SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Artemether 20mg and Lumefantrine 120mg dispersible Tablets

BRAND NAME: LARIACT DISPERSIBLE

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated dispersible tablet contains:
Artemether……..20 mg
Lumefantrine……120 mg
Excipients…….q.s.

3. PHARMACEUTICAL FORM:

Solid oral dosage form: uncoated tablets

Yellow coloured, circular uncoated flat beveled edges tablet, plain on both sides.

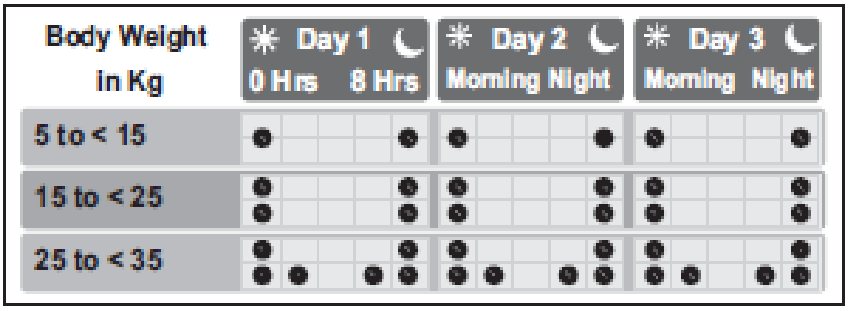
4. CLINICAL PARTICULARS

4.1 Therapeutic Indication:

The Artemether+Lumefantrine Dispersible Tablets are 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.

4.2 Posology and method of administration:

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



The dispersible tablets 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 to drink completely.

In case vomiting occurs within 1 hour of dose repeat the dose.

4.3 Contraindications:

Artemether + Lumefantrine tablets are contraindicated in:

- Patients with severe malaria.
- Patients who are taking any drug which is metabolised by the cytochrome enzyme CYP2D6 (eg. 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 known to prolong que are the QTc interval.

  These drugs include:
- Antiarrhythmics of IA and III classes, 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 arrhythmias or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricle ejection fraction.

4.4 Special warnings Warning and precautions for use

How to take drug: Artemether + Lumefantrine Tablets should be taken with food or drinks rich in fat such as milk.

If any dose missed: Try to make sure that you do not miss any doses. However, if you do forget a dose of Artemether + Lumefantrine Tablets, take the missed dose as soon as you remember unless it is almost time for your next dose. Then take your next dose at the usual time.

Ask doctor for advice. Do not take a double dose to make up for a forgotten dose

4.5 Interactions with other medicinal products and other forms of interaction :

Some medicines must not be taken with Artemether + Lumefantrine Tablets.

These include:

- Medicines used for the treatment of heart rhythm disturbances (eg. Flecainide, metoprolol),
- Certain medicines used to treat depression (such as imipramine, amitriptyline, clomipramine),
- Certain types of medicine used to treat infection, such as:
  - Rifampicin, an antibiotic to treat leprosy or tuberculosis
  - Antibiotics, including medicines of the classes: macrolides, fluoroquinolones, imidazole,
  - Triazole antifungal agents
- Certain medicines used to treat allergies or inflammation (eg. Non-sedating antihistaminics such as terfenadine or astemizole),
- A medicine called cisapride used to treat stomach disorders,
- Certain medicines used to treat epilepsy (such as carbamazepine, phenytoin)
- St. John's wort (Hypericum perforatum) a medicinal plant or extract of this medicinal plant used to treat for example depressed mood.
- Any other anti-malarial medicines
- Any anti-retroviral medicines or protease inhibitor
- An hormonal birth control medicine

4.6 Pregnancy & Lactation

Pregnancy - Artemether + Lumefantrine Tablets are 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 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 should’t only be considered if the expected benefit to the mother outweighs the risk to the fetus.

Lactation - Women taking Artemether + Lumefantrine Tablets 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 Tablets treatment.

4.7 Effects on ability to drive and use machines:

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

4.8 Undesirable Effects

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. 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.

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, ATC code: P01 BF01.

LARIACT comprises a fixed ratio of 1:6 parts of artemether and lumefantrine, respectively. The site of antiparasitic action of both components is the food vacuole of the malarial parasite, where they are thought to interfere with the conversion of haem, a toxic intermediate produced during haemoglobin breakdown, to the nontoxic haemozoin, malaria pigment. Lumefantrine is thought to interfere with the polymerisation process, while artemether generates reactive metabolites as a result of the interaction between its peroxide bridge and haem iron. Both artemether and lumefantrine have a secondary action involving inhibition of nucleic acid- and protein synthesis within the malarial parasite.

5.2 Pharmacokinetic properties

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

Absorption

Artemether is absorbed fairly rapidly and dihydroartemisinin, the active metabolite of artemether, appears rapidly in the systemic circulation with peak plasma concentrations of both compounds reached about 2 hours after dosing. Mean Cmax and AUC values of artemether ranged between 60.0-104 ng/mL and 146-338 ng·h/mL, respectively, in fed healthy adults after a single dose of LARIACT, 80 mg artemether/480 mg lumefantrine. Mean Cmax and AUC values of dihydroartemisinin ranged between 49.7-104 ng/mL and 169-308 ng·h/mL, respectively. Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentration (mean between 5.10-9.80 µg/mL) about 6-8 hours after dosing. Mean AUC values of lumefantrine ranged between 108 and 243 µg·h/mL. Food enhances the absorption of both artemether and lumefantrine: in healthy volunteers the relative bioavailability of artemether was increased more than two-fold, and that of lumefantrine sixteen-fold compared with fasted conditions when LARIACT 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 LARIACT, 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 LARIACT 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 LARIACT.

