SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Artemether/Lumefantrine Dispersible Tablets 20mg/120mg

2. Qualitative and quantitative composition

Artemether/Lumefantrine Dispersible Tablets 20mg/120mg are dispersible tablets and each tablet contains Artemether 20 mg and Lumefantrine 120 mg.

For a full list of excipients, see section 6.1.

3. Pharmaceutical Form

Artemether/Lumefantrine Dispersible Tablets 20mg/120mg are dispersible Tablets

Artemether/Lumefantrine Dispersible Tablets 20mg/120mg are yellow coloured circular, flat, bevel edged tablet with breakline on one side and plain on the other side. The scoreline is not intended for breaking the tablet

4. Clinical Particulars

4.1 Therapeutic indications

Artemether/Lumefantrine Dispersible Tablets 20mg/120mg contains two antimalarial medicines, artemether and lumefantrine. These ingredients work together to kill the *Plasmodium falciparum* parasite in uncomplicated or mixed infections of malaria. Malaria commonly occurs in subtropical and tropical areas. Artemether/Lumefantrine Dispersible Tablets 20mg/120mg is used to treat malaria acquired in areas where the parasite may be resistant to other antimalarial medicines. Malaria is an infectious mosquitoborne disease, spread to humans by the bite of the *Anopheles* mosquito. The mosquito carries parasites and injects them into the bloodstream when it bites a person. The parasites infect red blood cells, causing fever, chills, a general feeling of unwell (malaise), cough, nausea, headaches, vomiting and diarrhoea. Not all symptoms need to be present to suggest that you have malaria.

4.2 Posology and method of administration

Artemether/Lumefantrine Dispersible Tablets 20mg/120mg is not recommended for use in

children below 5 kg body weight due to a lack of data on safety and efficacy.

Dispersible tablets for oral administration. The dispersible tablet(s) for one dose should be stirred in a small amount of water (approximately 10 ml per tablet) so that the active substance can be better dispersed before the suspension is drunk. Stir gently and administer immediately to the patient. Pour some more water (approximately 10 ml) into the glass and give immediately to the patient. Foods or drinks (such as milk) that are rich in fat should be consumed following ingestion of the dose even though patients with acute malaria are frequently averse to food. Patients should be encouraged to resume normal eating as soon as possible, since this improves absorption of artemether and lumefantrine.

In the event of vomiting within one hour of administration, a repeat dose should be taken. The dispersible tablet is indicated only for infants and children. A separate tablet formulation is available for adolescents and adults.

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

Dosage for treatment and stand-by emergency treatment

A standard 2.5 day treatment schedule, with a total of 6 doses, is recommended as follows based on the child's body weight:

5 to < 15 kg body weight: one tablet per dose

15 to < 25 kg body weight: two tablets per dose

25 to < 35 kg body weight: three tablets per dose

≥ 35 kg body weight: four tablets per dose

Body Weight (in kg)	**DAY-1**		**DAY-2**		**DAY-3**	
	0 hours	**8 hours after**	**Morning**	**Evening**	**Morning**	**Evening**
5 to < 15 kg	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet
15 to < 25 kg	2 tablets	2 tablets	2 tablets	2 tablets	2 tablets	2 tablets
25 to < 35 kg	3 tablets	3 tablets	3 tablets	3 tablets	3 tablets	3 tablets
≥ 35 kg (or ≥ 12 years of age)	4 tablets	4 tablets	4 tablets	4 tablets	4 tablets	4 tablets

4.3 Contraindications

Artemether/Lumefantrine Dispersible Tablets 20mg/120mg are contraindicated in the following conditions

- Hypersensitivity to the active substances or to any of the excipients.
- Severe hepatic or renal impairment
- Patients with severe malaria
- First trimester of pregnancy in situations where other suitable and effective antimalarials 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, clinically relevant bradycardia or severe heart disease.
- Patients taking drugs that prolong the QTc interval, such as class IA and III antiarrhythmics, neuroleptics, antidepressants, certain antibiotics (including some agents in the following classes: macrolides, fluoroquinolones, imidazoles and triazoles), antifungal agents, certain non-sedating antihistamines (terfenadine, astemizole) and cisapride.
- Patients with known disturbances of electrolyte balance, e.g. hypokalaemia or hypomagnesaemia.
- Patients taking drugs metabolized by cytochrome CYP2D6 (e.g. flecainide, metoprolol, imipramine, amitriptyline, clomipramine).

