SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lumerax DT 20/120

Artemether 20 mg & Lumefantrine 120 mg dispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersible tablet.

Yellow coloured, circular, flat faced, bevelled edge uncoated tablets with "i" debossed on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lumerax DT 20/120 is indicated for the treatment of uncomplicated malaria due to *Plasmodium falciparum* in adults, children and infants.

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 Lumerax DT 20/120.

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.

Posology

Information on dosing for all the weight bands for which this tablet strength can be used is provided. Before passing this product on to the patient it is important to ensure that the pack size, i.e. the number of tablets included in this pack, is appropriate for a full treatment course according to the patient's weight.

Number of Lumerax DT 20/120 tablets for treatment according to body weight

Body weight	Daily dose
< 15 kg	1 tablet twice daily (2 x 20 mg/120 mg A/L[+])
15 kg to <25 kg*	2 tablets twice daily (2 x 40 mg/240 mg A/L)
25 kg to <35 kg*	3 tablets twice daily (2 x 60 mg/360 mg A/L)
≥ 35 kg*	4 tablets twice daily (2 x 80 mg/480 mg A/L)

[+] A/L=artemether/lumefantrine

*Other products containing a higher amount of artemether and lumefantrine may be available to reduce the patient's pill load.

The treatment should be given for three days.
The first dose should be followed by a second dose after 8 hours.
In the following two days the doses of Lumerax DT 20/120 should be given twice daily, in the morning and evening (i.e. 12 hours apart).

The tablets should be dispersed in drinking water before administration of the dose. Each tablet should be dispersed in a minimum of 10 mL water; the maximum volume of water recommended for dispersion of a dose is 50 mL.

Renal or hepatic impairment
No dose adjustments are necessary in patients with renal or hepatic impairment. However, caution is advised when administering Lumerax DT 20/120 to patients with severe renal or hepatic impairment (see section 4.4).

Elderly
No dosage adjustments are necessary in such patients.

Method of administration

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

Patients who vomit within 1 hour of taking the medicine 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.

Instructions for use

1. The required amount of drinking water should be taken in a small and clean cup and the required number of tablets should be added.

2. The cup should be gently swirled until tablets disperse, and the entire mixture should be given/taken immediately.

3. The cup should be rinsed with an additional 10 mL of water, which should be drunk by the patient to ensure the entire dose is taken.

4.3 Contraindications

Lumerax DT 20/120 should always be taken exactly as described by the health care provider.
You should check with your health care provider if you are not sure.

Weight range	Time					
	Day 1		Day 2		Day 3	
	Immediately after diagnosis/ onset of symptoms	8 hours after previous dose	12 hours after previous dose	12 hours after previous dose	12 hours after previous dose	12 hours after previous dose
Up to 15kg	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet
From 15kg up to 25kg	2 tablets	2 tablets	2 tablets	2 tablets	2 tablets	2 tablets
From 25kg up to 35kg	3 tablets	3 tablets	3 tablets	3 tablets	3 tablets	3 tablets
From 35kg (or ≥ 12 years of age)	4 tablets	4 tablets	4 tablets	4 tablets	4 tablets	4 tablets

Take the first dose immediately when your health care provider has diagnosed malaria.
Take the second dose 8 hours after the first dose.
Take the following doses 12 hours apart.

Take Lumerax DT 20/120 with food or a milky drink. If you are unable to tolerate food, Lumerax DT 20/120 should still be taken, 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.

If you take more Lumerax DT 20/120 than you should

If you take too many tablets, immediately contact your health care provider or the nearest hospital emergency department for further advice.

If you forget to take Lumerax DT 20/120

Try to make sure that you do not miss any dose. However, if you do forget a dose, take the missed dose as soon as you realise that you have forgotten it. Then take the next dose after the prescribed interval. Do not take a double dose to make up for a forgotten tablet. **Make sure you take all six doses of this regimen**.

If you stop taking Lumerax DT 20/120

You should keep taking the medicine for as long as your health care provider has ordered, even if you are feeling better. If you stop the medicine too soon, the infection may not be completely cured.

If you have any further questions on the use of this product, ask your health care provider.

4.4 Special warnings and precautions for use

Renal/hepatic dysfunction: Artemether/lumefantrine has not been studied in patients with severe renal or hepatic impairment. In these patients, ECG and blood potassium monitoring is advised.

Malaria prophylaxis: Artemether/lumefantrine has not been evaluated for malaria prophylaxis.

