SUMMARY OF PRODUCT CHARACTERISTICS

LINGOMAL Artemether 20 mg and Lumefantrine 120 mg Tablets

4. Clinical particulars

4.1 Therapeutic indications

This medicine is an antimalarial. It is used to treat a certain type of malaria infection in adults and children who weigh at least 5 kg.

LINGOMAL 20/120 mg Tablets contains two antimalarial drugs, artemether and lumefantrine in fixed dose, which work together to kill the malaria parasite (a tiny organism that is found inside the red blood cells). Your doctor has found that you have malaria and so has prescribed **LINGOMAL 20/120 mg Tablets**.

It is indicated only for the treatment of so called uncomplicated malarial attacks due to Plasmodium falciparum (a particular type of malaria parasite) against which the medicine is active. For complete cure it is important that you complete the prescribed dose as advised by your doctor, pharmacist or health care provider.

4.2 Posology and method of administration

LINGOMAL 20/120 mg Tablets should always be taken exactly as described by the doctor or health care provider. You should check with your doctor, health care provider or pharmacist if you are not sure.

The dose of **LINGOMAL 20/120 mg Tablets** is decided on the basis of you or your child's body weight.

Number of **LINGOMAL 20/120 mg Tablets** for treatment according to weight bands

Weight range	Time					
	Day 1		Day 2		Day 3	
*	Immediately after diagnosis/ onset of symptoms	8 hours after previous dose	24 hours after previous dose	36 hours after previous dose	48 hours after previous dose	60 hours after previous dose
From 5kg up to 14kg	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet
From 15kg up to 24kg	2 tablets	2 tablets	2 tablets	2 tablets	2 tablets	2 tablets
From 25kg up to 34kg	3 tablets	3 tablets	3 tablets	3 tablets	3 tablets	3 tablets
From 35kg (or ≥ 15 years of age)	4 tablets	4 tablets	4 tablets	4 tablets	4 tablets	4 tablets

The first dose should be followed by a second dose after 8 hours. The following two days the doses of **LINGOMAL 20/120 mg Tablets** should be taken 12 hours apart.

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LINGOMAL 20/120 mg Tablets should be taken with food or a milky drink. If you are unable to tolerate food, **LINGOMAL 20/120 mg Tablets** should still be administered, but your body may take up less of the medicine. If you vomit within 1 hour of taking the medication, you should repeat the dose.

For very young children, the tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately.

4.3 Contraindications
LINGOMAL 20/120 mg Tablets 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).
(*Presence of one or more of the following clinical or laboratory features:
Clinical manifestation: Prostration; impaired consciousness or unarousable coma; failure to feed; deep breathing, respiratory distress (acidotic breathing); multiple convulsions; circulatory collapse or shock; pulmonary edema (radiological); abnormal bleeding; clinical jaundice; hemoglobinuria
Laboratory test: Severe normocytic anemia; hemoglobuniuria; hypoglycemia; metabolic acidosis; renal impairment; hyperlactatemia; hyperparasitemia)

4.4 Special warnings and precautions for use
If you are pregnant, you must tell your doctor or health care provider. **LINGOMAL 20/120 mg Tablets** should only be used in pregnancy if it is considered absolutely necessary (see below Pregnancy and breast-feeding).

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LINGOMAL 20/120 mg Tablets can change your electrical recording of the heart (electrocardiogram, ECG,). Therefore, before taking, **LINGOMAL 20/120 mg Tablets**, inform your doctor of health care provider if you have:

• any condition with certain abnormal ECG changes
• a salt imbalance in the blood, especially low concentrations of potassium in the blood (hypokalaemia) which are currently not corrected by treatment.
• a very slow heart rate (bradycardia)
• a weak heart (heart failure)
• a history of abnormal heart rhythms (arrhythmias)

Also, inform your doctor or health care provider:
• if you are taking any medicine that lowers your blood potassium levels.
• if you are taking other medicines that result in certain abnormal ECG changes (see below, Other medicines and **LINGOMAL 20/120 mg Tablets**).

If you experience palpitations or an irregular heartbeat during treatment, you should tell your doctor immediately. He/she may wish to perform an ECG.

The use of **LINGOMAL 20/120 mg Tablets** has not been investigated in patients with kidney or liver disease. If you have any such condition, you should inform your doctor or health care provider before taking **LINGOMAL 20/120 mg Tablets**.

LINGOMAL 20/120 mg Tablets should not be used in patients with severe malaria for malaria prophylaxis or in combination with other drugs against malaria, unless your doctor or health care provider considers this appropriate in your particular case.

