1.3.1 Summary of Product Characteristics (SPC)

1. Name of the medicinal product

Artemether & Lumefantrine Tablets

2. Qualitative and quantitative composition

Each film coated tablet contains:

Artemether 80 mg

Lumefantrine 480 mg

Excipients Q.S.

3. Pharmaceutical form

Solid oral dosage form, film coated tablets

Yellow, biconvex, capsule shaped film coated tablets, having a break line on one side.

4. Clinical particulars

4.1 Therapeutic indications

An Artemether /Lumefantrine tablet is indicated for the treatment of acute uncomplicated cases of malaria due to Plasmodium falciparum in adults and children 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

Tablets for oral administration.

To increase absorption, Artemether & Lumefantrine should be taken with food or a milky drink. If patients are unable to tolerate food, Artemether & Lumefantrine should be administered, 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.

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.

4.3 Contraindications

Artemether & Lumefantrin is contraindicated in:

- Known hypersensitivity to artemether, lumefantrine or to any of the excipients of Artemether & Lumefantrin.
- 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

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

Artemether & Lumefantrine 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 & Lumefantrine should not be given concurrently with any other antimalarial agent unless there is no other treatment option.

If a patient deteriorates whilst taking Artemether & Lumefantrine, 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 & Lumefantrine.

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

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

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

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

Artemether & Lumefantrine 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 & Lumefantrine.

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

Caution is recommended when combining Artemether & Lumefantrine with drugs exhibiting variable patterns of inhibition, moderate induction or competition for CYP3A4 as the therapeutic effects of some drugs could be altered. Drugs that have a mixed inhibitory/induction effect on CYP3A4, especially anti-retroviral drugs such as HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors should be used with caution in patients taking Artemether & Lumefantrine.

Caution is recommended when combining Artemether & Lumefantrine with hormonal contraceptives. Artemether & Lumefantrine 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.

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.

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 & Lumefantrine in patients with renal impairment is recommended. Caution

is advised when administering Artemether & Lumefantrine to patients with severe renal impairment. In these patients, ECG and blood potassium monitoring is advised.

Hepatic impairment

No specific studies have been carried out in this group of patients. No dose adjustment is recommended for patients with mild to moderate hepatic impairment. Caution is advised when administering Artemether & Lumefantrine to patients with severe hepatic impairment. In these patients, ECG and blood potassium monitoring is advised.

Elderly

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

New infections

Data for a limited number of patients in a malaria endemic area show that new infections can be treated with a second course of Artemether & Lumefantrine. In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of Artemether & Lumefantrine cannot be recommended.

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

Artemether & Lumefantrin 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 Artemether

& Lumefantrin 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 CYP3A4 such as rifampicin

Oral administration of rifampicin (600 mg daily), a strong CYP3A4 inducer, with Artemether & Lumefantrin 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 Artemether & Lumefantrin alone. Concomitant use of strong inducers of CYP3A4 such as rifampicin, carbamazepine, phenytoin, St. John's wort is contraindicated with Artemether & Lumefantrin.

Interactions resulting in concomitant use not being recommended

Interaction with other antimalarial drugs

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

If Artemether & Lumefantrin 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 & Lumefantrin. In patients previously treated with halofantrine, Artemether & Lumefantrin should not be administered earlier than one month after the last halofantrine dose.

As patients to be treated with Artemether & Lumefantrin 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 Artemether & Lumefantrin 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 Artemether & Lumefantrin 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 Artemether & Lumefantrin 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 & Lumefantrin 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 & Lumefantrin.

In a clinical trial in Thailand some adult patients received Artemether & Lumefantrin following treatment failures with mefloquine or quinine. One hundred and twenty-one patients received Artemether & Lumefantrin 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 Artemether & Lumefantrin to patients who had no detectable levels of other antimalarials.

Interactions to be considered

Interactions affecting the use of Artemether & Lumefantrin

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 Artemether & Lumefantrin 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 & Lumefantrin 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, Artemether & Lumefantrin 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 Artemether & Lumefantrin 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 Artemether & Lumefantrin. Artemether & Lumefantrin 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 Artemether & Lumefantrin, and increased lumefantrine concentrations may cause QT prolongation.