4.4 Special warnings and precautions for use

Artemether/Lumefantrine Dispersible Tablets 20mg/120mg is not indicated in the following conditions;

- Prophylaxis
- Treatment of cerebral malaria, severe malaria, including pulmonary oedema or renal failure.
- Treatment of malaria due to *P. vivax*, *P. malariae* or *P. ovale*
- severe hepatic or renal impairment

Artemether/Lumefantrine Dispersible Tablets 20mg/120mg may prolong the QTc interval,

although no clinical adverse effect attributable to QTc prolongation.

Caution is required if other medicinal products are given concomitantly.

• Other medicines used to treat malaria

• Anti-retroviral medicines or protease inhibitors (used to treat HIV infections or AIDS)

• Hormonal birth control medication

• Medicines used to treat an abnormal heart rhythm, rhythm disturbance or affect heart beat

• Medicines that can have side effects on your heart, including some medicines used to treat depression or mental illnesses (such as imipramine, amitriptyline, clomipramine)

• Rifampicin, an antibiotic used to treat leprosy or tuberculosis

• Some antibiotic medicines (e.g. macrolides, fluoroquinolones, and imidazole)

• Cisapride, a medicine used to treat stomach disorders (such as hyperacidity, reflux and ulcers)

• Triazole antifungal agents (e.g. fluconazole, itraconazole)

• Certain medicines used to treat allergies or inflammation (e.g. non-sedating antihistaminics such as terfenadine or astemizole)

• A variety of other medicines that are removed from your body through your liver

• Certain medicines used to treat epilepsy (such as carbamazepine, phenytoin)

• St John's wort (Hypericum perforatum), a medicinal plant extract that is used to relieve some temporary feelings of sadness or low mood

4.5 Interaction with other medicinal products and other forms of interaction

Lumefantrine was found to inhibit CYP2D6 *in vitro*. Co-administration of Artemether/Lumefantrine Dispersible Tablets 20mg/120mg with drugs known to be metabolized by this isoenzyme (e.g. neuroleptics and tricyclic antidepressants) is contraindicated.

Combined administration of Artemether/Lumefantrine Dispersible Tablets 20mg/120mg and mefloquine should be avoided.

Prior administration of intravenous administration Artemether/Lumefantrine Dispersible Tablets 20mg/120mg to quinine increases the risk of QTc-prolongation

Caution is required when using Artemether/Lumefantrine Dispersible Tablets 20mg/120mg concomitantly with protease inhibitor antiretroviral drugs, especially fixed combinations thereof, due to variable patterns of inhibition, induction or competition for CYP3A4 with such drugs.

4.6 Pregnancy and lactation

Pregnancy:

Data from animal studies suggest that Artemether/Lumefantrine Dispersible Tablets 20mg/120mg may cause severe birth defects when administered during the first trimester of pregnancy.

In animals, reproductive toxicity studies with artemether have shown evidence of post-implantation losses and teratogenicity.

Other artemisinin derivatives have in addition demonstrated teratogenic potential, with increased risk during early gestation

During the second and the third trimesters, treatment should only be given if absolutely necessary.

Women of childbearing potential:

Artemether/Lumefantrine Dispersible Tablets 20mg/120mg is contraindicated during the first trimester of pregnancy, and women therefore should not conceive while undergoing malaria treatment with Artemether/Lumefantrine Dispersible Tablets 20mg/120mg.

Women of childbearing potential undergoing treatment with Artemether/Lumefantrine Dispersible Tablets 20mg/120mg should be advised to practice contraception until the start of the next menstruation following the end of treatment.

Lactation:

Animal data suggest that Artemether/Lumefantrine Dispersible Tablets 20mg/120mg passes into the breast milk but no data are available in humans. Women who are breastfeeding should not take Artemether/Lumefantrine Dispersible Tablets 20mg/120mg. Due to the long elimination half-life of lumefantrine (4 to 6 days), it is recommended that breastfeeding should not resume before day 28 unless the potential benefits to both mother and child outweigh the risks of treatment with Artemether/Lumefantrine Dispersible Tablets 20mg/120mg.

4.7 Effects on ability to drive and use machines

Artemether/Lumefantrine Dispersible Tablets 20mg/120mg has moderate influence on the ability to drive and use machines.

Patients receiving Artemether/Lumefantrine Dispersible Tablets 20mg/120mg should be warned that dizziness, fatigue or asthenia may occur, in which case their ability to drive or use machines

may be impaired.

4.8 Undesirable effects

Most of the side effects are mild to moderate and will generally disappear after a few days to a few weeks from treatment.