You should inform your doctor or health care provider about all malaria medicines that you have taken the last months, as the appropriateness of using **LINGOMAL 20/120 mg Tablets** may depend on this.

LINGOMAL 20/120 mg Tablets may lower the effects of hormonal contraceptives. Therefore a different or an additional method of contraception (e.g. condoms, intra-uterine device, pessary) should be used during treatment with **LINGOMAL 20/120 mg Tablets**.

It is important that your doctor or health care provider knows about all your symptoms, even when you think they are not related to malaria infection.

4.5 Interaction with other medicinal products and other forms of interaction
Contraindications of concomitant use
It is important that you tell your doctor, health care provider or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. These may affect the action of **LINGOMAL 20/120 mg Tablets**, or **LINGOMAL 20/120 mg Tablets** may affect their action. Side effects of either medicine may become worse and/or the medicines may become less effective.

Especially tell your doctor or health care provider if you take or have recently taken:
• Any other medicines to treat or prevent malaria • Medicines for your heart
• Antipsychotic medicines (for treatment of abnormal condition of the mind)
• Antidepressants (medication to alleviate mood disorders)
• Antibiotics
• Antihistamines (for treatment of, e.g., allergies)
• Cisapride (a medicine for improving gastric motility)
• Medicines to treat HIV infection
• Medicines against fungal infection
• Hormonal methods of birth control (for example birth control pills or contraceptive patch)

4.6 Fertility, pregnancy and lactation

Pregnancy

Do not use this drug during pregnancy without medical advice. This is particularly important during the first 3 months of pregnancy.

Breast-feeding

Breast-feeding can be considered after medical advice.

4.7 Effects on ability to drive and use machines

LINGOMAL 20/120 mg Tablets may cause dizziness and fatigue. If you feel dizzy or fatigued while taking **LINGOMAL 20/120 mg Tablets**, do not drive and do not use any tools or machines.

4.8 Undesirable effects

Like all medicines, **LINGOMAL 20/120 mg Tablets** can cause side effects, although not everybody gets them. When treating malaria, it is not always possible to differentiate between unwanted effects caused by **LINGOMAL 20/120 mg Tablets**, and those caused by any other medicines you may be taking at the same time. For this reason, it is important that you inform the doctor or health care provider of any change in your health.

The following side effects have been reported in patients treated with **LINGOMAL 20/120 mg Tablets**:

The most commonly reported side effects (greater than 1 in every 10 patients treated) include headache, dizziness, feeling sick, vomiting, abdominal pain, loss of appetite, palpitations, pain in muscles and joints, fatigue and disturbed sleep.

Commonly (greater than 1 in every 100 patients treated) reported side effects include alterations to the electrocardiogram (ECG), tingling in hands and feet, problems with walking, cough, diarrhoea, itching, rash and insomnia.

Uncommon side effects (greater than 1 in every 1000 patients treated but less than 1 in 100): involuntary muscle jerks, coordination disturbances, altered liver function tests and drowsiness.

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The following side effects have been reported in patients treated with **LINGOMAL 20/120 mg Tablets**. However, frequency estimates for these effects are not available: hypersensitivity reaction, hives, rapid swelling of the face and throat (angioedema).

A similar side effect profile was reported for children

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, health care provider or pharmacist as soon as possible.

4.9 Overdose

If you take too many tablets, you may develop an abnormal heartbeat. Immediately contact your doctor, health care provider or the nearest hospital emergency department for further advice.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antimalarials, blood schizontocide, ATC code: P01 BF01.

Pharmacodynamic effects

LINGOMAL 20/120 mg Tablets 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. **LINGOMAL 20/120 mg Tablets** has been reported to have potent activity in terms of clearing gametocytes.

By 2015, resistance to artemisinins emerged in Southeast Asia. Studies with **LINGOMAL 20/120 mg Tablets** 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 **LINGOMAL 20/120 mg 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

