1. NAME OF THE MEDICINAL PRODUCT

Artemether 20mg + Lumefantrine 120mg Dispersible Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains 20 mg artemether and 120 mg lumefantrine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solid Oral Dosage Form- Dispersible Tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Indications

The Lariact Dispersible is indicated only for infants and children. It is indicated for the treatment of acute uncomplicated Plasmodium falciparum malaria in children and infants of 5 kg and above.

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

4.2 Posology and method of administration

Artemether 20mg + Lumefantrine 120mg dispersible Tablets - 6 tablets

A six-dose regimen over 3 days is recommended, as described below:

5 to <15 kg bodyweight:

One dispersible tablet at the time of initial diagnosis, 1 dispersible tablet again after 8 hours and then 1 dispersible tablet twice daily (morning and evening) on each of the following two days (total course comprises 6 dispersible tablets).

15 to <25 kg bodyweight:

Two dispersible tablets at the time of initial diagnosis, 2 dispersible tablets again after 8 hours and then 2 dispersible tablets twice daily (morning and evening) on each of the following two days (total course comprises 12 dispersible tablets).

Treatment and stand-by emergency treatment

The treatment should be administered at the time of initial diagnosis or at onset of symptoms.

New and recrudescent infections

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

Special populations

Geriatricpatients

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 Lariact Dispersible 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 Lariact Dispersible.

A Six-dose regimen over 3 days is recommended, as described below:

Artemether + Lumefantrine (20 + 120 mg)
6 Dispersible Tablets

Body Weight in Kg.	1st day 0 Hrs – 8 Hrs	2nd day 24 Hrs – 36 Hrs	3rd day 48 Hrs – 60 Hrs
05 to < 15 kg	1 Tablets 1	1 Tablets 1	1 Tablets 1

Artemether + Lumefantrine (20 + 120 mg)
12 Dispersible Tablets

Body Weight in Kg.	1st day 0 Hrs – 8 Hrs	2nd day 24 Hrs – 36 Hrs	3rd day 48 Hrs – 60 Hrs
15 to < 25 kg	2 Tablets 2	2 Tablets 2	2 Tablets 2

Method of administration Tablets for oral administration

The dispersible tablet(s) composing 1 dose should be completely dispersed in a small amount of water (approximately 10 mL per tablet). Stir gently and administer immediately to the patient. Rinse the glass with an additional small amount of water (approximately 10 mL) and give immediately to the patient. The dose should be followed by 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. The dispersible tablet is indicated only for infants and children.

4.3 Contraindications

Artemether & Lumefantrine Dispersible tablets are contraindicated in:

- Patients with severe malaria.
- Patients who are taking any drug which is metabolised by the cytochrome enzyme CYP2D6 (e.g. flecainide, metoprolol, imipramine, amitryptyline, clomipramine).
- Patients with a family history of sudden death or of congenital prolongation of the QTc interval on electrocardiograms, or with any other clinical condition known to prolong the QTc interval.
- Patients taking drugs that are known to prolong the QTc interval. These drugs include:
- antiarrhythmics of classes IA and III, neuroleptics, antidepressive agents,
- Certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole and triazole antifungal agents,
- Certain non-sedating antihistamines (terfenadine, astemizole, cisapride).

  Patients with a history of symptomatic cardiac arythmias or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricle ejection fraction.

4.4 Special warnings and precautions for use

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

Artemether & Lumefantrine Dispersible tablets should not be given concurrently with any other antimalarial agent unless there is no other treatment option. If quinine is given after Artemether & Lumefantrine Dispersible tablets, close monitoring of the ECG is advised.

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

Artemether & Lumefantrine Dispersible tablets are not indicated for the treatment of malaria due to P. vivax, P. malariae or P. ovale, although some clinical studies patientsin had co-infection with P. falciparum and P.vivax at baseline.

Artemether & Lumefantrine Dispersible tablets are active against blood stages of Plasmodium vivax, but is not active against hypnozoites.

Artemether & Lumefantrine Dispersible tablets are not Indicated and has not been evaluated for prophylaxis.

Caution is advised when administering Artemether and lumefantrine Tablets to patients with severe renal, hepatic or cardiac problems.

Avoid concomitant use of drugs known to prolong QT interval to monitor such patients. Renal/hepatic disease. Avoid combination with Pyrimethamine / Sulfadoxine.

Paediatric: Reduce the dose according to body weight.

Pregnancy: Avoid, especially in 1st trimester.

Lactation: Use with caution.

Elderly: Reduce dose according to body weight.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with drugs that are known to prolong the QTc interval

Artemether & Lumefantrine Dispersible Tablet 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 & Lumefantrine Dispersible Tablet 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 & Lumefantrine Dispersible Tablet (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 & Lumefantrine Dispersible Tablet alone. Concomitant use of strong inducers of CYP3A4 such as rifampicin, carbamazepine, phenytoin, St. John's wort is contraindicated with Artemether & Lumefantrine Dispersible Tablet.

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

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

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

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

Interactions to be considered

Interactions affecting the use of Artemether & Lumefantrine Dispersible Tablet

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 & Lumefantrine Dispersible Tablet 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 Artemether & Lumefantrine Dispersible Tablet 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 & Lumefantrine Dispersible Tablet 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 & Lumefantrine Dispersible Tablet 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 & Lumefantrine Dispersible Tablet 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 & Lumefantrine Dispersible Tablet, and increased lumefantrine concentrations may cause QT prolongation.

Interaction with weak to moderate inducers of CYP3A4

When Artemether & Lumefantrine Dispersible Tablet is co-administered with weak to moderate inducers of CYP3A it may result in decreased concentrations of artemether and/or lumefantrine and loss of anti-malarial efficacy.