- Headache, loss of appetite
- Stomach pain
- Stomach problems
- Nausea (feeling sick) or vomiting
- Diarrhoea
- Unusual tiredness or general weakness
- Difficulty sleeping or sleepiness
- Aching muscles or joints
- Unsteadiness when walking
- Tingling or numbness of the hands or feet
- Sore throat
- Cough
- Fever
- shivering
- itching on the skin or a rash
- Decreased feeling of sensitivity (especially of the skin)
- Abnormal walk or inability to coordinate body movements
- Sudden signs of allergy such as rash, itching or hives on the skin; swelling of the face, lips, tongue or other parts of the body; wheezing or troubled breathing unusual bleeding or bruising under the skin
- Feeling of fast or irregular heart beat (palpitations)
- Dizziness, lightheadedness, fainting or near fainting
- Involuntary muscle contractions, sometimes in rapid spasms
- Unexplained persistent nausea signs of a possible liver problem such as persistent pain in the upper right abdomen, yellowing of the skin and/or eyes, dark urine or pale bowel motions.

- ➢ Some side effects may not give you any symptoms and can only be found when tests are done. Some of these side effects include:
- ➢ Heart rhythm disturbances (called
- ➢ QTc prolongation or abnormal ECG heart tracing)

- Tell your doctor if you notice anything else that is making you feel unwell.

4.9 Overdose

If overdosage is suspected, symptomatic and supportive therapy should be initiated based on the clinical picture. The ECG and electrolytes (e.g. potassium) should be monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Artemether/Lumefantrine Dispersible Tablets 20mg/120mg contain a fixed combination of artemether and lumefantrine, in the ratio of 1:6, which acts as an antimalarial agent against schizonts. Artemether is a semisynthetic chiral acetal derivative of artemisinin isolated from the plant *Artemisia annua*. Lumefantrine is a synthetic fluorene derivative. Like other antimalarials (quinine, mefloquine, halofantrine), lumefantrine belongs to the aryl-amino-alcohol family.
The site of antiparasitic action of both components is the food vacuole of the malaria parasite. Lumefantrine is thought to interfere with the polymerization process that brings about the conversion of haem, a toxic intermediate produced during haemoglobin breakdown, to the non-toxic haemozoin, malaria pigment. Artemether, on the other hand, may generate toxic, reactive metabolites as a result of the interaction between its endoperoxide bridge and haem iron. Both artemether and lumefantrine have a secondary action involving inhibition of nucleic acid and protein synthesis.

Data from *in vitro* and *in vivo* studies show that Artemether/Lumefantrine Dispersible Tablets 20mg/120mg has not induced resistance.
The efficacy of the combination of lumefantrine and artemether in Artemether/Lumefantrine Dispersible Tablets 20mg/120mg is greater than that of either substance alone. In a double-blind, comparative study in adults in China (n = 157), the cure rate for Artemether/Lumefantrine

Dispersible Tablets 20mg/120mg – given in 4 doses over a 28 day period – was 94%; it was 90% for lumefantrine monotherapy and 46% for artemether monotherapy (based on the intent-to-treat [ITT] population). For the evaluable population, the 28 day cure rates were 100% for Artemether/Lumefantrine Dispersible Tablets 20mg/120mg, compared with 92% for lumefantrine monotherapy and 55% for artemether monotherapy.

In the resident population of areas where multi-drug-resistant strains of *P. falciparum* malaria are common, 28 day cure rates with the six-dose regimen (given over 60 or 96 hours) were 81% and 90% for Artemether/Lumefantrine Dispersible Tablets 20mg/120mg versus 94% and 96% for mefloquine/artesunate (based on the ITT population). For the evaluable population, the 28 day cure rates were 97% and 95% for Artemether/Lumefantrine Dispersible Tablets 20mg/120mg and 100% for mefloquine/artesunate.

In 319 adult patients in whom gametocytes were present, the average time to gametocyte clearance with Artemether/Lumefantrine Dispersible Tablets 20mg/120mg was 96 hours. Artemether/Lumefantrine Dispersible Tablets 20mg/120mg showed more rapid gametocyte clearance than any comparator except mefloquine/artesunate. Artemether/Lumefantrine Dispersible Tablets 20mg/120mg is active against blood stages of *P. vivax*, but not against hypnozoites.

A similar efficacy and safety profile was shown in non-immune adult patients living in regions free of malaria but with malaria acquired when travelling in endemic regions. In an open-label study in adults (n = 165), the 28 day cure rate for Artemether/Lumefantrine Dispersible Tablets 20mg/120mg given in the 6 dose regimen was 96% (119/124) in the evaluable population and 74.1% (120/162) in the ITT population. The difference between evaluable and ITT population cure rates was due to 38 patients who were excluded from the evaluable population for the following reasons: 33 patients were lost to follow up, of whom 19 had no evaluation and 14 had parasitic clearance at day 7 (but unknown efficacy status at day 28); 5 patients took concomitant medications that were not permitted by the protocol. All these patients were considered as treatment failures in the ITT analysis.

