

FLOURISH PHARMA

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FIBADISPER TAB 20/120 (Artemether and Lumefantrine (20 /120 mg))

Summary of Product Characteristics**FIBADISPER TABLET****Artemether 20 and Lumefantrine 120 Dispersible Tablets****1. NAME OF THE MEDICINAL PRODUCT**

FIBADISPERSE TABLET 20/120 (Artemether and Lumefantrine (20 /120 mg))

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Sr. No	Ingredients	Grade	Rationale	Label Claim	Quantity per Unit (mg)	Quantity per Batch (Actual-Kg)
	Granulation					
1.	Lumefantrine	USP	Active	120	120	12.0
2	Artemether	USP	Active	20	20	2.00
3	Starch	BP	Binder		56.00	5.6
4	Sodium starch glycolate	BP	Superdisintegrant	-- -	15.00	1.5
5.	Microcrystalline cellulose	BP	Diluent	-- -	30	3.0
6	Colloidal silicon dioxide	BP	Glidant	-- -	2.50	0.25
7	Cross carmellose sodium	BP	Disintegrant	-- -	5.00	0.50
8	Lactose	BP	Vehicle	-- -	20.00	2.00
9	Starch (paste)	BP	Binder	-- -	7.00	0.70
10	PVPK-30	BP	Binder	-- -	2.50	0.25
11	Sodium Lauryl Sulphate	BP	Anionic surfactant	-- -	1.50	0.15
12	Sodium Methyl Paraben	BP	Preservative	-- -	0.16	0.016
13	Sodium Propyl Paraben	BP	Preservative	-- -	0.04	0.004
14	Colour Tartrazine Supra	BP	Colour	-- -	0.20	0.02

15	Aspartame	BP	Sweetner	-- -	1.0 0	0.10
Lubrication						
16.	Purified Talc	BP	Glidant	-- -	4. 00	0.40 0
17	Magnesium stearate	BP	lubricant	-- -	2. 0	0.2
18	Sodium starch glycolate	BP	Disintegrant		5.00	0.500
19.	Colloidal Silicon Dioxide	BP	Viscosity-increasing agent.	-- -	1.00	0.1
20	Cross carmellose sodium	BP	Diluent	-- -	5. 00	0.50 0
21	Maize starch	BP	Diluent	-- -	1.11	0.11
22	Flav Pineapple	BP	Flavour	-- --	1.00	0.1

3. PHARMACEUTICAL FORM

Dispersible tablets.

Yellow circular biconvex uncoated dispersible tablets having break line on other side and plain on the other

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for pediatric use only.

FIBADISPERSE TABLET 20/120 (Artemether and Lumefantrine (20 /120 mg)) is indicated for the treatment of children and infants with acute, uncomplicated infections due to *Plasmodium falciparum* or mixed infections including *P. falciparum*. FIBADISPERSE TABLET 20/120 (Artemether and Lumefantrine (20 /120 mg)) may be used for self-administration, as stand-by emergency treatment in cases of suspected malarial infection, when no doctor can be reached within 24 hours or the medicinal product is not locally available.

FIBADISPERSE TABLET 20/120 (Artemether and Lumefantrine (20 /120 mg)) is effective against both drug-sensitive and drug-resistant *P. falciparum*, and it is therefore also recommended for malaria infections acquired in areas where the parasites may be resistant to other antimalarials. Consideration should be given to official guidelines and to local recommendations based on the prevalence of resistance to antimalarial agents. Official guidelines are those issued by the WHO and by health authorities.

4.2 Posology and method of administration

FIBADISPERSE TABLET 20/120 (Artemether and Lumefantrine (20 /120 mg)) 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.

Food 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 3 day treatment schedule, with a total of 6 doses, is recommended as follows:

Dosage in infants and children ≤ 12 years of age weighing between 5 kg and < 35 kg

5 to < 15 kg body weight

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

15 to < 25 kg body weight

Two dispersible tablets as a single dose at the time of initial diagnosis or as soon as symptoms appear, two dispersible tablets again after 8 hours and then two dispersible tablets twice daily (in the morning and evening) on each of the following two days (total course comprises 12 dispersible tablets).

