SUMMARY OF PRODUCT CHARACTERISTICS

(SmPC)

1. NAME OF THE MEDICINAL PRODUCT

ARTEMETHER 80mg + LUMEFANTRINE 480mg TABLETS- LARTEM FORTE

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:

Artemether……..80mg

Lumefantrine……..480mg

Excipients……..q.s.

{For a full list of excipients, see section 6.1}

3. PHARMACEUTICAL FORM

Yellow colored, capsules shape, uncoated biconvex tablet, having central break line on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LARTEM FORTE is a fixed-dose combination of artemether and lumefantrine, which acts as a blood schizontocide. It is indicated for:

Treatment, including stand-by emergency treatment of adults, children and infants (weighing 5 kg or more) with acute, uncomplicated infections due to Plasmodium falciparum or mixed infections including P. falciparum. Because LARTEM FORTE 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.

Stand-by emergency treatment:

Most tourists and business travellers, considered to be non-immune, will be able to obtain prompt medical attention if malaria is suspected. However, a minority at risk of infection may be unable to obtain such care within 24 hours of the onset of symptoms, particularly if they are in an isolated location far from medical services. In such cases, prescribers are advised to issue LARTEM FORTE to be carried by the traveller for self-administration or by the parent or caregiver for administration to the traveling child (“stand-by emergency

treatment").

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

4.2 Posology and method of administration

Oral. Should be taken with food. In acute uncomplicated falciparum malaria. A six dose regimen over three days is recommended, as described below:

Tablets have to be taken at interval of 8 hours after each dose. Adults and adolescents weighing 35kg and above 80mg/480mg tablets:

Weight in kg	Total Tablets	Dosage Regimen					
		DAY -1		DAY- 2		DAY- 3	
35 kgs and above		0 Hour (initial dose)	8 Hours (after 1st dose)	24 Hours	36 Hours	48 Hours	60 Hours
	6	1 tab	1 tab	1 tab	1 tab	1 tab	1 tab

To benefit the full therapeutic effect, 1he full course of medication (i.e., all 6 tablets) Must be taken over the 60 hours al intervals 81 indicated.

• If you vomit with one hour of taking the tablets, accidentally taken too many tablets, forget a dose, contact your doctor or pharmacist immediately.

New and recrudescent infections

Data for a limited number of patients with LARTEM FORTE show that new and recrudescent infections can be treated with a second course of the medication.

Special populations

Geriatric patients

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

Dosage in patients with renal impairment

No specific studies have been carried out in these groups of patients. There was no significant renal excretion of lumefantrine, artemether and dihydroartemisinin (DHA) in studies conducted in healthy volunteers and clinical experience is limited. No dose adjustment for the use of LARTEM FORTE in patients with renal impairment is recommended.

Dosage in patients with hepatic impairment

No specific studies have been carried out in this group of patients. No dose adjustment is recommended for patients with mild to moderate hepatic impairment. Caution should be exercised in dosing patients with severe hepatic impairment. Most patients with acute malaria present with some degree of related hepatic impairment. The adverse event profile did not differ in patients with and those without hepatic impairment. Moreover, baseline abnormalities in liver function tests improved in nearly all patients after treatment with LARTEM FORTE.

Method of administration

Tablets for oral administration

The dose should be taken with food or drinks rich in fat such as milk. A standard African diet with fat content ranging between 30 and 60 g/day or breast milk were shown to be adequate in Africa. Patients with acute malaria are frequently averse to food. Patients should be encouraged to resume normal eating as soon as food can be tolerated since this improves absorption of artemether and lumefantrine.

In the event of vomiting within 1 hour of administration a repeat dose should be taken

4.3 Contraindications

Artemether+ Lumefantrine tablet is contraindicated in:

- Known hypersensitivity to artemether, lumefantrine or to any of the excipients of Artemether+ Lumefantrine.
- Patients with severe malaria according to WHO definition.
- First trimester of pregnancy in situations where other suitable and effective anti-malarials are available.
- Patients with a family history of congenital prolongation of the QTc interval or sudden death or with any other clinical condition known to prolong the QTc interval such as patients with a history of symptomatic cardiac arrhythmias, with clinically relevant bradycardia or with severe cardiac disease.
- Patients taking drugs that are known to prolong the QTc interval such as:
  - antiarrhythmics of classes IA and III,
  - neuroleptics and antidepressant agents,
  - certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal agents,

- certain non-sedating antihistaminics (terfenadine, astemizole),
- cisapride.