Malaria not caused by P. falciparum: Artemether/lumefantrine has not been evaluated for the treatment of malaria due to *P. vivax, P. malariae, P. ovale* or *P. knowlesi* (see section 5.1).
Following treatment of mixed infections including *P. vivax*, follow-up treatment must be given in order to eradicate the exoerythrocytic forms of *P. vivax*.

Other antimalarials:

Unless there is no other treatment option, Lumerax DT 20/120 should not be given concurrently with any other antimalarial agent due to limited data on safety and efficacy.

If a patient deteriorates while taking Lumerax DT 20/120 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.

Due to the potential of additive/synergistic QT-prolongation, close ECG-monitoring is advised when quinine is given after Lumerax DT 20/120 (see section 5.1).

If Lumerax DT 20/120 is given after mefloquine, close monitoring of food intake is advised (see section 4.5).

In patients previously treated with halofantrine, Lumerax DT 20/120 should not be administered earlier than one month after the last halofantrine dose (see section 4.5).

Hormonal contraceptives: Lumerax DT 20/120 may reduce the effectiveness of hormonal contraceptives. Patients should be advised to use an additional non-hormonal (i.e. barrier) method of birth control for one month after therapy with artemether/lumefantrine.

Antiretroviral drugs: Caution is recommended when combining Lumerax DT 20/120 with drugs exhibiting variable patterns of inhibition, moderate induction or competition for CYP3A4 as the therapeutic effects of some drugs could be altered. Concomitant use may lead to decreased artemether, DHA, and/or lumefantrine concentrations, which may result in a decrease of antimalarial efficacy of artemether/lumefantrine. 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 (see sections 4.5 and 5.2).

Intake with food and drinks: Patients who remain averse to food during treatment should be closely monitored, as the risk of recrudescence may be greater.

4.5 Interaction with other medicinal products and other forms of interaction

Lumerax DT 20/120 should not be used in patients taking drugs that are known to prolong the QTc interval (see section 4.3), as effects may be additive and increase the risk of cardiac arrhythmia.

Interaction with CYP450 enzymes
Both artemether and lumefantrine are metabolised predominantly by the cytochrome enzyme CYP3A4, but do not inhibit this enzyme at therapeutic concentrations. Studies in humans have demonstrated that artemisinins have some capacity to induce CYP3A4 and CYP2C19 and inhibit CYP2D6 and CYP1A2. Although the magnitude of the changes was generally low it is possible that these effects could alter the therapeutic response or safety profile of drugs that are predominantly metabolised by these enzymes.

Lumefantrine was found to inhibit CYP2D6 in vitro. This may be of particular clinical relevance for compounds with a narrow therapeutic index (see section 4.3).

Other antimalarials
Lumerax DT 20/120 should not be given concurrently with any other antimalarial agent (see section 4.4). In addition, due to the propensity of some antimalarial agents to prolong the QTc interval, caution is advised when administering Lumerax DT 20/120 to patients in whom there may still be detectable concentrations of these drugs in the plasma following prior treatments.

In patients previously treated with *halofantrine*, Lumerax DT 20/120 should be dosed at least one month after the last halofantrine dose due to the long elimination half-life of halofantrine and the potential additive/synergistic effects on the QT-interval.

Administration of a six-dose regimen of artemether/lumefantrine (over 60 hours) starting 12 hours after completion of a three-dose regimen of *mefloquine* or placebo in healthy volunteers showed no effect of mefloquine on plasma concentrations of artemether or the artemether/dihydroartemisinin ratio, but a 30-40% reduction in plasma levels of lumefantrine. This is possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production. Patients that have been pretreated with mefloquine should

be encouraged to eat at dosing times to compensate for the decrease in bioavailability. Plasma mefloquine concentrations from the time of addition of artemether/lumefantrine were not affected compared with a group that received mefloquine followed by placebo.

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 (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 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 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.

Antiretrovirals

- HIV-nucleoside and nucleotide reverse transcriptase inhibitors

  (NTRIs, e.g. abacavir,emtricitabine, lamivudine, tenofovir [TDF or TAF], zidovudine.)
  Co-administration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely.