Interaction with weak to moderate inducers of CYP3A4

When Artemether & Lumefantrin 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 Artemether & Lumefantrin on other drugs

Interaction with drugs metabolized by CYP450 enzymes

When Artemether & Lumefantrin 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, Artemether & Lumefantrin 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

Artemether & Lumefantrin 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 Artemether & Lumefantrin treatment.

4.6 Pregnancy and lactation

Women of child-bearing potential and contraceptive measures

As Artemether & Lumefantrin is contraindicated during the first trimester of pregnancy, women should not conceive while on Artemether & Lumefantrin treatment for malaria.

This includes women prescribed Artemether & Lumefantrin 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 Artemether & Lumefantrin 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, Artemether & Lumefantrin 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.

Safety data from an observational pregnancy study of approximately 500 pregnant women who were exposed to Artemether & Lumefantrin (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.

Artemether & Lumefantrin treatment is contraindicated during the first trimester of pregnancy in situations where other effective anti-malarials are available. However, it should not be withheld in life threatening situations where no other effective anti-malarials are available. During the second and the 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. Breastfeeding women should not take Artemether & Lumefantrin. 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 Artemether & Lumefantrin treatment.

Fertility

There is no information on the effects of Artemether & Lumefantrine on human fertility.

4.7 Effects on ability to drive and use machines

Patients receiving Artemether & Lumefantrine 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/lumefantrine has been evaluated in 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/lumefantrine 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 2: Frequency of undesirable effects

	Adults and adolescents above 12 years of age	**Infants and children of 12 years of age and below (incidence estimates*)**
Cardiac disorders		
Palpitations	Very common	Common
Electrocardiogram QT prolonged	Common	Common
Nervous system disorders		
Headache	Very common	Very common
Dizziness	Very common	Common
Paraesthesia	Common	--
Gait disturbance	Common	--
Ataxia, hypoaesthesia	Uncommon	--
Clonic movements, somnolence	Uncommon	Uncommon

Respiratory, thoracic and mediastinal disorders		
Cough	Common	Very common
Gastrointestinal disorders		
Vomiting	Very common	Very common
Abdominal pain	Very common	Very common
Nausea	Very common	Common
Anorexia	Very common	Very common
Diarrhoea	Common	Common
Skin and subcutaneous tissue disorders		
Rash	Common	Common
Pruritus	Common	Uncommon
Urticaria, angioedema*	Not known	Not known
Arthralgia	Very common	Common
Myalgia	Very common	Common

* These adverse reactions were reported during post-marketing experience. Because these spontaneously reported events are from a population of uncertain size, it is difficult to estimate their frequency.

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 and derivatives, combinations, ATC code: P01BF01

Pharmacodynamic effects

Artemether /Lumefantrine comprise 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 secondary action involving inhibition of nucleic acid- and protein synthesis within the malarial parasite.

The antimalarial activity of the combination of lumefantrine and artemether in Artemether /Lumefantrine tablets is greater than that of either substance alone. In a double-blind comparative study in adults in China (n=157), the 28-day cure rate of artemether/lumefantrine when given at four doses was 94% compared with 90% for lumefantrine and 46% for artemether based on intent-to-treat (ITT) population, when given as monotherapy. For the evaluable population, 28-day cure rates were 100% for artemether/lumefantrine, compared with 92% for lumefantrine and 55% for artemether when given as monotherapy.

In areas where multi-drug-resistant strains of *P. falciparum* malaria are common and in the resident population, 28-day cure rates with the 6 dose regimen (given over 60 to 96 h) were 81% and 90% for artemether/lumefantrine versus 94% and 96% for mefloquine/artesunate, based on the ITT population. For the evaluable population, 28-day cure rates were 97% and 95% for artemether/lumefantrine and 100% for mefloquine/artesunate.

In an open, multicenter clinical study conducted in Africa in 310 children weighing 5 kg to less than 25 kg and receiving a six-dose artemether/lumefantrine regimen according to their body weight range, Artemether/Lumefantrine 40mg/240mg Tablets, the mean 28-day parasitological cure rate (PCR-corrected) was 93.9% for the ITT population and 96.7% for the evaluable population.