- Patients with known disturbances of electrolyte balance e.g. hypokalemia or hypomagnesaemia.
- Patients taking any drug which is metabolized by the cytochrome enzyme CYP2D6 (e.g. flecainide, metoprolol, imipramine, amitriptyline, clomipramine).
- Patients taking drugs that are strong inducers of CYP3A4 such as rifampicin, carbamazepine, phenytoin, St. John's wort (Hypericum perforatum).

4.4 Special warnings and precautions for use

LARTEM FORTE has not been evaluated for prophylaxis and is therefore not indicated for prophylaxis.

LARTEM FORTE has not been evaluated for the treatment of cerebral malaria or other severe manifestations of severe malaria including pulmonary edema or renal failure.

LARTEM FORTE 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. LARTEM FORTE is active against blood stages of *Plasmodium vivax*, but is not active against hypnozoites.

Like other antimalarials (e.g. halofantrine, quinine, quinidine), LARTEM FORTE has the potential to cause QTc prolongation.

Patients who remain averse to food during treatment should be closely monitored as the risk of recrudescence may be greater.

If a patient deteriorates whilst taking LARTEM FORTE, 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 LARTEM FORTE.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions Resulting In A Contraindication

Interaction with drugs that are known to prolong the QTc interval

LARTEM FORTE 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.

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 LARTEM FORTE with drugs that are metabolised by this iso-enzyme is contraindicated (e.g. neuroleptics, flecainide, metoprolol, and tricyclic antidepressants such as imipramine, amitriptyline, clomipramine) is contraindicated.

Interaction with strong inducers of CYP3A4such as rifampicin

Oral administration of rifampicin (600 mg daily), a strong CYP3A4 inducer, with LARTEM FORTE Tablets (6-dose regimen over 3 days) in six HIV-1 and tuberculosis co-infected adults without malaria resulted in significant decreases in exposure to artemether (89%), DHA (85%) and lumefantrine (68%) when compared to exposure values after LARTEM FORTE alone. Concomitant use of strong inducers of CYP3A4 such as rifampicin, carbamazepine, phenytoin, St. John's wort is contraindicated with LARTEM FORTE.

Interactions resulting in concomitant use not being recommended Interaction with other antimalarial drugs

Data on safety and efficacy are limited, and LARTEM FORTE should therefore not be given concurrently with other antimalarials unless there is no other treatment option.

If LARTEM FORTE 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 LARTEM FORTE. In patients previously treated with halofantrine, LARTEM FORTE should not be administered earlier than one month after the last halofantrine dose. As patients to be treated with LARTEM FORTE may have recently been treated with other antimalarials, interactions with mefloquine and quinine were studied in healthy volunteers. The sequential oral administration of mefloquine prior to LARTEM FORTE had no effect on plasma concentrations of artemether or the artemether/ dihydroartemisinin ratio but there was a significant (around 30 to 40%) reduction in plasma levels (Cmax and AUC) 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 this decrease in bioavailability.

The concurrent i.v. administration of quinine (10 mg/kg BW) with LARTEM FORTE had no effect on plasma concentrations of lumefantrine or quinine. Plasma concentrations of artemether and dihydroartemisinin (DHA) appeared to be lower. In this study, administration of LARTEM FORTE 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 LARTEM FORTE 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 LARTEM FORTE. In a clinical trial in Thailand some adult patients received LARTEM FORTE following treatment failures with mefloquine or quinine. One hundred and twenty-one patients received LARTEM FORTE without any previous antimalarial treatment whereas 34 and 9 patients had measurable quinine or mefloquine, respectively, at enrolment. These patients showed similar safety and pharmacokinetic profiles of LARTEM FORTE to patients who had no detectable levels of other antimalarials.

Interactions to be considered

Interactions affecting the use of LARTEM FORTE Interaction with CYP 3A4 inhibitors

Both artemether and lumefantrine are metabolized by the cytochrome enzyme CYP3A4, and do not inhibit this enzyme at therapeutic concentrations. The concurrent oral administration of ketoconazole with LARTEM FORTE led to a modest increase (121-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 LARTEM FORTE is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors. However, due to the potential for increased concentrations of lumefantrine which could lead to QT prolongation, LARTEM FORTE should be used cautiously with drugs that inhibit CYP3A4. Administration of artemether with double concentrated grapefruit juice in healthy adult subjects resulted in an approximately two-fold increase in systemic exposure to the parent drug. Grapefruit juice should be avoided during LARTEM FORTE treatment.

