# 1. NAME OF THE MEDICINAL PRODUCT

Lumerax Tablets 80/480

# 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 80 mg artemether and 480 mg lumefantrine.

*Excipients with potential clinical effect*

Each tablet also contains 219 mg anhydrous lactose.

For a full list of excipients, see section 6.1.

# 3. PHARMACEUTICAL FORM

Yellow coloured, biconvex, capsule shaped, uncoated tablet with break line on one side and "i" debossed on other side.
The score line is not intended for breaking the tablet.

# 4. CLINICAL PARTICULARS

## 4.1 Therapeutic indications

**5.** Lumerax Tablets 80/480 is indicated for the treatment of uncomplicated malaria due to *Plasmodium falciparum*.Treatment regimens should take into account the most recent official treatment guidelines (e.g. those of the WHO) and local information on the prevalence of resistance to antimalarial drugs.

## 5.1 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***

The recommended daily dose range of artemether/lumefantrine is between 5–24 mg of artemether and 29–144 mg of lumefantrine per kg body weight.

Lumerax Tablets 80/480 may be used in patients weighing 35 kg or more. For patients in lower weight bands, another formulation should be used to supply the correct dose.

*Patients weighing 35 kg or more:*

One tablet (80mg/480mg artemether/lumefantrine) should be taken twice daily; treatment should be given for 3 days (a total of 6 doses).

The first and second doses should be given 8 hours apart. Subsequent doses of Lumerax Tablets 80/480 should be given 12 hours apart, in the morning and evening.

*Missed dose and vomiting after a 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.

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

**Special populations**

*Pregnancy*

Treatment with artemether/lumefantrine at standard doses is recommended by WHO to treat uncomplicated falciparum malaria during the first trimester of pregnancy. The combination can also be used during the second and third trimester of pregnancy.

*Renal or hepatic impairment*

No dose adjustments are necessary in patients with renal or hepatic impairment. However, caution is advised when administering Lumerax Tablets 80/480to patients with severe renal or hepatic impairment (see section 4.4).

*Elderly*

No dosage adjustments are necessary in elderly patients.

***Method of administration***

To increase absorption, Lumerax Tablets 80/480should be taken with food or a milky drink (see section 5.2). If a patient is unable to tolerate food, Lumerax Tablets 80/480should still be administered, but the systemic exposure may be reduced.

For young children or patients not able to swallow the tablets whole , the tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately.

## 5.2 Contraindications

Lumerax Tablets 80/480 is contraindicated in:

- patients with known hypersensitivity to artemether, lumefantrine or to any of the excipients.
- patients with severe malaria according to WHO definition.
- patients with a personal or family history of congenital prolongation of the QTc interval or sudden death, or with any other clinical condition known to prolong the QTc interval, such as patients with a history of symptomatic cardiac arrhythmias, clinically relevant bradycardia or severe cardiac diseases.
- patients taking medicines that are known to prolong QTc interval 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).
- patients with known disturbances of electrolyte balance e.g. hypokalaemia or hypomagnesaemia.
- patients taking any drug which is metabolized by the cytochrome enzyme CYP2D6 (e.g.flecainide, metoprolol, imipramine, amitriptyline, clomipramine.
- patients taking drugs that are strong inducers of CYP3A4 such as rifampicin, carbamazepine, phenytoin, St John's wort.

## 5.3 Special warnings and precautions for use

To improve absorption, Lumerax Tablets 80/480 should be taken with food or a milky drink. Patients who are unable or unwilling to eat during treatment should be closely monitored, as the risk of recrudescence may be greater.

If a patient deteriorates while taking Lumerax Tablets 80/480 alternative treatment for malaria should be started without delay (but see also under section 4.5). In such cases, monitoring of the ECG is recommended and steps should be taken to correct any electrolyte disturbances.

*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*.

*Excipients*

Patients with congenital lactase deficiency, galactosaemia or glucose-galactose intolerance must not be given this medicine unless strictly necessary.

The small amount of lactose in each dose is unlikely to cause symptoms of lactose intolerance in other patients.

Patients who are allergic to cow's milk proteins must not be given this medicine unless strictly necessary.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

## 5.4 Interaction with other medicinal products and other forms of interaction

Lumerax Tablets 80/480 should not be used in patients taking medicines that are known to prolong the QTc interval (see section 4.3), as effects may be additive and increase the risk of cardiac arrhythmia.