Limited urinary excretion data are available for humans. In 16 healthy volunteers, neither lumefantrine nor artemether was found in urine after administration of LARIACT, 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 LARIACT dose. No conclusive data is available for artemether.

Bioavailability/bioequivalence studies

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

Systemic exposure to lumefantrine was similar following administration of LARIACT dispersible tablets and intact tablets in healthy adults. However, exposure to artemether and dihydroartemisinin was significantly lower (by 20-35%) for the dispersible than for the intact tablet. These findings are not considered to be clinically relevant for the use of the dispersible tablets in the paediatric population since adequate efficacy of LARIACT dispersible 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 LARIACT) 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 LARIACT) 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 LARIACT in patients with renal impairment is advised.

5.3 Preclinical safety data

General toxicity

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

Neurotoxicity

Studies in dogs and rats have shown that intramuscular injections of artemether resulted in brain lesions. Changes observed mainly in brainstem nuclei included chromatolysis, eosinophilic cytoplasmic granulation, spheroids, apoptosis and dark neurons. Lesions were observed in rats dosed with artemether at 25 mg/kg for 7 or 14 days and dogs dosed at 20 mg/kg for 8 days or longer, but lesions were not observed after shorter courses of drug or after oral dosing. The estimated artemether 24 h AUC after 7 days of dosing at the no observed effect level (10 mg/kg/day given intramuscularly) is approximately 7-fold greater than the estimated artemether 24 h AUC in humans on day 1 of the standard 3-day oral treatment regimen; oral

exposure in humans decreases on subsequent days, thus the exposure margin increases. Dogs dosed orally with 143 mg/kg artemether showed a statistically measureable effect on the hearing threshold at 20 dB. This dose is equivalent to about 29 times the highest artemether clinical dose (160 mg/day) based on body surface area comparisons. Most nervous system disorder adverse events in the studies of the 6-dose regimen were mild in intensity and resolved by the end of the study.

Mutagenicity

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.

Fertility

After artemether-lumefantrine administration for 10 weeks in males and 2 weeks in females, reduced fertility occurred at 1000 mg/kg/day where altered sperm motility, abnormal sperm, reduced epididymal sperm count, increased testes weight, and embryotoxicity and other reproductive effects (decreased implants and viable embryos, increased preimplantation loss) were also observed. General toxicity was observed in males and females at doses ≥ 300 mg/kg/day. The no adverse effect level for fertility was 300 mg/kg/day. The relevance to this finding in humans is unknown.

Juvenile toxicity studies

A specific study to investigate the neurotoxicity of artemether in juvenile rats involved oral administration of artemether during four different dosing intervals, at doses of 30 or 80 mg/kg/day on post partum days 7 to 13, and at doses of 30 or 120 mg/kg/day on post partum days 14 to 21, 22 to 28, or 29 to 36. Mortality, clinical signs and reductions in body weight parameters occurred most notably during the first two dosing intervals. Despite the systemic toxicity noted, there were no effects of artemether on any of the functional tests performed and there was no evidence of a direct neurotoxic effect of orally administered artemether on the brain of juvenile rats.

Juvenile studies in the rat indicate that very young animals (aged 7-21 days) are more sensitive to artemether than adult animals. There is no difference in sensitivity in slightly older (3-5 weeks of age) animals following 13 weeks of artemether/lumefantrine administration. Consistent with the later data, clinical studies have established the safety of artemether and lumefantrine administration in patients weighing 5 kg and above.

Cardiovascular Safety Pharmacology

In toxicity studies in dogs at doses ≥600 mg/kg/day only, there was some evidence of prolongation of the QTc interval (safety margin of 1.3-fold to 2.2-fold for artemether using calculated free Cmax), at higher doses than intended for use in man. In an *in vitro* assay of HERG channels stably expressed in HEK293 cells, lumefrantrine and the main metabolite desbutyl-lumefantrine showed some inhibitory potential in one

of the currents responsible for cardiac repolarization. The potency was lower than the other antimalarial drugs tested. From the estimated IC_{50} values, the order of potency of HERG current block was halofantrine (IC_{50} = 0.04 μM) >chloroquine (2.5 μM) >mefloquine 2.6 μM) >desbutyl-lumefantrine (5.5 μM)
>lumefantrine (8.1 μM).

Additional studies were performed to evaluate the in vitro effects of artemether and its active metabolite, dihydroartemisinin, on the HERG current. At concentrations that produced significant inhibition, the safety margins for artemether and dihydroartemisinin are greater than 100 if they are estimated using the total therapeutic concentration at Cmax or greater than 1000 if they are estimated using the calculated free Cmax. Based on the available non-clinical data, a potential for QTc prolongation in the human cannot be discounted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose Powder, Croscarmellose Sodium, Hydroxyl Propyl Methyl Cellulose, Saccharin Sodium, Polysorbate 80, Purified water, Purified Talc, Crospovidone, Colloidal Anhydrous Silica, Magnesium Stearate, Flavour Strawberry powder.

6.2 Incompatibilities

Not Applicable

6.3 Shelf Life

24 Months.

6.4 Special precautions for storage:

Store in a dry place below 30°C. Protect from light. Keep the medicine out of reach of children.

6.5 Nature and contents of container

6 Tablets in a blister pack.

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

Manufactured by:

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06373/07111/NMR/2018

9. DATE OF AUTHORISATION

27-06-2023

10. DATE OF REVISION OF THE TEXT

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