25 to < 35 kg body weight

Three dispersible tablets as a single dose at the time of initial diagnosis or as soon as symptoms appear, three dispersible tablets again after 8 hours and then three dispersible tablets twice daily (in the morning and evening) on each of the following two days (total course comprises 18 dispersible tablets).

Dosage in patients with impaired renal or hepatic function

No specific studies have been performed in these patient populations. No specific dose adjustment recommendations can be made for these patients (see sections 4.3 and 4.4). Most patients with acute malaria present with some degree of hepatic impairment. In clinical trials the adverse event profile did not differ in patients with and those without hepatic impairment (see also section 4.4).

Moreover, baseline abnormalities in liver function tests improved in nearly all patients after treatment with FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)).

New and recrudescence infections

Data for a limited number of patients show that new and recrudescence infections can be treated with a second course of FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)).

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.

Severe hepatic or renal impairment (see also section 4.4).

Patients with severe malaria according to the WHO definition.

First trimester of pregnancy in situations where other suitable and effective antimalarials are available (see also section 4.6).

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 AND LUMEFANTRINE (20 /120 MG) has not been evaluated for prophylaxis and is therefore not indicated for this use.

ARTEMETHER AND LUMEFANTRINE (20 /120 MG) has not been investigated in the treatment of cerebral malaria or other severe manifestations of severe malaria, including pulmonary oedema or renal failure. Severe malaria

In addition to the lack of clinical experience, use of FIBADISPERSE TABLET 20/120 in such cases is also inadvisable on pharmacokinetic grounds (the bioavailability of artemether and, in particular, of lumefantrine is uncertain in patients with high parasitaemia and little or no food intake). ARTEMETHER AND LUMEFANTRINE (20 /120 MG) has not been evaluated in, and is not indicated for, 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 (20 /120 MG) is active against blood stages of *P. vivax*, but not against hypnozoites (= dormant form / dormant stage in hepatocytes).

Like other antimalarials (e.g. halofantrine, quinine, quinidine), ARTEMETHER AND LUMEFANTRINE (20 /120 MG) may prolong the QTc interval, although no clinical adverse effect attributable to QTc prolongation (e.g. syncope, sudden death) has been reported (see section 5.1).

Artemether and Lumefantrine (20 /120 mg) has not been studied for efficacy and safety in patients with severe hepatic or renal impairment, and therefore no recommendations can be made for these patient populations.

Patients who remain averse to food during treatment should be closely monitored. The risk of recurrence of disease may be greater.

If the patient's condition worsens during treatment with FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)), alternative antimalarial treatment should be started without delay. In such cases, ECG monitoring is recommended and steps should be taken to correct any electrolyte disturbances.

Following treatment of mixed infections including *P. vivax*, follow-up treatment must be given in order to eradicate the exoerythrocytic forms of *P. vivax*.

Caution is required if other medicinal products are given concomitantly.

Patients treated concomitantly with other antimalarials

Data on safety and efficacy are limited, and FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) should therefore not be given concurrently with other antimalarials unless there is no other treatment option. The long elimination half-life of lumefantrine must be taken into account when administering quinine in patients previously treated with FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)). The ECG should be closely monitored in this case, as well as when FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) is administered following treatment with quinine, due to a possible additive prolongation of the QTc interval that has been observed in healthy subjects.

Patients previously treated with other antimalarials

Should FIBADISPERSE TABLET 20/120 be administered following treatment with mefloquine, it is particularly important to ensure that FIBADISPERSE TABLET 20/120 is taken together with food as lumefantrine levels may otherwise be insufficient.

In patients previously treated with halofantrine, FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) should be administered no earlier than one month after the last halofantrine dose (see section 4.5).

Patients treated concomitantly with other medicinal products

FIBADISPERSE TABLET 20/120 should not be used concomitantly with drugs metabolized by CYP2D6 (see section 4.3). Additionally, caution is required when combining FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) with substrates, inhibitors or inducers of CYP3A4 as the therapeutic effects of some drugs might be altered (see sections 4.5 and 5.2).