Study No.	Age	Polymerase chain reaction (PCR)-corrected 28-day cure rate[1] n/N (%) in evaluable patients	Median FCT[2] [25th, 75th percentile]	Median PCT[2] [25th, 75th percentile]	Year/ Study location
A025[4]	3-62 years	93/96 (96.9)	n[3]=59 35 hours [20, 46]	n=118 44 hours [22, 47]	1996-97 Thailand
A026	2-63 years	130/133 (97.7)	n[3]=87 22 hours [19, 44]	NA	1997-98 Thailand
A028	12-71 years	148/154 (96.1)	n[3]=76 29 hours [8, 51]	n=164 29 hours [18, 40]	1998-99 Thailand
A2401	16-66 years	119/124 (96.0)	n[3]=100 37 hours [18, 44]	n=162 42 hours [34, 63]	2001-05 Europe, Columbia
A2403	2 months-9 years	289/299 (96.7)	n[3]=309 8 hours [8, 24]	n=310 24 hours [24, 36]	2002-03 3 countries in Africa
B2303[CT]	3 months-12 years	403/419 (96.2)	n[3]=323 8 hours [8, 23]	n=452 35 hours [24, 36]	2006-07 5 countries in Africa
B2303[DT]	3 months-12 years	394/416 (94.7)	n[3]=311 8 hours [8, 24]	n=446 34 hours [24, 36]	2006-07 5 countries in Africa

[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

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LINGOMAL Artemether 20 mg and Lumefantrine 120 mg Tablets

[CT] **– LINGOMAL 20/120 mg Tablets** administered as crushed tablets

[DT] **– LINGOMAL 20/120 mg Tablets** Dispersible tablets

LINGOMAL 20/120 mg Tablets 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 **LINGOMAL 20/120 mg Tablets** was 96 hours. **LINGOMAL 20/120 mg Tablets** 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

Study No. **Weight category**	**Median PCT[1]** **[25th, 75th percentile]**	**PCR-corrected 28-day cure rate[2] n/N (%) in evaluable patients**
Study A2403		
5 - <10 kg	24 hours [24, 36]	145/149 (97.3)
10 - <15 kg	35 hours [24, 36]	103/107 (96.3)
15 -25 kg	24 hours [24, 36]	41/43 (95.3)
Study B2303[CT]		
5 - <10 kg	36 hours [24, 36]	65/69 (94.2)
10 - <15 kg	35 hours [24, 36]	174/179 (97.2)
15 -<25 kg	35 hours [24, 36]	134/140 (95.7)
25-35 kg	26 hours [24, 36]	30/31 (96.8)

[1] mITT population

[2] Efficacy cure rate based on blood smear microscopy

[CT] **LINGOMAL 20/120 mg Tablets** administered as crushed tablets

Study B2306, was a multi-centre, open-label, single-arm study conducted in 20 infants in Africa, Benin and Burkina Faso to evaluate the efficacy, safety and pharmacokinetics of dispersible tablets in infants aged >28 days and <5 kg of body weight, who were treated with one dispersible tablet (20 mg artemether/120 mg lumefantrine) given twice-daily for three days and followed up for six weeks (core follow-up) and at the age of 12 months (long-term follow-up).

Dispersible tablets were well tolerated with reported adverse events of mild to moderate severity. In the per protocol population, PCR-corrected cure rate at days 28 and 42 was 100% (95% CI: 79.4, 100). For important exposure results, see section 5.2. Although neurotoxicity was not observed in the patients in Study B2306, artemether has been associated with neurotoxicity in studies in rats and dogs, see section 5.3.

QT/QTc Prolongation:

Adults and children with malaria

For information on the risk of QT/QTc prolongation in patients see section 4.4

Healthy adults

In a healthy adult volunteer parallel group study including a placebo and moxifloxacin control group (n=42 per group), the administration of the six dose regimen of **LINGOMAL 20/120 mg Tablets** was associated with prolongation of QTcF. The mean changes from baseline at 68, 72, 96, and 108 hours post first dose were 7.45, 7.29, 6.12 and 6.84 msec, respectively. At 156 and 168 hours after first dose, the changes from baseline for QTcF had no difference from zero. No subject had a >30 msec increase from baseline nor an absolute increase to >500 msec. Moxifloxacin control was associated with a QTcF increase as compared to placebo for 12 hours after the single dose with a maximal change at 1 hour after dose of 14.1 msec.

In the adult/adolescent population included in clinical trials, 8 patients (0.8%) receiving **LINGOMAL 20/120 mg Tablets** experienced a QTcB >500 msec and 3 patients (0.4%) a QTcF >500 msec. Prolongation of QTcF interval >30 msec was observed in 36% of patients.

In clinical trials conducted in children with the 6-dose regimen, no patient had post-baseline QTcF >500 msec whereas 29.4% had QTcF increase from baseline >30 msec and 5.1% >60 msec. In clinical trials conducted in adults and adolescents with the 6-dose regimen, post-baseline QTcF prolongation of >500 msec was reported in 0.2% of patients, whereas QTcF increase from baseline >30 msec was reported in 33.9% and >60 msec in 6.2% of patients.

