1. NAME OF THE MEDICINAL PRODUCT

LIVETHER 20/120

ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition

Each Uncoated Tablet
Contains Artemether ..... 20 mg
Lumefantrine..... 120 mg
Excipients……..Q.S

3. PHARMACEUTICAL FORM

Uncoated tablets
Yellow colour, round shaped, uncoated, biconvex tablets Plain on both sides.

4. Clinical particulars

4.1 Therapeutic indications

ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG is indicated for the treatment of uncomplicated cases of malaria due to Plasmodium falciparum in adults and children of 35 kg and above.
The most recent official guidelines on the appropriate use of antimalarial agents and local information on the prevalence of resistance to antimalarial drugs must be taken into consideration for deciding on the appropriateness of therapy with ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG

4.2 Posology and method of administration

Oral use

Treatment should be administered at the time of initial diagnosis or at the onset of symptoms. It is preferable that the patient has a positive diagnostic test before administration.

One tablet should be taken twice a day for three days (total six doses).The first dose should be followed by a second dose after 8 hours. The following two days the doses of ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG should be given twice daily, morning and evening (i.e. 12 hours apart).

To increase absorption, ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG should be taken with food or a milky drink (see section 5.2). If a patient is unable to tolerate food, ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG should still be administered, but the systemic exposure may be reduced.

Patients who vomit within 1 hour of taking the medication should repeat the dose.

If a dose is missed, it should be taken as soon as realized and then the recommended regimen continued until the full course of treatment has been completed.

Method of administration

Oral Route

4.3 Contraindications

ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG is contraindicated in:
patients with known hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
patients with severe malaria according to WHO definition*.
Patients who are taking any drug which is metabolised by the cytochrome enzyme CYP2D6 (e.g. 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 (proarrythmic). 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.

- flecainide

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

Patients with disturbances of electrolyte balance e.g. hypokalemia or hypomagnesemia.

patients taking drugs that are strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's wort (*Hypericum perforatum*).

4.4 Special warnings and precautions for use

ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG is not recommended during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available (see section 4.6).

ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG has not been evaluated for the treatment of severe malaria, including cases of cerebral malaria or other severe manifestations such as pulmonary oedema or renal failure.

Due to limited data on safety and efficacy, ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG should not be given concurrently with any other antimalarial agent (see section 4.5) unless there is no other treatment option.

If a patient deteriorates whilst taking ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG, alternative treatment for malaria should be started without delay. In such cases, monitoring of the ECG is recommended and steps should be taken to correct any electrolyte disturbances.

The long elimination half-life of lumefantrine must be taken into account when administering quinine in patients previously treated with ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG.

If quinine is given after ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG, close monitoring of the ECG is advised (see section 4.5).

If ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG is given after mefloquine, close monitoring of food intake is advised (see section 4.5).

In patients previously treated with halofantrine, ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG should not be administered earlier than one month after the last halofantrine dose.

ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG is not indicated and has not been evaluated for prophylaxis of malaria.

ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG should be used cautiously in patients on anti-retroviral drugs (ARTs) since decreased artemether, DHA, and/or lumefantrine concentrations

may result in a decrease of antimalarial efficacy of ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG, (see section 4.5).

Like other antimalarials (e.g. halofantrine, quinine and quinidine) ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG has the potential to cause QT prolongation (see section 5.1).

Caution is recommended when combining ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG with drugs exhibiting variable patterns of inhibition, moderate induction or competition for CYP3A4 as the therapeutic effects of some drugs could be altered. Drugs that have a mixed inhibitory/induction effect on CYP3A4, especially anti-retroviral drugs such as HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors should be used with caution in patients taking ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG (see sections 4.5 and 5.2).

Caution is recommended when combining ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG with hormonal contraceptives. ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control for about one month (see sections 4.5).

Patients who remain averse to food during treatment should be closely monitored as the risk of recrudescence may be greater.