In non-immune patients living in regions free of malaria but with malaria acquired when travelling in endemic regions, a similar efficacy and safety profile was shown. In an open study (n=165) in adults the 28-day cure rate for artemether/lumefantrine given as the six-dose regimen was 96% (119/124) for the evaluable and 74.1% (120/162) for the ITT population. The main causes of the difference between the evaluable and ITT cure rates were “lost to follow up” (33 patients) or protocol violations (intake of prohibited

concomitant medications). These two groups were considered as treatment failures in the ITT analysis.

Artemether/lumefantrine is active against blood stages of Plasmodium vivax, but is not active against hypnozoites.

QT/QTc Prolongation:

For information on the risk of QT/QTc prolongation in patients.

In a healthy adult volunteer parallel group study including a placebo and moxifloxacin control group (n = 42 per group), the administration of the six dose regimen of artemether/lumefantrine with food was associated with a moderate prolongation of QtcF (QT interval corrected by Fridericias formula). 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.

5.2 Pharmacokinetic properties

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

Absorption

Artemether is absorbed fairly rapidly and dihydro-artemisinin, the active metabolite of artemether, appears rapidly in the systemic circulation with peak plasma concentrations of both compounds reached about 2 hours after dosing. Mean Cmax and AUC values of artemether ranged between 60.0-104 ng/mL and 146-338 ng• h/mL, respectively, in fed healthy adults after a single dose of Artemether & Lumefantrine, 80 mg artemether/480 mg lumefantrine. Mean Cmax and AUC values of dihydro-artemisinin ranged between 49.7-104 ng/mL and 169-308 ng• h/mL, respectively. Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma

concentration (mean between 5.10-9.80 µg/mL) about 6-8 hours after dosing. Mean AUC values of lumefantrine ranged between 108 and 243 µg• h/mL. Food enhances the absorption of both artemether and lumefantrine: in healthy volunteers the relative bioavailability of artemether was increased more than two-fold, and that of lumefantrine sixteen-fold compared with fasted conditions when Artemether & Lumefantrine was taken after a high-fat meal.

Food has also been shown to increase the absorption of lumefantrine in patients with malaria, although to a lesser extent (approximately two-fold), most probably due to the lower fat content of the food ingested by acutely ill patients. The food interaction data indicate that absorption of lumefantrine under fasted conditions is very poor (assuming 100% absorption after a high-fat meal, the amount absorbed under fasted conditions would be <10% of the dose). Patients should therefore be encouraged to take the medication with a normal diet as soon as food can be tolerated.

Distribution

Artemether and lumefantrine are both highly bound to human serum proteins *in vitro* (95.4% and 99.7%, respectively). Dihydroartemisinin is also bound to human serum proteins (47-76%).

Metabolism

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 Artemether & Lumefantrine, plasma artemether levels decreased significantly, while levels of the active metabolite (dihydroartemisinin) increased, although not to a statistically significant degree. The ratio of day 3/day 1 AUC for artemether was between 0.19 and 0.44, and was between 1.06 and 2.50 for dihydroartemisinin. This suggests that there was induction of the enzyme responsible for

the metabolism of artemether. Artemether and dihydroartemisinin were reported to have a mild inducing effect on CYP3A4 activity.

Lumefantrine is N-debutylated, mainly by CYP3A4, in human liver microsomes. *In vivo* in animals (dogs and rats), glucuronidation of lumefantrine takes place directly and after oxidative biotransformation. In humans, the exposure to lumefantrine increases with repeated administration of Artemether & Lumefantrine over the 3-day treatment period, consistent with the slow elimination of the compound. 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 Artemether & Lumefantrine.

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

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

Dose proportionality

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

Bioavailability/bioequivalence studies

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

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

Special populations

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.

In paediatric malaria patients, mean Cmax (CV%) of artemether (observed after first dose of Artemether & Lumefantrine) were 223 (139%), 198 (90%) and 174 ng/mL (83%) for body weight groups 5-<15, 15-<25 and 25-<35 kg, respectively, compared to 186 ng/mL (67%) in adult malaria patients. The associated mean Cmax of DHA were 54.7 (108%), 79.8 (101%) and 65.3 ng/mL (36%), respectively compared to 101 ng/mL (57%) in adult malaria patients. AUC of lumefantrine (population mean, covering the six doses of Artemether & Lumefantrine) were 577, 699 and 1150 µg•h/mL for paediatric malaria patients in body weight groups 5-<15, 15-<25 and 25-<35 kg, respectively, compared to a mean AUC of 758 µg•h/mL (87%) in adult malaria patients. The elimination half-lives of artemether and lumefantrine in children are unknown.