- HIV-non-nucleoside reverse transcriptase inhibitors (NNRTIs)

  *Efavirenz:*Co-administration of efavirenz and artemether/lumefantrine lead to decreases in artemether exposure (51% and 79%), dihydroartemisinin exposure (46% and 75%) and lumefantrine exposure by (21% and 56%). Lumefantrine had no significant effect on efavirenz exposure in either study. Use with caution as decreased concentrations of artemether, dihydroartemisinin, or lumefantrine may result in a decrease of antimalarial efficacy.

  *Etravirine:*Coadministration of lumefantrine/artemether and etravirine decreased lumefantrine AUC and C_{min} by 13% and 3%, and increased C_{max} by 7%. Etravirine AUC, C_{min} and C_{max} increased by 10%, 8% and 11%. Concentrations of artemether and dihydroartemisinin decreased. Caution and close monitoring of antimalarial response is warranted when co-administering etravirine and lumefantrine/artemether as it is unknown whether the decrease in exposure of artemether or its active metabolite, dihydroartemisinin could result in decreased antimalarial efficacy. No dose adjustment is needed for etravirine.

  Nevirapine: Lumefantrine is metabolised predominantly by CYP3A4. Upon co-administration withartemether/lumefantrine with nevirapine decreased the AUCs of artemether and dihydroartemisinin. In a cross-over study lumefantrine exposure was decreased by 20% and lumefantrine reduced nevirapineexposure by 46%. Use with caution.

  Rilpivirine: Co-administration has not been studied but based on metabolism and clearance a pharmacokinetic interaction is unlikely. However, since rilpivirine at higher doses has been shown to prolong the QT interval, caution should be exercised when co-administering rilpivirine and artemether/lumefantrine.

- HIV Protease Inhibitors (PIs)

  Atazanavir: Co-administration may increase plasma levels of artemisinins and lumefantrine. Both lumefantrine and atazanavir have been shown to prolong the QT interval.

  Darunavir: Co-administration may increase plasma levels of artemisinins and lumefantrine.

  Lopinavir/ritonavir: Data from clinical studies and population modelling suggest that co-administration of lopinavir/ritonavir and artemether decreases exposure of dihydroartemisinin (the biologically active metabolite) by ~40-60%.Lumefantrine AUC was significantly increased by 2.3-fold and there was trend towards increased C_{max} (1.4-fold). The clinical meaning of these opposite effects on artemether and lumefantrine is not clear. Both lumefantrine and lopinavir have been shown to prolong the QT interval.

Ritonavir: see "Pharmacokinetic enhancers" below.

- HIV Integrase Strand-Transfer Inhibitors (INSTIs)

  Dolutegravir, raltegravir; bictegravir, cabotegravir: Co-administration has not been studied but based on metabolism/elimination and toxicity profiles there is little potential for interaction.

  Elvitegravir/cobicistat: Co-administration has not been studied. Artemether and lumefantrine are metabolized by CYP3A4. Elvitegravir/cobicistat may increase concentrations of artemisinins and lumefantrine.

- Pharmacokinetic Enhancers

  Ritonavir: Co-administration may increase plasma levels of artemisinins and lumefantrine, as both are metabolised by CYP3A4. Caution is recommended.

  Cobicistat: Co-administration has not been studied. Cobicistat may increase concentrations of artemisinins and lumefantrine by inhibition ofCYP3A4.

Antivirals against Hepatitis B or C

Ombitasvir/paritaprevir/ritonavir: Coadministration is not recommended unless there is no alternative. Lumefantrine is a substrate of CYP3A4 and its exposure may increase due to CYP3A4 inhibition by ritonavir. Subjects should be closely monitored.

Hormonal contraceptives

In vitro, the metabolism of ethinyl estradiol and levonorgestrel was not induced by artemether, DHA, or lumefantrine. However, artemether has been reported to weakly induce, in humans, the activity of CYP2C19, CYP2B6, and CYP3A. Therefore, artemether/lumefantrine may potentially reduce the effectiveness of hormonal contraceptives. 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 4.4 and 4.6).

Ketoconazole

The concurrent oral administration of ketoconazole with artemether/lumefantrine led to a modest increase (2 fold) in artemether, DHA, and lumefantrine exposure in healthy adult subjects. This increase in exposure to the antimalarial combination was not associated with increased side effects or changes in electrocardiographic parameters. Dose adjustment of Lumerax DT 20/120 is not considered necessary when administered concomitantly with ketoconazole or other azole antifungals, but such combinations should be used with caution.

Drug-food/drink interactions

Artemether/lumefantrine should be taken with food or drinks rich in fat such as milk as the absorption of both artemether and lumefantrine is increased (see section 4.2).