In the infant/children population included in clinical trials, 3 patients (0.2%) experienced a QTcB >500 msec. No patient had QTcF >500 msec. Prolongation of QTcF intervals >30 msec was observed in 34% of children weighing 5-10 kg, 31% of children weighing 10-15 kg and 24% of children weighing 15-25 kg, and 32% of children weighing 25-35 kg.

5.2 Pharmacokinetic properties

Pharmacokinetic characterisation of **LINGOMAL 20/120 mg Tablets** 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 **LINGOMAL 20/120 mg Tablets**, 20 mg artemether/120 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 **LINGOMAL 20/120 mg Tablets** 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 **LINGOMAL 20/120 mg Tablets**, 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 **LINGOMAL 20/120 mg Tablets** 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 **LINGOMAL 20/120 mg Tablets**.

Limited urinary excretion data are available for humans. In 16 healthy volunteers, neither lumefantrine nor artemether was found in urine after administration of **LINGOMAL 20/120 mg Tablets**, 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 **LINGOMAL 20/120 mg Tablets** dose. No conclusive data is available for artemether.

Bioavailability/bioequivalence studies

Systemic exposure to lumefantrine, artemether and dihydroartemisinin was similar following administration of **LINGOMAL 20/120 mg Tablets** as dispersible tablets and crushed tablets in healthy adults.

Systemic exposure to lumefantrine was similar following administration of **LINGOMAL 20/120 mg Tablets** 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 **LINGOMAL 20/120 mg Tablets** dispersible tablets was demonstrated in this population. The dispersible tablet is not recommended for use in adults.

Older people

No specific pharmacokinetic studies have been performed in elderly patients. However, there is no information suggesting that the dosage in patients over 65 years of age should be different than in younger adults.

Paediatric population

In paediatric malaria patients, mean Cmax (CV%) of artemether (observed after first dose of **LINGOMAL 20/120 mg Tablets**) were 223 (139%), 198 (90%) and 174 ng/ml (83%) for body weight groups 5-<15, 15-<25 and 25-<35 kg, respectively, compared to 186 ng/ml (67%) in adult malaria patients. The associated mean Cmax of DHA were 54.7 (108%), 79.8 (101%) and 65.3 ng/mL (36%), respectively compared to 101 ng/ml (57%) in adult malaria patients. AUC of lumefantrine (population mean, covering the six doses of **LINGOMAL 20/120 mg Tablets**) were 577, 699 and 1150 µg•h/ml for paediatric malaria patients in body weight groups 5-<15, 15-<25 and 25-<35 kg, respectively, compared to a mean AUC of 758 µg•h/ml (87%) in adult malaria patients. The elimination half-lives of artemether and lumefantrine in children are unknown.

Infants weighing <5 kg

Study B2306 (see section 5.1) showed that the C_{max} of artemether and DHA in infants with uncomplicated *P. falciparum* malaria weighing <5 kg and older than 28 days of age who were treated with artemether/lumefantrine dispersible tablets, was on average 2- to 3-fold higher than that in pediatric patients with a body weight ≥5 kg and children up to 12 years of age treated with the same dose of **LINGOMAL 20/120 mg Tablets**. The mean C_{max} of lumefantrine was similar to that observed in pediatric patients with a body weight ≥5 kg.

Race/Ethnicity

Pharmacokinetics of artemether, DHA and lumefantrine in the Japanese population was found to be consistent with other populations.

Hepatic and Renal impairment

No specific pharmacokinetic studies have been performed either in patients with hepatic or renal insufficiency or elderly patients. The primary clearance mechanism of both artemether and lumefantrine may be affected in patients with hepatic impairment. In patients with severe hepatic impairment, a clinically significant increase of exposure to artemether and lumefantrine and/or their metabolites cannot be ruled out. Therefore, caution should be exercised in dosing patients with severe hepatic impairment. Based on the pharmacokinetic data in 16 healthy subjects showing no or insignificant renal excretion of lumefantrine, artemether and dihydroartemisinin, no dose adjustment for the use of **LINGOMAL 20/120 mg Tablets** in patients with renal impairment is advised.

5.3 Preclinical safety data

General toxicity

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

Neurotoxicity

Studies in dogs and rats have shown that intramuscular injections of artemether resulted in brain lesions. Changes observed mainly in brainstem nuclei included chromatolysis, eosinophilic cytoplasmic granulation, spheroids, apoptosis and dark neurons. Lesions were observed in rats dosed 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.