4.5 Interaction with other medicinal products and other forms of interaction

The mechanisms of the pharmacological and pharmacokinetic interactions are not all known. Artemether and lumefantrine are substrates of CYP3A4. Administration of inducers or inhibitors of CYP3A4 may therefore lead to an increase or a reduction in exposure to lumefantrine and artemether.

Further interactions with CYP450 isoenzymes

Lumefantrine was found to inhibit CYP2D6 in vitro. This might be of particular clinical relevance for substances with a narrow therapeutic index. Co-administration of FIBADISPERSE TABLET 20/120 (Artemether and Lumefantrine (20 /120 mg)) with drugs known to be metabolized by this isoenzyme (e.g. neuroleptics and tricyclic antidepressants) is contraindicated (see section 4.3).

Induction of CYP450 enzymes

Whereas in vitro studies with artemether at therapeutic concentrations revealed no significant inhibition with CYP450 enzymes, artemether and dihydroartemisinin (DHA) were reported to have a mild inducing effect on CYP3A4 activity. Although the changes have generally been slight and are unlikely to pose any problems in the general patient population, CYP3A4 induction might alter the therapeutic effects of drugs that are predominantly metabolized by this enzyme class.

Three specific pharmacokinetic and pharmacodynamic interaction studies with ketoconazole (a potent inhibitor of CYP3A4), mefloquine and quinine have been carried out in healthy volunteers.

Interactions with antimalarial drugs

Patients who are to receive Artemether and Lumefantrine (20 /120 mg)may previously have been treated with other antimalarials. Interactions with mefloquine and quinine were therefore studied in healthy volunteers.

Sequential oral administration of mefloquine prior to FIBADISPERSE TABLET 20/120 (Artemether and Lumefantrine (20 /120 mg)) had no effect on plasma concentrations of artemether or the artemether/dihydroartemisinin (DHA) ratio, but there was a significant (approximately 30–40%) reduction in plasma levels (C_{max} and AUC) of lumefantrine due to lower absorption, possibly secondary to a mefloquine-induced decrease in bile production.

Patients should be particularly advised to compensate for this decrease in bioavailability by eating something when taking FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)). As a rule, therefore, combined administration of FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) and mefloquine should be avoided.

In a drug interaction study in healthy subjects, administration of FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) alone to 14 subjects had no effect on the QTc interval, while i.v. infusion of quinine alone in 14 other subjects caused a transient prolongation of the QTc interval, which was consistent with the known cardiotoxicity of quinine. This effect was slightly, but significantly, greater when quinine was infused after FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) in 14 additional subjects. Prior administration of FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) thus appears to increase the risk of QTc- prolongation associated with intravenous administration of quinine.

Concurrent intravenous administration of quinine (10 mg/kg body weight) with FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) had no effect on plasma concentrations of lumefantrine or quinine. Plasma concentrations of artemether and DHA appear to be lower.

In a clinical study (carried out in Thailand), FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) was given to some adult patients who had not responded to mefloquine or quinine. 121 patients received FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) without any previous antimalarial treatment, whereas in 34 and 9 patients, respectively, blood levels of quinine or mefloquine were measurable at the start of the study. These patients showed safety and pharmacokinetic profiles for FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) similar to those in patients who had no detectable levels of other antimalarials.

Interaction with a CYP450 3A4 inhibitor (ketoconazole)

Both artemether and lumefantrine are metabolized predominantly by CYP3A4, and at therapeutic concentrations do not inhibit this enzyme. In healthy adult subjects, concomitant oral administration of ketoconazole with FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) leads to a modest increase ($\leq$ 2-fold) in exposure: artemether (+130% in AUC and +116% in C_{max}), DHA (+51% and +37%, respectively), and lumefantrine (+61% and +28%, respectively). This increase in exposure to the antimalarial combination was not associated with increased adverse effects or changes in electrocardiographic parameters. Based on this study, dose adjustment of FIBADISPERSE TABLET 20/120 (Artemether and Lumefantrine (20 /120 mg)) is not considered necessary in *P. falciparum* malaria patients given ketoconazole or other potent CYP3A4 inhibitors concomitantly.

