1. Name of the medicinal product

LOKMAL (Artemether and Lumefantrine Tablets 20/100 mg)

2. Qualitative and quantitative composition

Each uncoated tablet contains:

Artemether 20mg

Lumefantrine 100 mg

3. Pharmaceutical form

Uncoated Tablets for Oral administration

4. Clinical particulars

4.1 Therapeutic indications

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 Artemether and Lumefantrine Tablets 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 Artemether and Lumefantrine Tablets 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.

4.3 Contraindications

Artemether and Lumefantrine Tablets is contraindicated in:

- Known hypersensitivity to artemether, lumefantrine or to any of the excipients of Artemether and Lumefantrine Tablets.
- 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).

* Presence of one or more of the following clinical or laboratory features: Clinical manifestation: Prostration; impaired consciousness or unarousable coma; failure to feed; deep breathing, respiratory distress (acidotic breathing); multiple convulsions; circulatory collapse or shock; pulmonary edema (radiological); abnormal bleeding; clinical jaundice; hemoglobinuria Laboratory test: Severe normocytic anemia; hemoglobuniuria; hypoglycemia; metabolic acidosis; renal impairment; hyperlactatemia; hyperparasitemia.

4.4 Special warnings and precautions for use

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

Artemether and Lumefantrine Tablets has not been evaluated for the treatment of cerebral malaria or other severe manifestations of severe malaria including pulmonary edema or renal failure.

Artemether and Lumefantrine Tablets 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. Artemether and Lumefantrine Tablets is active against blood stages of Plasmodium vivax, but is not active against hypnozoites.
Like other antimalarials (e.g. halofantrine, quinine, quinidine), Artemether and Lumefantrine Tablets 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 Artemether and Lumefantrine Tablets, alternative treatment for malaria should be started without delay. In such cases, monitoring of the ECG is recommended and steps should be taken to correct any electrolyte disturbances. The long elimination half-life of lumefantrine must be taken into account when administering quinine in patients previously treated with Artemether and Lumefantrine Tablets.

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 and Lumefantrine Tablets is contraindicated with concomitant use of drugs (they may cause prolonged QTc interval and Torsade de Pointes) such as:
antiarrhythmics of classes IA and III, neuroleptics and antidepressant agents, certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and 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 and Lumefantrine Tablets 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 and Lumefantrine Tablets 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 and Lumefantrine Tablets alone. Concomitant use of strong inducers of CYP3A4 such as rifampicin, carbamazepine, phenytoin, St. John’s wort is contraindicated with Artemether and Lumefantrine Tablets.

Interactions resulting in concomitant use not being recommended

Interaction with other antimalarial drugs

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

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

As patients to be treated with Artemether and Lumefantrine Tablets 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 and Lumefantrine Tablets 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 and Lumefantrine Tablets 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 and Lumefantrine 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 Artemether and Lumefantrine 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 Artemether and Lumefantrine Tablets.

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

Interactions to be considered

Interactions affecting the use of Artemether and Lumefantrine Tablets

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 2-fold) in artemether, DHA, and≤of ketoconazole with Artemether and Lumefantrine Tablets led to a modest increase (lumefantrine exposure in healthy adult subjects. This increase in exposure to the antimalarial combination was not associated with increased side effects or changes in electrocardiographic parameters. Based on this study, dose adjustment of Artemether and Lumefantrine Tablets is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors. However, due to the potential for increased concentrations of lumefantrine which could lead to QT prolongation, Artemether and Lumefantrine Tablets 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 and Lumefantrine Tablets 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 and Lumefantrine Tablets. Artemether and Lumefantrine Tablets 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 and Lumefantrine Tablets, and increased lumefantrine concentrations may cause QT prolongation.

Interaction with weak to moderate inducers of CYP3A4

When Artemether and Lumefantrine Tablets 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 and Lumefantrine Tablets on other drugs

Interaction with drugs metabolized by CYP450 enzymes
When Artemether and Lumefantrine Tablets is co-administered with substrates of CYP3A4 it may result in decreased concentrations of the substrate and potential loss of substrate efficacy. 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 and Lumefantrine Tablets may potentially reduce the effectiveness of hormonal contraceptives. Patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control.

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

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential and contraceptive measures
As Artemether and Lumefantrine Tablets is contraindicated during the first trimester of pregnancy, women should not conceive while on Artemether and Lumefantrine Tablets treatment for malaria. This includes women prescribed Artemether and Lumefantrine Tablets 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 and Lumefantrine Tablets 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 and Lumefantrine Tablets 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 and Lumefantrine Tablets (including a third of patients who were exposed in the first trimester), and published data of another over 500 pregnant women who were exposed to artemether-lumefantrine (including over 50 patients who were exposed 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 and Lumefantrine Tablets 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 lifethreatening 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 and Lumefantrine Tablets. 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 and Lumefantrine Tablets treatment.

Fertility
There is no information on the effects of Artemether and Lumefantrine Tablets on human fertility.

4.7 Effects on ability to drive and use machines

No effect on the ability to drive and use machines has been observed.

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

Artemether and Lumefantrine Tablets although a causal relationship with the use of Artemether and Lumefantrine Tablets 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.

Tabulated summary of adverse drug reactions from clinical trials adverse drug reactions from clinical trials are ranked under headings of frequency, the most frequent first, using the following 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 the available data).