Renal impairment

No specific studies have been carried out in this group of patients. There is no significant renal excretion of lumefantrine, artemether and dihydroartemisinin in studies conducted in healthy volunteers and clinical experience is limited. No dose adjustment for the use of ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG in patients with renal impairment is recommended. Caution is advised when administering ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG to patients with severe renal impairment. In these patients, ECG and blood potassium monitoring is advised.

Hepatic impairment

No specific studies have been carried out in this group of patients. In patients with severe hepatic impairment, a clinically relevant 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 (see section 5.2). In these patients, ECG and blood potassium monitoring is advised. No dose adjustment is recommended for patients with mild to moderate hepatic impairment.

New infections

Data for a limited number of patients in a malaria endemic area show that new infections can be treated with a second course of ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG. In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG cannot be recommended.

Excipient with known effect:

This medicine contains less than 1 mmol sodium (23 mg) per tablet, i.e. is essentially "sodium-free."

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 TABLETS 20MG/120MG 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 antihistamines (terfenadine, astemizole), cisapride, flecainide (see section 4.3)

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 TABLETS 20MG/120MG with drugs that are metabolised by this iso-enzyme is contraindicated (e.g. neuroleptics, metoprolol, and tricyclic antidepressants such as imipramine, amitriptyline, clomipramine) is contraindicated (see sections 4.3 and 5.2).

Interaction with strong inducers of CYP3A4 such as rifampin

Oral administration of rifampin (600 mg daily), a strong CYP3A4 inducer, with ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG Tablets (6-dose regimen over 3 days) in six HIV- 1 and tuberculosis coinfected 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 TABLETS 20MG/120MG alone. Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's Wort is contraindicated with ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG (see section 4.3).

Inducers should not be administered at least one month after ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG administration, unless critical to use as judged by the prescriber.

Mefloquine

A drug interaction study with ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG in man involved administration of a 6-dose regimen over 60 hours in healthy volunteers which was commenced at 12 hours after completion of a 3-dose regimen of mefloquine or placebo. Plasma mefloquine concentrations from the time of addition of ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG were not affected compared with a group which received mefloquine followed by placebo.

Pre-treatment with mefloquine had no effect on plasma concentrations of artemether or the artemether/dihydroartemisinin ratio but there was a significant reduction in plasma levels 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 the decrease in bioavailability.

Quinine

A drug interaction study in healthy male volunteers showed that the plasma concentrations of lumefantrine and quinine were not affected when i.v. quinine (10 mg/kg BW over 2 hours) was given sequentially 2 hours after the last (sixth) dose of ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG (so as to produce concurrent plasma peak levels of lumefantrine and quinine). Plasma concentrations of artemether and dihydroartemisinin (DHA) appeared to be lower. In this study, administration of ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG 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 TABLETS 20MG/120MG 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 TABLETS 20MG/120MG.

4.6 Pregnancy and Lactation

Women of childbearing potential

Women using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control for about one month (see section 4.4).

Pregnancy

A meta-analysis of observational studies including over 500 artemether-lumefantrine exposed women in their first trimester of pregnancy assessed adverse pregnancy outcomes. The data showed that compared to quinine, artemisinin treatment, including artemether-lumefantrine, was

not associated with an increased risk of miscarriage, stillbirth or congenital anomalies. However, due to the limitations of these studies, the risk of adverse pregnancy outcomes for artemether-lumefantrine exposed women in early pregnancy cannot be excluded.

Safety data from pregnancy studies including over 1200 pregnant women who were exposed to artemether-lumefantrine during the second or third trimester did not show an increase in adverse pregnancy outcomes or teratogenic effects over background rates.

Studies in animals have shown reproductive toxicity (see section 5.3).

ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG treatment is not recommended during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available (see section 4.4). However, it should not be withheld in life-threatening situations, where no other effective antimalarials are available. During the second and third trimester, ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG treatment should be considered if the expected benefit to the mother outweighs the risk to the foetus.