Interaction with antiretroviral drugs

There have been no formal studies of interactions between FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) and antiretroviral drugs. Caution is

required when using FIBADISPERSE TABLET 20/120 (Artemether and Lumefantrine (20 /120 mg)) concomitantly with protease inhibitor antiretroviral drugs, especially fixed combinations thereof, due to variable patterns of inhibition, induction or competition for CYP3A4 with such drugs (see section 4.4 and 5.2).

4.6 Pregnancy and lactation

Pregnancy

There have been no controlled clinical studies of the safety of FIBADISPERSE TABLET 20/120 (Artemether and Lumefantrine (20 /120 mg)) during pregnancy.

Data from animal studies suggest that FIBADISPERSE TABLET 20/120 (Artemether and Lumefantrine (20 /120 mg)) may cause severe birth defects when administered during the first trimester of pregnancy (see sections 4.3 and 5.3). 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 (see section 5.3).

FIBADISPERSE TABLET 20/120 (Artemether and Lumefantrine (20 /120 mg)) is contraindicated during the first trimester of pregnancy if other effective antimalarials are available. However, it should not be withheld in life-threatening situations where no other effective antimalarials are available (see section 4.3).

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

Women of childbearing potential

FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) is contraindicated during the first trimester of pregnancy, and women therefore should not conceive while undergoing malaria treatment with FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)). This includes women who are travelling, for whom FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) has been prescribed as stand-by emergency treatment of malaria, should such treatment be required.

Women of childbearing potential undergoing treatment with FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)), including stand-by emergency treatment during travel, should be advised to practice contraception until the start of the next menstruation following the end of treatment.

Lactation

Animal data suggest that FIBADISPERSE TABLET 20/120 (Artemether and Lumefantrine (20 /120 mg)) passes into the breast milk but no data are available in humans. Women who are breastfeeding should not take FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)). 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 FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)).

4.7 Effects on ability to drive and use machines

FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) has moderate influence on the ability to drive and use machines. Patients receiving FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) 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 reported events were mild to moderate in severity and of short to moderate duration. They were probably related more to the underlying malaria and/or to an inadequate response to treatment rather than to FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) treatment, although a causal relationship with FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) cannot be ruled out in some of the reported cases. In other reports, other factors (e.g. concomitant drug therapy, concurrent infections) were presumed to be the more likely cause of the events, or the available information was too meagre to allow any conclusions to be drawn. Frequencies are defined as very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1,000$, $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1 Adverse reactions reported in patients

Immune system disorders	
Rare	Hypersensitivity reactions
Metabolism and nutrition disorders	
Very common	Loss of appetite (10.8%)
Psychiatric disorders	
Uncommon	Sleep disturbances
Nervous system disorders	
Common	Headache
Common	Dizziness
Uncommon	Drowsiness
Cardiac disorders	
Common	QT interval prolonged in electrocardiogram (including QTc prolongations > 60 msec and/or absolute QTc intervals > 500 msec)
Uncommon	Palpitations
Respiratory, thoracic and mediastinal disorders	
Very common	Cough (23.5%)
Gastrointestinal disorders	
Very common	Vomiting (17.5%)
Common	Abdominal pain
Common	Diarrhoea
Common	Nausea
Hepatobiliary disorders	
Common	Elevated liver function values
Skin and subcutaneous tissue disorders	
Common	Rash
Uncommon	Pruritus
Musculoskeletal and connective tissue disorders	
Common	Arthralgia, myalgia
General disorders and administration site conditions	
Common	Asthenia, fatigue

In this pooled safety analysis, mood swings were reported in fewer than 1.2% of the paediatric patients treated with FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)), but they were not considered drug-related by the investigators.

Adverse effects found in non-recommended regimens not included in this pooled safety analysis are: paraesthesia (1.2% of adolescents and adults, no cases in children); involuntary muscle contractions (1.3% of children); non-specific personality disorders which have been reported in 1.1% of children under 5 years of age who were treated with FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) during clinical studies. This incidence is 2–3 times lower than that observed in children of the same age who were treated with the reference antimalarials used in these studies (mefloquine/artesunate, quinine or sulphadoxine/pyrimethamine).