No specific pharmacokinetic studies have been performed either in patients with hepatic or renal insufficiency or elderly patients. The primary clearance mechanism of both artemether and lumefantrine may be affected in patients with hepatic impairment. In patients with severe hepatic impairment, a clinically significant increase of exposure to artemether and lumefantrine and/or their metabolites cannot be ruled out. Therefore

caution should be exercised in dosing patients with severe hepatic impairment. Based on the pharmacokinetic data in 16 healthy subjects showing no or insignificant renal excretion of lumefantrine, artemether and dihydroartemisinin, no dose adjustment for the use of Artemether & Lumefantrine in patients with renal impairment is advised.

5.3 Preclinical safety data

General toxicity

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

Mutagenicity

No evidence of mutagenicity was detected in in-vitro or in-vivo tests with an artemether: lumefantrine combination (consisting of 1 part artemether: 6 parts lumefantrine). In the micronucleus test myelotoxicity was seen at all dose levels (500, 1,000 and 2,000 mg/kg), but recovery was almost complete 48 hours after dosing.

Carcinogenicity

Carcinogenicity studies with the artemether/lumefantrine combination were not conducted.

Reproductive toxicity studies

Reproductive toxicity studies performed with the artemether/lumefantrine combination caused maternal toxicity and increased post-implantation loss in rats and rabbits at doses 50 mg/kg/day (corresponding to approximately 7 mg/kg/day artemether) and 175 mg/kg/day (corresponding to 25 mg/kg/day artemether) respectively. These effects were not observed at lower doses.

Lumefantrine alone caused no sign of reproductive or development toxicity at doses up to 1,000 mg/kg/day in rats and rabbits.

Embryotoxicity has been observed in rat and rabbit reproductive toxicity studies conducted with artemether, a derivative of artemisinin. Artemisinins (e.g. artesunate) are known to be embryotoxic.

Artemether caused increases in post-implantation loss and teratogenicity (characterised as a low incidence of cardiovascular and skeletal malformations) in rats at 19.4 mg/kg, and in rabbits at 30 mg/kg. Maternal toxicity was also observed in rabbits at 30 mg/kg/day. No other adverse effects were observed at lower doses in rabbits. The no observed effect dose was 3 mg/kg/day in rats and 25 mg/kg/day in rabbits.

The embryotoxic artemether dose, 20 mg/kg/day in the rat, yields artemether and dihydroartemisinin exposures similar to those achieved in humans.

Artesunate, a structurally related compound, also caused increases in post-implantation loss and teratogenicity (low incidence of cardiovascular and skeletal malformations) in rats at 6 mg/kg and in the lowest dose tested in the rabbits, 5 mg/kg/day.

Cardiovascular Pharmacology

In toxicity studies in dogs at doses > 600 mg/kg/day only, there was some evidence of prolongation of the QTc interval, at higher doses than intended for use in man. In an in vitro assay of HERG channels, lumefantrine and the main metabolite desbutyl-lumefantrine showed some inhibitory potential in one of the currents responsible for cardiac repolarization. From the estimated IC50 values, the order of potency of HERG current block was halofantrine (IC50 = 0.04 μM) > chloroquine (2.5 μM) > mefloquine 2.6 μM) > desbutyl-lumefantrine (5.5 μM) > lumefantrine (8.1 μM). Clinical studies show, that prolongation of QTcF can occur with standard dosing of artemether/lumefantrine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Croscarmellose Sodium, HPMC E-5, Tween 80, Lactose, Talcum, Magnesium Stearate, Isopropyl alcohol, Colloidal silicon dioxide, Lake col: Tartrazine, H.P.M.C. E15, Titanium dioxide, P.E.G.-4000 and Methylene chloride.

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

3 years

6.4 Special precautions for storage

Store in dry & dark place, below 30°C.

6.5 Nature and contents of container

10 x 1 x 6 tablet packs in unit carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

Afrigenerics Pharmaceutical Limited

Flat 1 No 2, Iringa Street, Wuse Zone 6, Abuja, FCT.