Efficacy data in infants and children:

In a randomized, investigator-blinded, multicentre trial in sub-Saharan Africa comparing the efficacy of 6 dose Artemether/Lumefantrine Dispersible Tablets 20mg/120mg and (crushed) Artemether/Lumefantrine Dispersible Tablets 20mg/120mg administered according to body

weight in 899 children 12 years of age or younger with between 5 kg and 35 kg body weight, the 28 day parasitological (PCR-corrected) cure rate was 97.8% and 98.5%, respectively, in the primary analysis population and 95% and 96.2%, respectively, in the ITT population.
The mean 28 day parasitological (polymerase-chain-reaction [PCR]-corrected) cure rate was 93.9% in the ITT population and 96.7% in the evaluable population in an open, multicentre clinical study conducted in Africa in 310 children, weighing between 5 kg and 25 kg, who received a 6 dose Artemether/Lumefantrine Dispersible Tablets 20mg/120mg regimen that varied according to body weight.
Children from non-endemic countries were not included in the clinical trials.

QT/QTc prolongation
The administration of the six dose regimen of Artemether/Lumefantrine Dispersible Tablets 20mg/120mg was associated with QTcF prolongation in a parallel study in healthy adults that included placebo and moxifloxacin control groups (n = 42 per group). The mean change from baseline at 68, 72, 96, and 108 hours after the first dose were 7.45, 7.29, 6.12 and 6.84 milliseconds, respectively. The change from baseline QTcF was zero at 156 and 168 hours after the first dose. No subject had an increase from baseline > 30 milliseconds, nor an absolute value > 500 milliseconds. As compared with the placebo group, the moxifloxacin control was associated with a QTcF prolongation for 12 hours after the single dose, with the maximum change 1 hour after the dose amounting to 14.1 milliseconds.
QTcB prolongation > 500 milliseconds was reported in one patient (0.1%) in clinical trials in children. No patient had a QTcF interval > 500 milliseconds. In clinical studies in adults, QTcB prolongation > 500 milliseconds was reported in 0.9% of patients and QTcF prolongation > 500 milliseconds was reported in 0.3% of patients.
There have been no reports of clinical adverse effects attributable to QTc prolongation (e.g. syncope, sudden death).

5.2 Pharmacokinetic properties
Pharmacokinetic characterization of Artemether/Lumefantrine Dispersible Tablets 20mg/120mg 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 attained approx. 2 hours after administration. 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 administration. Food enhances the absorption of both artemether and lumefantrine: In healthy volunteers given a high-fat meal, the relative bioavailability of artemether was increased more than two-fold, and that of lumefantrine sixteen-fold compared with fasted conditions. 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. Food interaction data indicate that absorption of lumefantrine under fasted conditions is very poor (probably less than 10% of the dose). Patients should therefore be strongly encouraged to take the medication with a normal diet as soon as food can betolerated.

Distribution:

Artemether and lumefantrine are both highly bound to human serum proteins *in vitro* (95.4% and 99.7%, respectively).

DHA is also bound to human serum proteins (47%–76%). Protein binding to human plasma protein is linear.

Biotransformation:

Artemether is rapidly and extensively metabolized (substantial first-pass metabolism). *In vitro* data show that human liver microsomes metabolize artemether to the biologically active main metabolite DHA (demethylation), predominantly by way of CYP3A4/5.

The pharmacokinetics of this metabolite have also been described in humans *in vivo*.

The artemether/DHA AUC ratio is 1.2 after a single dose and 0.3 after the last of 6 doses given over 3 days. Artemether and DHA were reported to have a mild inducing effect on CYP3A4 activity that is not expected to pose a problem in the general patient population.

Plasma levels of artemether decreased markedly during repeated administration of Artemether/Lumefantrine Dispersible Tablets 20mg/120mg, while levels of the active metabolite (DHA) increased, although not to a statistically significant degree. This confirms that there was

induction of the enzyme responsible for the metabolism of artemether.

In vitro, 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, systemic exposure to the desbutyl-lumefantrine metabolite – which has an *in vitro* antiparasitic effect 5 to 8 times higher than that of lumefantrine – amounted to less than 1% of the exposure to the parent compound.