Breast-feeding

Animal data suggest excretion into breast milk but no data are available in humans. Women taking ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG should not breast-feed during their treatment. Due to the long elimination half-life of lumefantrine (2 to 6 days), it is recommended that breast-feeding should not resume until at least one week after the last dose of ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG unless potential benefits to the mother and child outweigh the risks of ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG treatment.

Fertility

There is no information on the effects of ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG on human fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients receiving ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG should be warned that dizziness or fatigue/asthenia may occur in which case they should not drive or use machines.

4.8 Undesirable effects

The safety of ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG has been evaluated in 20 clinical trials with more than 3500 patients. A total of 1810 adults and adolescents above 12 years of age as well as 1788 infants and children of 12 years of age and below have received ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG in clinical trials.

Adverse reactions reported from clinical studies and post-marketing experience are listed below according to system organ class.

Adverse reactions are ranked under headings of frequency using the MedDRA frequency convention:

Very common (≥1/10) Common

(≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <1/1,000)

Very rare (<1/10,000)

Not known (cannot be estimated from available data).

Table 1 Frequency of Undesirable effects

	dults and adolescents above 2 years of age	**nfants and children of 12 years f age and below (incidence stimates)**
lood and lymphatic system disorders		
elayed haemolytic anaemia[#]	ot Known	ot Known
mmune system disorders		
ypersensitivity	ot known	are
letabolism and nutrition disorders		
ecreased appetite	ery common	ery common (16.8 %)
sychiatric disorders		
leep disorders	ery common	ommon (6.4 %)
nsomnia	ommon	ncommon
ervous system disorders		
eadache	ery common	ery common (17.1 %)
izziness	ery common	ommon (5.5 %)
araesthesia	ommon	·
taxia, hypoaesthesia	ncommon	·

omnolence	ncommon	ncommon
lonus	ommon	ncommon
ardiac disorders		
alpitations	ery common	ommon (1.8 %)
lectrocardiogram QT prolonged	ommon	ommon (5.3 %)

espiratory, thoracic and mediastinal disorders		
ough	ommon	ery common (22.7 %)
astrointestinal disorders		
omiting	ery common	ery common (20.2 %)
bdominal pain	ery common	ery common (12.1 %)
ausea	ery common	ommon (6.5 %)
iarrhoea	ommon	ommon (8.4 %)
epatobiliary disorders		
ver function tests increased	ncommon	ommon (4.1 %)
kin and subcutaneous tissue disorders		
ash	ommon	ommon (2.7 %)
ruritus	ommon	ncommon
rticaria	ncommon	ncommon
ngioedema*	ot known	ot known
lusculoskeletal and connective tissue disorders		
rthralgia	ery common	ommon (2.1 %)
lyalgia	ery common	ommon (2.2 %)
eneral disorders and administration site conditions		
sthenia	ery common	ommon (5.2 %)
atigue	ery common	ommon (9.2 %)

ait disturbance	ommon	.

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 Pharmacodynamics properties

Pharmacotherapeutic group: Antimalarials,

ATC code: P01 BF01

Pharmacodynamic effects

ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG 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. ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG has been reported to have potent activity in terms of clearing gametocytes.

By 2015, resistance to artemisinins emerged in Southeast Asia. Studies with ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG in this region showed delayed parasite clearance (manifested as a higher proportion of patients with parasitemia on Day 3 after initiation of treatment), although overall efficacy as measured by cure rates after 28 days, remained high (WHO 2014). In Africa, only isolated reports on delayed parasite clearance are available and a clear trend towards resistance development was not observed.

Treatment of Acute Uncomplicated P. falciparum Malaria

The efficacy of ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG Tablets was evaluated for the treatment of acute, uncomplicated malaria (defined as symptomatic P. falciparum malaria without signs and symptoms of severe malaria or evidence of vital organ dysfunction) in five 6-dose regimen studies and one study comparing the 6-dose regimen with the 4-dose regimen.