Grapefruit juice should be used cautiously during artemether/lumefantrine treatment. Administration of artemether with grapefruit juice in healthy adult subjects resulted in an approximately two fold increase in systemic exposure to the parent drug.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

While available studies cannot definitively establish the absence of risk, a meta-analysis of observational studies including over 500 artemether/lumefantrine-exposed women in their first trimester of pregnancy, data from observational, and open label-studies including more than 1200 pregnant women in their second- or third trimester exposed to artemether/lumefantrine compared to other antimalarials, and pharmacovigilance data have not demonstrated an increase in major birth defects, miscarriage, or adverse maternal or foetal outcomes. Published epidemiologic studies have important methodological limitations which hinder interpretation of data, including inability to control for confounders, such as underlying maternal disease, and maternal use of concomitant medications and missing information on the dose and duration of use
These data provide assurance in counselling women exposed to artemether/lumefantrine early in the first

trimester and indicated that there is no need for them to have their pregnancy interrupted because of this exposure.

Lumerax DT 20/120 can be used during the first trimester of pregnancy if no alternative effective antimalarial is available. Lumerax DT 20/120 can be used during second and third trimester of pregnancy.

Breast-feeding
The amounts of artemether, dihydroartemisinin and lumefantrine in breast milk are small. Therefore, breast-feeding women can receive artemisinin-based combination therapies (including Lumerax DT 20/120) for malaria treatment.

Fertility
There is no information on the effects of Lumerax DT 20/120 on fertility in humans.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients receiving Lumerax DT 20/120 should be warned that dizziness, fatigue or asthenia may occur, in which case their ability to drive or operate machines may be impaired.

4.8 Undesirable effects

The safety of artemether/lumefantrine has been evaluated in adults, adolescents and children in clinical trials with more than 3500 patients.

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).

Frequency of undesirable effects

	Adults and adolescents above 12 years of age	**Infants and children of 12 years of age and below (incidence estimates*)**
Cardiac disorders		
Palpitations	Very common	Common
Electrocardiogram QT prolonged	Common	Common
Nervous system disorders		
Headache	Very common	Common
Dizziness	Very common	Common
Paraesthesia	Common	--
Ataxia, hypoaesthesia	Uncommon	--
Clonic movements	Common	Uncommon
Somnolence	Uncommon	Uncommon
Respiratory, thoracic and mediastinal disorders		
Cough	Common	Very common
Gastrointestinal disorders		
Vomiting	Very common	Very common
Abdominal pain	Very common	Very common
Nausea	Very common	Common
Diarrhoea	Common	Common

Skin and subcutaneous tissue disorders		
Rash	Common	Common
Pruritus	Common	Uncommon
Urticaria	Uncommon	Uncommon
Angioedema*	Not known	Not known
Musculoskeletal and connective tissue disorders		
Arthralgia	Very common	Common
Myalgia	Very common	Common
General disorders and administration site conditions		
Asthenia	Very common	Common
Fatigue	Very common	Common
Gait disturbance	Common	
Immune system disorders		
Hypersensitivity	Not known	Rare
Blood and lymphatic system disorders		
Delayed haemolytic anaemia*[#]	Not known	Not known
Metabolism and nutrition disorders		
Decreased appetite	Very common	Very common
Hepatobiliary disorders		
Liver function tests abnormal	Uncommon	Common
Psychiatric disorders		
Sleep disorders	Very common	Common
Insomnia	Common	Uncommon

* These adverse reactions were reported during post-marketing experience. Because these spontaneously reported events are from a population of uncertain size, it is difficult to estimate their frequency.

[#]Has been reported up to a few weeks after treatment has been stopped.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose

Experience of overdosage with artemether/lumefantrine is limited. In cases of suspected overdosage symptomatic and supportive therapy should be given as appropriate, which should include monitoring of ECG and serum electrolytes.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimalarials, blood schizontocide, ATC code: P01BF01

Pharmacodynamic effects

Lumerax DT 20/120 comprises a fixed ratio of 1:6 parts of artemether/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.

Resistance

By 2015, resistance to artemisinins emerged in Southeast Asia. Studies with artemether/lumefantrine in this

region showed delayed parasite clearance (manifested as a higher proportion of patients with parasitaemia 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.