Interaction with anti-retroviral drugs

Both artemether and lumefantrine are metabolized by CYP3A4. Anti-retroviral drugs, such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, are known to have variable patterns of inhibition, induction or competition for CYP3A4. 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, and efavirenz decreased the exposures to artemether, DHA, and lumefantrine by approximately 50%, 45%, and 20%, respectively. Exposures to lopinavir/ritonavir and efavirenz were not significantly affected by concomitant use of LARTEM FORTE should be used cautiously in patients on anti-retroviral drugs since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of AMATEM, and increased lumefantrine concentrations may cause QT prolongation.

Interaction with weak to moderate inducers of CYP3A4

When LARTEM FORTE is co-administered with weak to moderate inducers of CYP3A4 it may result in decreased concentrations of artemether and/or lumefantrine and loss of anti-malarial efficacy.

Interactions resulting in effects of LARTEM FORTE on other drugs Interaction with drugs metabolized by CYP450 enzymes

When LARTEM FORTE is co-administered with substrates of CYP3A4 it may result in decreased concentrations of the substrate and potential loss of substrate efficacy. Whereas in-vitro studies with artemether at therapeutic concentrations revealed no significant inhibition of CYP450 enzymes, artemether and DHA were reported to have a mild inducing effect on CYPs (2C19, 2B6 and 3A4) activity. Although the magnitude of the changes was generally low and is not expected to present a problem in the general patient population, it is possible that CYP3A4 induction could alter the therapeutic effects of drugs that are predominantly metabolised by this enzyme.

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, LARTEM FORTE 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.

Drug-food/drink interactions

LARTEM FORTE 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 avoided during LARTEM FORTE treatment.

4.6 Pregnancy and Lactation

Women of child-bearing potential and contraceptive measures

As LARTEM FORTE is contraindicated during the first trimester of pregnancy, women should not conceive while on LARTEM FORTE treatment for malaria. This includes women prescribed LARTEM FORTE for stand-by emergency treatment of malaria during their travel, in case they may require treatment for malaria.

Women of child-bearing potential should be advised to practice contraception during travel with stand-by emergency treatment, while on LARTEM FORTE and until the start of the next menstruation after the treatment.

Women using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control.

Pregnancy

Based on animal data, LARTEM FORTE is suspected to cause serious birth defects when administered during the first trimester of pregnancy.

Reproductive toxicity studies with artemether have shown evidence of post-implantation losses and teratogenicity in rats. Other artemisinin derivatives have in addition demonstrated teratogenic potential with an increased risk during early gestation.

Breast-feeding

Animal data suggest excretion into breast milk but no data are available in humans. Breast-feeding women should not take LARTEM FORTE. Due to the long elimination half-life of lumefantrine (2 to 6 days), it is recommended that breast-feeding should not resume before day 28 unless potential benefits to mother and child outweigh the risks of LARTEM FORTE treatment.

Fertility

There is no information on the effects of LARTEM FORTE on human fertility.

4.7 Effects on ability to drive and use machines

Not reported.

4.8 Undesirable effects

Summary of the safety profile

Most of the reported events were of mild to moderate severity and duration, and likely related to the underlying malaria and/or to an unsatisfactory response to the treatment rather than to LARTEM FORTE although a causal relationship with the use of LARTEM FORTE could not be excluded for some reports. For other reports alternative factors were identified as the more likely cause of the events (e.g. concomitant drugs, concomitant infections) or the information provided was too scarce to draw any conclusion.

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with LARTEM FORTE via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Hypersensitivity reactions including urticaria and angioedema.

4.9 Overdose

In cases of suspected overdosage, symptomatic and supportive therapy should be given as appropriate. ECG and electrolytes (e.g. potassium) should be monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeuticgroup: Antimalarial ATCcode:

QT/QTc Prolongation

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 LARTEM FORTE was associated with prolongation of QTcF. The mean changes compared to placebo from baseline at 68, 72, 96, and 108 h post first dose were 7.45, 7.29, 6.12 and 6.84 msec, respectively. At 156 and 168 h 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 h after the single dose with a maximal change at 1 h after dose of 14.1 msec.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.

5.2 Pharmacokinetic properties

Pharmacokinetic characterisation of LARTEM FORTE is limited by the lack of an intravenous formulation, and the very high inter-and intrasubject variability of artemether and lumefantrine plasma concentrations and derived pharmacokinetic parameters (AUC, Cmax).