In vitro, therapeutic plasma concentrations of lumefantrine significantly inhibit the activity of CYP2D6.

Elimination:

Artemether and DHA are 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. Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of Artemether/Lumefantrine Dispersible Tablets 20mg/120mg.

No data are available on urinary excretion of artemether and lumefantrine in humans. In rats and dogs, unchanged artemether has not been detected in the faeces and the urine due to its rapid and high first-pass metabolism, but numerous metabolites (identified in part) have been detected in the faeces, the bile and the urine. Lumefantrine is eliminated into the bile in rats and dogs, with excretion primarily in the faeces. Metabolites (glucuronides of lumefantrine and of the desbutyl metabolite) were eliminated into the bile following oral administration in rats and dogs. Most of the dose was recovered in the faeces in the form of parent drug (this included unabsorbed drug components and drug components released from glucuronides).

Pharmacokinetics in special patient populations:

No specific pharmacokinetic studies have been performed in patients with hepatic or renal impairment.

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

5.3 Preclinical safety data

Mutagenicity:

There have been no reports of mutagenicity in *in vitro* and *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, 1000 and 2000 mg/kg), but recovery was reported to be almost complete 48 hours after dosing.

Carcinogenicity:

Due to the short period of treatment, carcinogenicity studies with the artemether: lumefantrine combination were not carried out.

Reproductive toxicity:

Reproductive toxicity studies in rats given oral doses of the artemether:lumefantrine combination showed maternal toxicity and increased post-implantation loss at doses ≥ 50 mg/kg (corresponding to approximately 7 mg/kg artemether). The artemether:lumefantrine combination was not embryotoxic in rats at a dose of 25 mg/kg (corresponding to approximately 3.6 mg/kg artemether). Following oral administration of the artemether:lumefantrine combination in rabbits, maternal toxicity and increased post-implantation loss were seen at a dose of 175 mg/kg (corresponding to 25 mg/kg artemether), while the next lowest dose level of 105 mg/kg (corresponding to 15 mg/kg artemether) was free of treatment-induced effects.

Artemisinins are known to be embryotoxic in animals. Reproductive toxicity studies with artemisinin derivatives demonstrated increased post-implantation loss and teratogenicity (a low incidence of cardiovascular and skeletal malformations) in rats at a dose of 6 mg/kg artesunate and 19.4 mg/kg artemether. In rats, 3 mg/kg artemether was established as the non-toxic dose.

In rabbits, artemether produced maternal toxicity and an increase in post-implantation loss at a dose of 30 mg/kg, but no maternal toxicity, embryotoxicity or fetotoxicity at doses up to 25 mg/kg. The artemisinin derivative artesunate produced a low incidence of cardiovascular and skeletal malformations in rabbits at 5 mg/kg, the lowest dose used.

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

Cardiovascular pharmacology:

In toxicity studies in dogs, there was some evidence of QTc prolongation at doses higher than the

therapeutic doses used in man (≥ 600 mg/kg/day). In an *in vitro* assay of HERG channels stably expressed in an HEK293 cell line, lumefantrine and the main metabolite desbutyl-lumefantrine showed some inhibitory potential on one of the ion channels responsible for cardiac repolarization. However, this potency was lower than that of the other antimalarial drugs tested. From the estimated IC50 values, the order of potency of HERG current block was: halofantrine (IC50 = 0.04 micromolar) > chloroquine (2.5 micromolar) >mefloquine (2.6 micromolar) >desbutyl-lumefantrine (5.5 micromolar) > lumefantrine (8.1 micromolar). A study in healthy adults shows that the QTcF interval may be prolonged by standard dosing of Artemether/Lumefantrine Dispersible Tablets 20mg/120mg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Artemether/Lumefantrine Dispersible Tablets 20mg/120mg contains the following excipients:

- Microcrystalline Cellulose
- Croscarmellose sodium
- Hypromellose
- Polysorbate 80
- Flavour Cherry
- Saccharin sodium
- Colloidal silicon dioxide
- Crospovidone
- Magnesium Stearate

6.2 Incompatibilites

None known.

6.3 Shelf life

The product has a shelf life of 24 Months.

6.4 Special precautions for storage

Store below 30°C. Avoid excursions above 30°C. Protect from light and moisture. Store Tablets in blisters in the provided carton. Keep out of reach of children.

6.5 Nature and contents of container

Clear transparent PVC/PE/PVDC-Alu blisters.

Below presentations are available:

30x6s, 30x12s, 1x6s, 1x12s

6.6 Special precautions for disposal

No special requirements

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

7. Manufacturer

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