Adverse drug reactions compiled from a pooled safety analysis in clinical trials in adults and adolescents >12 years of age using the recommended 6-dose regimen

Metabolism and nutrition disorders
Very common: Decreased appetite
Psychiatric disorders
Very common: Sleep disorder
Nervous system disorders
Very common: Headache, dizziness
Common: Clonus
Uncommon: Somnolence, hypoesthesia, ataxia
Cardiac disorders
Very common: Palpitations
Respiratory, thoracic and mediastinal disorders
Common: Cough
Gastrointestinal disorders
Very common: Vomiting, abdominal pain, nausea
Common: Diarrhea
Skin and subcutaneous tissue disorders
Common: Rash, pruritus
Uncommon: Urticaria
Musculoskeletal and connective tissue disorders
Very common: Arthralgia, myalgia
General disorders and administration site conditions
Very common: Asthenia, fatigue
Uncommon: Gait disturbance
Investigations
Uncommon: Electrocardiogram QT prolonged, liver function tests increased

Adverse drug reactions compiled from a pooled safety analysis of 4 studies in infants and children ≤12 years of age receiving a 6-dose regimen of Artemether and Lumefantrine Tablets or Artemether and Lumefantrine Tablets/Riamet Dispersible

Immune system disorders
Rare: Hypersensitivity
Metabolism and nutrition disorders
Very common: Decreased appetite
Psychiatric disorders
Uncommon: Sleep disorder
Nervous system disorders
Common: Headache, dizziness
Uncommon: Clonus, somnolence
Cardiac disorders
Uncommon: Palpitations
Respiratory, thoracic and mediastinal disorders
Very common: Cough
Gastrointestinal disorders
Very common: Vomiting
Common: Abdominal pain, diarrhea, nausea
Skin and subcutaneous tissue disorders
Common: Rash
Uncommon: Urticaria, pruritus
Musculoskeletal and connective tissue disorders
Common: Arthralgia, myalgia
General disorders and administration site conditions
Common: Asthenia, fatigue
Investigations
Common: Liver function tests increased
Rare: Electrocardiogram QT prolonged

Adverse events found in non-recommended regimens not included in this pooled safety analysis: paraesthesia (1.2% of adolescents and adults, no cases in children). The following adverse reactions were reported in adults with a frequency of uncommon but were not reported in infants or children: hypoesthesia, ataxia, and gait disturbance.

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 Artemether and Lumefantrine Tablets 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 Pharmacodynamic properties

Mechanism of action (MOA)

Artemether and Lumefantrine Tablets contain a fixed ratio of 1:6 parts of artemether and lumefantrine, respectively. Artemether is a semisynthetic chiral acetal derived from the naturally occurring substance artemisinin. Lumefantrine is a racemic mixture of a synthetic fluorene derivative. Like other antimalarials (quinine, mefloquine, halofantrine), lumefantrine belongs to the aryl-aminoalcohol family. 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 non-toxic 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. Data from invitro and in-vivo studies show that Artemether and Lumefantrine Tablets did not induce resistance.

Pharmacodynamic properties

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

Distribution

Artemether and lumefantrine are both highly bound to human serum proteins in vitro (95.4% and 99.7%, respectively). Dihydroartemisinin (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 Artemether and Lumefantrine Tablets, 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. 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 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 halflife of about 2 hours, while lumefantrine is eliminated very slowly with an elimination halflife of 2 to 6 days. Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of Artemether and Lumefantrine Tablets. In healthy volunteers, neither lumefantrine nor artemether was found in urine after administration of Artemether and Lumefantrine Tablets, 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.

Dose Proportionality
No specific dose proportionality studies were performed. Limited data suggest a doseproportional increase of systemic exposure to lumefantrine when doubling the Artemether and Lumefantrine Tablets dose. No conclusive data is available for artemether.

Bioavailability/bioequivalence studies
Systemic exposure to lumefantrine, artemether and dihydroartemisinin was similar following administration of Artemether and Lumefantrine Tablets/Riamet as dispersible tablets and crushed tablets of 20 mg/120 mg in healthy adults.
Systemic exposure to lumefantrine was similar following administration of Artemether and Lumefantrine Tablets/Riamet 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 and Lumefantrine Tablets/Riamet 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 Artemether and Lumefantrine Tablets 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

Excipients used are Povidone, Hypromellose, Microcrystalline cellulose, isopropyl alcohol, Colloidal silicon dioxide, Croscarmellose sodium, Magnesium stearte.

6.2 Incompatibilities

This medicinal product must not be used with other medicinal products.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in a cool dry place below 30° C, Protect from light.

Keep all medicines out of reach of children.

6.5 Nature and contents of container

Alu alu blister of 6 tablets is packed in a carton along with Pack Insert.

6.6 Special precautions for disposal and other handling

No Special precautions for disposal and other handling.

7. Manufactured By

EMZOR PHARMACEUTICAL INDUSTRIES LIMITED
FLOWER GATE MIXED DEVELOPMENT SCHEME
SAGAMU/BENIN EXPRESSWAY.SAGAMU,OGUN
STATE
NIGERIA.

9. Date of first authorization/renewal of the authorization

4th March 2018

10. Date of revision of the text

Not Applicable .