Lumerax Tablets 80/480should not be given concurrently with any other antimalarial agent unless there is no other treatment option, due to limited data on safety and efficacy.. In addition, due to the propensity of some antimalarial agents to prolong the QTc interval, caution is advised when administering Lumerax Tablets 80/480to patients in whom there may still be detectable concentrations of these drugs in the plasma following prior treatments. See also the table below.

*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).

*Interactions with particular medicines*

Whenever co-prescribing any drug together with [MA160 trade name], the possibility of a drug-drug interaction should be considered. The following list of drug interactions with Lumerax Tablets 80/480is not exhaustive, but is a selection of interactions of potential relevance.

| **Drugs** (grouped by therapeutic area) | **Interaction** | **Recommendation on co-administration** |
|---|---|---|
| **Antimalarials** | | |
| Halofantrine | Potential additive/synergistic effects on QT-interval | Lumerax Tablets 80/480should not be given until at least one month after the last halofantrine dose due to the long elimination half-life of halofantrine. |
| Mefloquine | lumefantrine plasma concentrations ↓ 30-40%<br>possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production | Patients who have been pretreated with mefloquine should be encouraged to take doses of Lumerax Tablets 80/480with food, to compensate for the decrease in bioavailability. |

| **Drugs** (grouped by therapeutic area) | **Interaction** | **Recommendation on co-administration** |
|---|---|---|
| Quinine | risk of QTc prolongation associated with i.v. quinine was enhanced by prior administration of artemether/lumefantrine | Use with caution and appropriate monitoring. |
| **HIV antiretrovirals** | | |
| *Nucleoside/nucleotide transcriptase inhibitors* | | |
| Abacavir<br>Emtricitabine<br>Lamivudine<br>Tenofovir disoproxil or alafenamide<br>Zidovudine | Co-administration has not been studied but based on metabolism and clearance a clinically significant interaction is considered unlikely | No additional measures needed. |
| *Non-nucleoside/nucleotide transcriptase inhibitors* | | |
| Efavirenz | artemether AUC ↓ 50-80%<br>dihydroartemsisin AUC ↓ 45-75%<br>lumefantrine AUC ↓ 20-55%<br><br>No significant effect on efavirenz exposure | Lumerax Tablets 80/480should be used with caution in patients receiving efavirenz, as antimalarial efficacy may be decreased. |
| Etravirine | artemether AUC ↓<br>dihydroartemsisin AUC ↓<br>lumefantrine AUC ↓ 13%, $C_{min}$ ↓ 3%<br><br>Etravirine AUC ↑ 10%, $C_{min}$ ↑ 8%, $C_{max}$ ↑ 11% | 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.<br>No dose adjustment is needed for etravirine. |
| Nevirapine | artemether AUC ↓ 72%<br>dihydroartemisinin AUC ↓ 37%<br>lumefantrine AUC ↓ 20%<br><br>Nevirapine AUC ↓ 46% | Use with caution. |
| Rilpivirine | Co-administration has not been studied but based on metabolism and clearance a pharmacokinetic interaction is unlikely. | Caution is nonetheless advisable with co-administration since rilpivirine may prolong the QT-interval at higher doses. |
| *HIV protease inhibitors* | | |
| Atazanavir | artemisinins $C_{max}$ ↑<br>lumefantrine $C_{max}$ ↑ | Caution is required since both lumefantrine and atazanavir may prolong the QT-interval. |

