administration of FALCEE PLUS 80 / 480 MG TABLETS, 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 FALCEE PLUS 80 / 480 MG TABLETS dose. No conclusive data is available for Artemether.

Bioavailability/bioequivalence studies

Systemic exposure to Lumefantrine, Artemether and dihydroartemisinin was similar following administration of FALCEE PLUS 80 / 480 MG TABLETS as dispersible tablets and crushed

tablets in healthy adults.

Systemic exposure to Lumefantrine was similar following administration FALCEE PLUS 80 / 480 MG TABLETS 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 FALCEE PLUS 80 / 480 MG TABLETS 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 FALCEE PLUS 80 / 480 MG TABLETS) 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 FALCEE PLUS 80 / 480 MG TABLETS) were 577, 699 and 1150 µg•h/mL for paediatric malaria patients in body weight groups 5-<15, 15-<25 and 25-<35 kg, respectively, compared to a mean AUC of 758 µg•h/mL (87%) in adult malaria patients. The elimination half-lives of Artemether and Lumefantrine in children are unknown.

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 FALCEE PLUS 80 / 480 MG TABLETS 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 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 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.

6 Pharmaceutical particulars

6.1 List of excipients

Starch

Microcrystalline Cellulose BP

Croscarmellose Sodium BP

Povidone BP

Isopropyl Alcohol BP

Colloidal Anhydrous Silica BP

Croscarmellose Sodium BP

Sodium Starch Glycolate BP

Purified Talc BP

Magnesium Stearate BP

Hydroxy Propyl Methyl Cellulose BP

Polyethylene Glycol – 400 (PEG – 400)

Titanium Dioxide BP

Purified Talc

Colour: Tartrazine Yellow Lake IHS

Isopropyl Alcohol BP

Dichloromethane BP

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Keep out of reach of children Protect from light.
Store in a cool, & dry and dark place.

6.5 Nature and contents of container

6 Tablets packed in each blister, such 1 blister packed in each carton, such 10 cartons packed in each shrink such 20 shrinks packed in each shipper.

6.6 Special precautions for disposal and other handling

None stated.

7 Manufactured by

Hab Pharmaceuticals & Research Ltd.,
10, Pharmacity,
Selaqui, Dehradun,
Uttarakhand - 248011,
India.

8 Marketing authorisation holder

HAB PHARMACEUTICALS & RESEARCH LTD. **10, Pharmacity, Selaqui, Dehradun, Uttarakhand - 248011**	
PRODUCT NAME	**FALCEE PLUS 80 / 480 MG**
GENERIC NAME	**Artemether and Lumefantrine Tablets**

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