Reproductive toxicity studies

Embryotoxicity was observed in rat and rabbit reproductive toxicity studies conducted with artemether, a derivative of artemisinin. Artemisinins are known to be embryotoxic. Lumefantrine alone caused no sign of reproductive or development toxicity at doses up to 1,000 mg/kg/day in rats and rabbits, doses which are at least 10 times higher than the daily human dose based on body surface area comparisons.

Reproductive toxicity studies performed with the artemether-lumefantrine combination caused maternal toxicity and increased post-implantation loss in rats and rabbits.

Artemether caused increases in post-implantation loss and teratogenicity (characterised as a low incidence of cardiovascular and skeletal malformations) in rats and rabbits. The embryotoxic artemether dose in the rat yields artemether and dihydroartemisinin exposures similar to those achieved in humans based on AUC.

Fertility

Artemether-lumefantrine administration yielded altered sperm motility, abnormal sperm, reduced epididymal sperm count, increased testes weight, and embryotoxicity; other reproductive effects (decreased implants and viable embryos, increased preimplantation loss) were also observed. The no adverse effect level for fertility was 300 mg/kg/day. The relevance to this finding in humans is unknown.

Juvenile toxicity studies

A study investigated the neurotoxicity of oral artemether in juvenile rats. Mortality, clinical signs and reductions in body weight parameters occurred most notably in younger rats. Despite the systemic toxicity noted, there were no effects of artemether on any of the functional tests performed and there was no evidence of a direct neurotoxic effect in juvenile rats.

Very young animals are more sensitive to the toxic effect of artemether than adult animals. There is no difference in sensitivity in slightly older animals compared to adult animals. Clinical studies have established the safety of artemether and lumefantrine administration in patients weighing 5 kg and above.

Cardiovascular Safety Pharmacology

In toxicity studies in dogs at doses $\geq$600 mg/kg/day, there was some evidence of prolongation of the QTc interval (safety margin of 1.3-fold to 2.2-fold for artemether using calculated free Cmax), at higher doses than intended for use in man. In vitro hERG assays showed a safety margin of >100 for artemether and dihydroartemisinin. The hERG IC_{50} was 8.1 µM for lumefantrine and 5.5 µM for its desbutyl metabolite.

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

6. Pharmaceutical particulars

6.1 List of excipients

Lactose	BP
Microcrystalline Cellulose	BP
Maize Starch	BP
Methyl Paraben	BP
Propyl Paraben	BP
P.V.P.K - 30	BP
Tartrazine Yellow Supra	BP
Purified Talcum	BP
Sodium Starch Glycolate	BP
Magnesium Stearate	BP
Colloidal Silicon Dioxide	BP
Croscarmellose Sodium	BP
Isopropyl Alcohol	BP

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store in a cool & dry place, store below 30°C.
Protect from light.

Do not use **LINGOMAL 20/120 mg Tablets** after the expiry date which is stated on the blister and the outer packaging after EXP. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6.5 Nature and contents of container
A Blister of 24 Tablets each, packed in one inner carton along with the Pack Insert.

6.6 Special precautions for disposal and other handling
For the treatment of children and infants, the 24-tablets pack should be prescribed. The prescriber and pharmacist should instruct the parent or care giver on the posology for their child and that a variable number of tablets (depending on the child's body weight) will be requested for the full treatment. Therefore, the whole pack may not be used. After successful treatment the remaining tablets should be discarded or returned to the pharmacist.

SUMMARY OF PRODUCT CHARACTERISTICS

LINGOMAL Artemether 20 mg and Lumefantrine 120 mg Tablets

7. Marketing authorisation holder

7.1 Marketing Authorisation Holder
PATRICKLINGO PHARMACEUTICALS LTD.
107 UPPER IWEKA ROAD, ONITSHA, ANAMBRA STATE

7.2 Manufacturer
GLOW PHARMA PVT. LTD.
UNIT NO. 217/218, HUBTOWN VIVA,
W.E. HIGHWAY, JOGESHWARI (EAST), MUMBAI – 400 060
INDIA

8. Marketing authorisation number(s)
Not applicable

9. Date of first authorisation/renewal of the authorisation
Not applicable

10. Date of revision of the text
Not applicable

SUMMARY OF PRODUCT CHARACTERISTICS

LINGOMAL Artemether 20 mg and Lumefantrine 120 mg Tablets