Absorption

Artemether is absorbed fairly rapidly with peak plasma concentrations reached about 2 hours after dosing. Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentration about 6 to 8 hours after administration. 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 LARTEM FORTE 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 (DHA) is also bound to human serum proteins (47% to 76%). Protein binding to human plasma protein is linear.

Biotransformation/Metabolism

Artemether is rapidly and extensively metabolised (substantial first-pass metabolism). Human liver microsomes metabolise artemether to the biologically active main metabolite dihydroartemisinin (demethylation), predominantly through the enzyme CYP3A4/5. The pharmacokinetics of this metabolite has also been described in humans in vivo. The artemether/dihydroartemisinin AUC ratio is 1.2 after a single dose and 0.3 after 6 doses given over 3 days. Artemether and DHA were reported to have a mild inducing effect on CYP3A4 activity, which is not expected to present a problem in the general patient population.

During repeated administration of LARTEM FORTE, plasma artemether levels decreased significantly, while levels of the active metabolite (dihydroartemisinin) increased, although not to a statistically significant degree. This confirms that there was induction of the enzyme responsible for the metabolism of artemether.

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 systemic exposure to the metabolite desbutyl-lumefantrine, for which the in vitro antiparasitic effect is 5 to 8 fold higher than lumefantrine, was less than 1% of the exposure to the parent compound.

In vitro lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations.

Elimination

Artemether and dihydroartemisinin are rapidly cleared from plasma with an elimination half-life of about 2 hours, while 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 LARTEM FORTE.

In healthy volunteers, neither lumefantrine nor artemether was found in urine after administration of LARTEM FORTE, and urinary excretion of DHA 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. Lumefantrine was excreted unchanged in

faeces and with traces only in urine. Metabolites of both drug components were eliminated in bile/faeces and urine.

5.3 Preclinical safety data

Dose Proportionality

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

Bioavailability /bioequivalencestudies

Systemic exposure to lumefantrine, artemether and dihydroartemisinin was similar following administration of LARTEM FORTE as dispersible tablets and crushed tablets of 20 mg/120 mg in healthy adults.

Systemic exposure to lumefantrine was similar following administration of Artemether/Lumefantrine dispersible tablets and intact tablets of 20 mg/120 mg in healthy adults. However, exposure to artemether and dihydroartemisinin was significantly lower (by 20-35%) for the dispersible than for the intact tablet of 20 mg/120 mg. These findings are not considered to be clinically relevant for the use of the dispersible tablets in the pediatric population since adequate efficacy of Artemether/Lumefantrine dispersible tablets was demonstrated in this population. The dispersible tablet is not recommended for use in adults.

The 80 mg/480 mg tablet was shown to be bioequivalent to 4 tablets of 20 mg/120 mg in healthy adults.

Special populations Elderly patients

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.

Pediatrics

Systemic exposure to artemether, DHA, and lumefantrine when dosed on a mg/kg body weight basis in paediatric malaria patients (≥5 to <35 kg body weight) is comparable to that of the recommended dosing regimen in adult malaria patients.

Renal impairment

No specific pharmacokinetic studies have been performed in patients with renal impairment. However, based on the pharmacokinetic data in healthy subjects showing no or insignificant

renal excretion of lumefantrine, artemether and DHA, no dose adjustment for the use of LARTEM FORTE in patients with renal impairment is advised.

Hepatic impairment

No specific pharmacokinetic studies have been performed in patients with hepatic impairment. Metabolism is the primary clearance mechanism of both artemether and lumefantrine and 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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose Powder, Hypromellose E15 (Dry Mix) (Hydroxy Propyl Methyl Cellulose E15), Polysorbate 80, Maize Starch, Purified Water, Purified Talc, Magnesium Stearate, Crospovidone, Colloidal Anhydrous Silica.

6.2 Incompatibilities

Nil

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 30^0C in a dry place, Protect from light.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

Aluminium-PVDC coated PVC foil containing 6 tablets in one blister, such blister is packed in a printed carton along with pack insert

6.6 Special precautions for disposal <and other handling>

No special requirements.

7. APPLICANT/MANUFACTURER

Manufactured by:

S Kant
HEALTHCARE Ltd.
1802-1805, G.I.D.C.,Phase III,
Vapi - 396 195. Gujarat, INDIA.