Baseline parasite density ranged from 500/µl - 200,000/µl (0.01% to 4% parasitemia) in the majority of patients. Studies were conducted in otherwise healthy, partially immune or non-immune adults and children (≥5kg body weight) with uncomplicated malaria in Thailand, sub-Saharan Africa, Europe, and South America.

Efficacy endpoints consisted of:

- 28-day cure rate, proportion of patients with clearance of asexual parasites within 7 days without recrudescence by day 28
- parasite clearance time (PCT), defined as time from first dose until first total and continued disappearance of asexual parasite which continues for a further 48 hours
- fever clearance time (FCT), defined as time from first dose until the first time body temperature fell below 37.5°C and remained below 37.5°C for at least a further 48 hours (only for patients with temperature >37.5°C at baseline)

The modified intent to treat (mITT) population includes all patients with malaria diagnosis confirmation who received at least one dose of study drug. Evaluable patients generally are all patients who had a day 7 and a day 28 parasitological assessment or experienced treatment failure by day 28. The results are presented in the table below:

Table 2 Clinical efficacy results

tudy No.	**ge**	**olymerase chain eaction (PCR)-orrected 28-day ure rate[1] n/N (%) in valuable patients**	**ledian FCT[2] 25th, 5th percentile]**	**ledian PCT[2] 25th, 5th percentile]**	**ear/ Study ocation**
025[4]	-62 years	3/96 (96.9)	[3]=59 5 hours [20, 46]	=118 4 hours [22, 47]	996-97 hailand
026	-63 years	30/133 (97.7)	[3]=87 2 hours [19, 44]	A	997-98 hailand
028	2-71 years	48/154 (96.1)	[3]=76 9 hours [8, 51]	=164 9 hours [18, 40]	998-99 hailand

2401	6-66 years	19/124 (96.0)	[3]=100 7 hours [18, 44]	=162 2 hours [34, 63]	001-05 urope, olumbia
2403	months-9 ears	89/299 (96.7)	3=309 hours [8, 24]	=310 4 hours [24, 36]	002-03 countries in frica
2303CT	months-12 ears	03/419 (96.2)	3=323 hours [8, 23]	=452 5 hours [24, 36]	006-07 countries in frica
2303DT	months-12 ears	94/416 (94.7)	3=311 hours [8, 24]	=446 4 hours [24, 36]	006-07 countries in frica

[1] Efficacy cure rate based on blood smear microscopy

[2] mITT population

[3] For patients who had a body temperature >37.5°C at baseline only

[4]Only the 6-dose regimen over 60 hours group data is presented

[CT] –ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG tablets administered as crushed tablets

[DT] –ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG Dispersible tablets ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG is not indicated for, and has not been evaluated in, the treatment of malaria due to *P. vivax*, *P. malariae* or *P. ovale*, although some patients in clinical studies had co-infection with *P. falciparum* and *P. vivax* at baseline. In 319 adult patients in whom gametocytes were present, the median time to gametocyte clearance with ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG was 96 hours. ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG is active against blood stages of *Plasmodium vivax*, but is not active against hypnozoites.

Paediatric population

Three studies have been conducted

Study A2403 was conducted in Africa in 310 infants and children aged 2 months to 9 years, weighing 5 kg to 25 kg, with an axillary temperature ≥37.5°C. Results of 28-day cure rate (PCR-

corrected), median parasite clearance time (PCT), and fever clearance time (FCT) are reported in table 3 below.

Study B2303 was conducted in Africa in 452 infants and children, aged 3 months to 12 years, weighing 5 kg to <35 kg, with fever (≥37.5°C axillary or ≥38°C rectally) or history of fever in the preceding 24 hours. This study compared crushed tablets and dispersible tablets. Results of 28-day cure rate (PCR-corrected), median parasite clearance time (PCT), and fever clearance time (FCT) for crushed tablets are reported in table 3 below.