Interactions resulting in effects of Artemether & Lumefantrine Dispersible Tablet on other drugs Interaction with drugs metabolized by CYP450 enzymes

When Artemether & Lumefantrine Dispersible Tablet 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 & Lumefantrine Dispersible Tablet 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/drinkinteractions

Artemether & Lumefantrine Dispersible Tablet 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 & Lumefantrine Dispersible Tablet treatment.

4.6 Pregnancy and Lactation

Pregnancy

Artemether & Lumefantrine Dispersible Tablet is suspected to cause serious birth defects when administered during the first trimester of pregnancy, so it must not be used during the first 3 months of pregnancy. If it is possible to use an alternative medicine first. However, it should not be withheld in life threatening situations, where no other effective antimalarials are available. During the second and third trimester, treatment shouldn't only be considered if the expected benefit to the mother outweighs the risk to the fetus.

Lactation

Women taking Artemether & Lumefantrine Dispersible Tablet should not breast-feed during their treatment. Due to the long elimination half-life of lumefantrine (4 to 6 days), it is recommended that breast-feeding should not resume until atleast one week after the last dose of Artemether & Lumefantrine tablets unless potential benefits to the mother and child outweigh the risks of Artemether & Lumefantrine Dispersible Tablet treatment.

4.7 Effects on ability to drive and use machines

Patients receiving Artemether & Lumefantrine Dispersible Tablet should be warned that dizziness or fatigue/asthenia may occur in which case they should not drive or use machines.

4.8 Undesirable effects

Like all medicines, Artemether & Lumefantrine Dispersible Tablet can cause side effects although not everybody gets them. Most of the side effects are mild to moderate and generally disappear after a few days to a few weeks after treatment. Some side effects are more commonly reported in children and others are more commonly reported in adults. In cases where there is a difference, the frequency listed below is the more common one.

Some side effects could be serious and need immediate medical attention (affecting less than 1 in 1,000 patients). If you get a rash, swelling of the face, lips, tongue or throat with difficulty in swallowing or breathing, tell your doctor straight away. These are signs of an allergic reaction.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

In cases of suspected over dosage symptomatic and supportive therapy should be given as appropriate, which should include ECG and blood potassium monitoring.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeuticgroup: antimalarials, blood schizonticide. ATC code: P01 BF01.

Artemether involves an interaction with ferriprotoporphyrin IX ("heme"), or ferrous ions, in the acidic parasite food vacuole, which results in the generation of cytotoxic radical species. The generally accepted mechanism of action of peroxide antimalarials involves interaction of the peroxide-containing drug with heme, a hemoglobin degradation byproduct, derived from proteolysis of hemoglobin. This interaction is believed to result in the formation of a range of potentially toxic oxygen and carbon-centered radicals.

The exact mechanism by which lumefantrine exerts its antimalarial effect is unknown. However, available data suggest that lumefantrine inhibits the formation of β-hematin by forming a complex with hemin and inhibits nucleic acid and protein synthesis.

5.2 Pharmacokinetic properties

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 6-8 hours after dosing.

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 twofold), most probably due to the lower fat content of the food ingested by acutely ill patients. The food inter-action 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 (97.9% and 99.9%, respectively). Comparable binding values were observed in animals. Distribution has not been further investigated in humans, but in rats artemether is well distributed throughout the body, with some affinity for the brown fat and adrenal glands, while lumefantrine has an affinity for adipose and glandular tissue and to some extent for the lungs, spleen (due to slow elimination from lymphoid tissue) and bone marrow.

Metabolism

Artemether is rapidly and extensively metabolized (substantial first-pass metabolism) both in vitro and in humans. Human liver microsomes metabolize artemether to the biologically active main metabolite dihydroartemisinin (demethy-lation), predominantly through the, enzyme CYP3A4/5. This metabolite has also been detected in humans in VIVO. 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 vitro lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations.

Elimination

Artemether is rapidly cleared from plasma with an elimination half-life of about 2 hours.

Lumefantrine is eliminated very slowly with a terminal half-life of 2-3 days in healthy volunteers and 4-6 days in patients with falciparum malaria. No urinary excretion data are available for humans. In rats and dogs unchanged artemether has not been detected in faeces and urine due to its rapid and high-first-pass metabolism, but several metabolites (unidentified) have been detected in both faeces and urine. Lumefantrine is eliminated via the bile in rats and dogs, with excretion primarily in the faeces. After oral dosing in rats and dogs qualitative and quantitative recovery of metabolites in bile and faeces was relatively low, most of the dose being recovered as parent drug

5.3 Preclinical safety data

Based on the available non-clinical data, a potential for QTc prolongation in the human cannot be discounted. For effects in the human see sections 4.3, 4.4 and 5.1.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose Powder, Croscarmellose sodium, Hypromellose E15 (Dry Mix) (Hydroxy Propyl Methyl Cellulose E15), saccharin Sodium, Polysorbate 80, Purified Water, Purified Talc, Magnesium Stearate, Crospovidone, Colloidal Anhydrous Silica, Flavour Strawberry Powder.

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 months.

6.4 Special precautions for storage

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

Keep the medicine out of reach of children.

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.

Aluminium-PVDC coated PVC foil containing 12 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>

Any unused product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT/MANUFACTURER

M/s OLPHARM NIGERIA LIMITED

13, AGBAOKU STREET,

OPEBI, LAGOS,

NIGERIA.

Manufactured by:

S Kant

HEALTHCARE Ltd.

1802-1805, G.I.D.C.,Phase III,

Vapi - 396 195. Gujarat, INDIA.