Clinical efficacy

The efficacy of artemether/lumefantrine 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% parasitaemia) 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:

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
[CT] –Artemether/lumefantrine tablets administered as crushed tablets
[DT] –Artemether/lumefantrine Dispersible tablets

Artemether/lumefantrine 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. Artemether/lumefantrine is active against blood stages of *Plasmodium vivax*, but is not active against hypnozoites.

Paediatric population

Two major 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 the table 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 artemether/lumefantrine 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 the tablebelow.

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]Artemether/lumefantrine tablets administered as crushed tablets

QT/QTc Prolongation:

For information on the risk of QT/QTc prolongation in patients see section 4.3 and 4.4.

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 artemether/lumefantrine with food was associated with a moderate prolongation of QTcF (QT interval corrected by Fridericias formula). 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 artemether/lumefantrine 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

Pharmacokinetics of Artemether and Lumefantrine

	Artemether	Lumefantrine
General		
Absorption		
Absolute bioavailability	NA*	NA*
Oral bioavailability	NA	NA
Food effect	A high fat meal increased bioavailability more than 2-fold.	A high fat meal increased bioavailability 16- fold.
Distribution		
Volume of distribution (mean)		
Plasma protein binding *in vitro*	Artemether: 95.4%. Dihydroartemisinin: 47-76%	99.7%
Tissue distribution		
Metabolism		
	Extensively metabolised predominantly through isoenzyme CYP3A4/5.	Lumefantrine is mainly metabolised by CYP3A4.
Active metabolites	Dihydroartemisinin is further metabolised through glucuronidation	Desbutyl-lumefantrine, but exposure less than 1% compared to parent.
Elimination		
Elimination half life	Artemether: about 2 h Dihydroartemisinin: about 2 h	3 – 6 days
Mean systemic clearance (Cl/F)	NA*	NA*

% of dose excreted in urine	Artemether: NA* Dihydroartemisinin:<0.01%	NA*
% of dose excreted in faeces	Not detected	Excreted primarily in faeces
Pharmacokinetic linearity	NA*	linear
Drug interactions *(in vitro*)		
Transporters		
Metabolising enzymes	May induce CYP2C19, CYP2B6, and CYP3A	Inhibits CYP 2D6

*Information not available

Pharmacokinetics in special patient populations

Older people

No specific pharmacokinetic studies have been performed in elderly patients (see section 4.2).

Hepatic and Renal impairment

Specific pharmacokinetic studies have not been performed in patients with hepatic or renal insufficiency. No pharmacokinetic studies are available in 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. 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 in patients with renal impairment is advised.

Paediatric population

In paediatric malaria patients, mean C_{max} (CV%) of artemether (observed after first dose) 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 C_{max} 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 artemether/lumefantrine) were 577, 699 and 1150 µgh/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 paediatric patients with a body weight ≥5 kg and children up to 12 years of age treated with the same dose of artemether/lumefantrinetablets. The mean C_{max} of lumefantrine was similar to that observed in paediatric 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.

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.

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

Carcinogenicity
Carcinogenicity studies with the artemether/lumefantrine combination 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 >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 C_{max}), 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 IC50 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

Microcrystalline cellulose
Croscarmellose sodium
Colloidal anhydrous silica
Hypromellose

Polysorbate 80
Saccharin sodium
Crospovidone
Flavour cherry
Permaseal
Magnesium stearate

6.2 **Incompatibilities**

Not applicable.

6.3 **Shelf life**

24 months

6.4 **Special precautions for storage**

Do not store above 30°C. Protect from light. Store tablets in blisters in the provided carton.

6.5 Nature and contents of container

PVC/PCTFE/PVC-Alu blisters. Each blister pack contains 6 tablets or 12 tablets.

PVC/PCTFE/PVC-Alu blister of 6 or 12 tablets in a printed show box along with a leaflet. 30 such show boxes packed in a printed outer carton.

6.6 **Special precautions for disposal**

No special requirements.

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

7. SUPPLIER

Ipca Laboratories Limited
48, Kandivli Industrial Estate
Kandivli (West)
Mumbai 400 067
India
Tel: +91-22-6210 5100/6210 5000
Fax: +91-22-6210 5105/+91-22-6210 5005
Email: ipca@ipca.com

8. MARKET AUTHORIZATION NUMBER

05694/07332/NMR/2019

9. DATE OF FIRST AUTHORISATION

24 February 2021

10. DATE OF REVISION OF THE TEXT

March 2022