Table 3 Clinical efficacy by weight for pediatric studies

tudy No. **/eight category**	**ledian PCT[1]** **25th, 75th percentile]**	**CR-corrected 28-day cur** **ate[2] n/N (%) in evaluabl** **atients**
tudy A2403 5 <10 kg 0 - <15 kg 5 -25 kg	4 hours [24, 36] 5 hours [24, 36] 4 hours [24, 36]	45/149 (97.3) 03/107 (96.3) 1/43 (95.3)
tudy B2303[CT] 5 <10 kg 0 - <15 kg 5 -<25 kg 5-35 kg	6 hours [24, 36] 5 hours [24, 36] 5 hours [24, 36] 6 hours [24, 36]	5/69 (94.2) 74/179 (97.2) 34/140 (95.7) 0/31 (96.8)

5.2 Pharmacokinetic properties

Pharmacokinetic Characterisation of ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG 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 ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG, 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 ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG 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%).

Biotransformation

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*.

Glucuronidation of dihydroartemisinin is predominately catalysed by UGT1A9 and UGT2B7.

Dihydroartemisinin is further converted to inactive metabolites.

The pharmacokinetics of artemether in adults is time-dependent. During repeated administration of ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG, 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. The clinical evidence of induction is consistent with the *in vitro* data described in section 4.5

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 ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG over the 3-day treatment period, consistent with the slow elimination of the compound (see section 5.2 Elimination). 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 (see sections 4.3 and 4.5).

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 ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG. Limited urinary excretion data are available for humans. In 16 healthy volunteers, neither lumefantrine nor artemether was found in urine after administration of ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG, 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 ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG dose. No conclusive data is available for artemether.

Bioavailability/bioequivalence studies

Systemic exposure to lumefantrine, artemether and dihydroartemisinin was similar following administration of ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG as dispersible tablets and crushed tablets in healthy adults.

Systemic exposure to lumefantrine was similar following administration of ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG 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 ARTEMETHER & LUMEFANTRINE TABLETS 20MG/120MG dispersible tablets was demonstrated in this population. The dispersible tablet is not recommended for use in adults.

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 for at least 7 days and dogs for at least 8 days, but lesions were not observed after shorter intramuscular treatment courses or after oral dosing. The estimated artemether 24 h AUC after 7 days of dosing at the no observed effect level is approximately

7-fold greater or more than the estimated artemether 24 h AUC in adult humans. The hearing threshold was affected at 20 dB by oral artemether administration to dogs at a dose of 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

Artemether and lumefantrine were not genotoxic/clastogenic based on *in vitro* and *in vivo* testing.

Carcinogenicity

Carcinogenicity studies were not conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ingredients Name	Specification
Maize Starch	BP
Dicalcium Phosphate	BP
Micro Crystalline Cellulose	BP
P.V.P.K -30	BP
Methyl Paraben	BP
Propyl Paraben	BP
Purified Water	BP
Purified Talcum	BP
Magnesium stearate	BP
Colloidal Silicon Dioxide	BP
Sodium Starch Glycolate	BP

6.2 Incompatibilities

None

6.3 Shelf life

36 Months.

6.4 Special precautions for storage

Store in a cool & dry place, below 30°C.

Keep all medicines out of reach of children.

6.5 Nature and contents of container and special equipment for use, administration or implantation.

Tablets pack in a Alu/PVDC Blister, such 1 blister pack in a monocarton with pack insert.

Pack Style: 3 x 8, 1 x 12,1x18,1x6 & 1 x 24 Tablets.

6.6 Special precautions for disposal and other handling

No special requirements

7.0 APPLICANT/MANUFACTURER

Name of Manufacture:
LESANTO LABORATORIES
Plot No. 9, 10, 11 & 20,
Survey No. 53, Palghar (E),
Dist.Palghar,401404 INDIA