There were uncommon reports of the following adverse effects in adults, but not in infants or children: hypoaesthesia, ataxia, and abnormal gait.

4.9 Overdose

No case of overdose has been reported.

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

Pharmacotherapeutic group: Artemisinin and derivatives, ATC code: P01BE52.

FIBADISPERSE TABLET 20/120 (Artemether and Lumefantrine (20 /120 mg)) contains 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 racemic mixture of 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.

To date, data from in vitro and in vivo studies show that FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) has not induced resistance.

The efficacy of the combination of lumefantrine and artemether in FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) is greater than that of either substance alone. In a double-blind, comparative study in adults in China (n = 157), the cure rate for FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) – 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 FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)), 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 FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) 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 LONART DISPERSIBLE and 100% for mefloquine/artesunate.

In 319 adult patients in whom gametocytes were present, the average time to gametocyte clearance with FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) was 96 hours. FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) showed more rapid gametocyte clearance than any comparator except mefloquine/artesunate. FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) 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 FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) 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 FIBADISPERSE TABLET 20/120 (Artemether and Lumefantrine (20 /120 mg)) tablets and (crushed) FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) 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 FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) 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 FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) 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.

cB 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 FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) is limited by the lack of an intravenous formulation, and the very high inter- and insubject variability of artemether and lumefantrine plasma concentrations and derived pharmacokinetic parameters (AUC, C_{max}).

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 be tolerated. In healthy (adult) volunteers, systemic exposure to artemether, its metabolite dihydroartemisinin (DHA) and lumefantrine was similar with dispersible and crushed tablets (see table 2).

Table 2: Pharmacokinetic parameters following a single dose (4 tablets) – containing 80 mg artemether / 480 mg lumefantrine – administered as either dispersible or crushed tablets

	Dispersible tablets	Crushed tablets
	Artemether	
	(n = 54)	(n = 50)
C _{max} (ng/ml)	73.3 ± 39.5	67.4 ± 35.5
T _{max} (hours)	2.02 [0.50-4.02]	2.05 [0.52-4.07]
AUC _{last} (ngxhours/ml)	263 ± 143	229 ± 136
	DHA	
	(n = 54)	(n = 50)
C _{max} (ng/ml)	48.6 ± 23.2	48.8 ± 26.0
T _{max} (hours)	2.98 [0.75-5.98]	2.54 [0.75-4.07]
AUC _{last} (ngxhours/ml)	171 ± 59.5	160 ± 68.0

	Lumefantrine	
	(n = 55)	(n = 52)
C _{max} (ng/ml)	10.2 ± 3.08	10.0 ± 2.57
T _{max} (hours)	8.00 [4.98-24.02]	8.00 [4.98-24.02]
AUC _{last} (ngxhours/ml)	295 ± 107	280 ± 93.2

Table shows mean ± standard deviation for C_{max} und AUC_{last}, median values and [min-max] ranges for t_{max}.

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 FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)), 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. The clinical evidence of induction is consistent with the in vitro data in the section 4.5.

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 (see sections 4.4, 4.5 and 4.3).

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 FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)). 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 firstpass 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.

5.2 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.

Artemisinin derivatives 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 FIBADISPERSE TABLET 20/120 (ARTEMETHER AND LUMEFANTRINE (20 /120 MG)) (see sections 4.3, 4.4 and 5.1).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Starch

Sodium starch glycolate

Microcrystalline cellulose

Colloidal silicon dioxide

Cross carmellose sodium

Lactose

Starch (paste)

PVPK-30

Sodium Lauryl Sulphate

Sodium Methyl Paraben

Sodium Propyl Paraben

Colour Tartrazine Supra

Aspartame

Purified Talc

Magnesium stearate

Sodium starch glycolate

Collidal Silicon Dioxide

Cross carmellose sodium

Maize starch

Flav Pineapple

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in dry place, below 30°C.

Keep out of reach of children.

6.5 Nature and contents of container

Aluminium/PVC foil blisters.

1 x 6 tablets packed in one mono carton along with pack insert.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

ST JUDE PHARMACY LTD

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KADUNA, KADUNA NORTH, KADUNA

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