| **Drugs** (grouped by therapeutic area) | **Interaction** | **Recommendation on co-administration** |
|---|---|---|
| Darunavir | artemether AUC ↓ 16%<br>lumefantrine AUC ↑ 175%<br>lumefantrine $C_{min}$ ↑ 126%<br>lumefantrine $C_{max}$ ↑ 65% | Use with caution due to the increase in lumefantrine exposure. |
| Lopinavir/ritonavir | dihydroartemisinin AUC ↓ 40-60%<br>lumefantrine AUC ↑ 2.3-fold, $C_{max}$ ↑ 1.4-fold | Clinical significance unclear but caution is required since both lumefantrine and lopinavir can prolong the QT-interval. |
| *Integrase strand transfer inhibitors (INSTIs)* | | |
| Dolutegravir<br>Raltegravir<br>Bictegravir<br>Cabotegravir | Co-administration has not been studied but based on metabolism/elimination and toxicity profiles there is little potential for interaction | No additional measures needed. |
| Elvitegravir/cobicistat | Co-administration has not been studied. Elvitegravir/cobicistat may increase concentrations of artemisinins and lumefantrine | Monitor patients if co-administration is required. |
| *Pharmacokinetic enhancers* | | |
| Ritonavir | Co-administration may increase plasma levels of artemisinins and lumefantrine, as both are metabolised by CYP3A4 | Caution is recommended in co-administration. |
| Cobicistat | Co-administration has not been studied. Cobicistat may increase concentrations of artemisinins and lumefantrine by inhibition of CYP3A4. | Monitor patients if co-administration is required. |
| **Antivirals for hepatitis B/C** | | |
| Ombitasvir/paritaprevir/ritonavir | Lumefantrine exposure may ↑<br>Lumefantrine is a substrate of CYP3A4, which is inhibited by ritonavir. | Co-administration is not recommended unless there is no alternative.<br>If unavoidable, patients should be closely monitored. |
| **Antifungals** | | |
| Ketoconazole<br>Itraconazole<br>Voriconazole | Modest increase (2 fold or less) in artemether, DHA and lumefantrine exposure | No dose adjustment required but use with caution. |
| **Hormonal contraceptives** | | |
| Ethinylestradiol<br>Levonorgestrel | No interaction seen in vitro. However, artemether may weakly induce CYP2C19, 2B6 and 3A | 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). |

*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 Lumerax Tablets 80/480 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.

## 5.5 Fertility, pregnancy and breastfeeding

*Pregnancy*

Lumerax Tablets 80/480 is recommended by WHO to treat uncomplicated falciparum malaria during the first trimester of pregnancy. Lumerax Tablets 80/480can also be used during the second and third trimester of 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 fetal outcomes. Artemether/lumefantrine in the first trimester of pregnancy appeared to have a lower risk for adverse pregnancy outcomes than previously recommended alternative regimens. Published epidemiological 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.

*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 [MA160 trade name]) for malaria treatment.

*Fertility*

There is no information on the effects of Lumerax Tablets 80/480 on fertility in humans.

## 5.6 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 Tablets 80/480 should be warned that dizziness, fatigue or asthenia may occur, in which case their ability to drive or operate machines may be impaired.

## 5.7 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 in the following table 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 | Very 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***

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

## 5.8 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.

# 6. PHARMACOLOGICAL PROPERTIES

## 6.1 Pharmacodynamic properties

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

***Pharmacodynamic effects***

Lumerax Tablets 80/480comprises 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 to 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 (≥5 kg 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<br>35 hours [20, 46] | n=118<br>44 hours [22, 47] | 1996-97<br>Thailand |

| | | | | | |
|---|---|---|---|---|---|
| A026 | 2-63 years | 130/133 (97.7) | n[3]=87<br>22 hours [19, 44] | NA | 1997-98<br>Thailand |
| A028 | 12-71 years | 148/154 (96.1) | n[3]=76<br>29 hours [8, 51] | n=164<br>29 hours [18, 40] | 1998-99<br>Thailand |
| A2401 | 16-66 years | 119/124 (96.0) | n[3]=100<br>37 hours [18, 44] | n=162<br>42 hours [34, 63] | 2001-05<br>Europe, Columbia |
| A2403 | 2 months-9 years | 289/299 (96.7) | n[3]=309<br>8 hours [8, 24] | n=310<br>24 hours [24, 36] | 2002-03<br>3 countries in Africa |
| B2303[CT] | 3 months-12 years | 403/419 (96.2) | n[3]=323<br>8 hours [8, 23] | n=452<br>35 hours [24, 36] | 2006-07<br>5 countries in Africa |
| B2303[DT] | 3 months-12 years | 394/416 (94.7) | n[3]=311<br>8 hours [8, 24] | n=446<br>34 hours [24, 36] | 2006-07<br>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 table below.

**Clinical efficacy by weight for paediatric studies**

| **Study No.**<br>**Weight category** | **Median PCT[1]**<br>**[25th, 75th percentile]** | **PCR-corrected 28-day cure rate[2] n/N (%) in evaluable patients** |
|---|---|---|
| Study A2403 | | |
| 5 to less than 10 kg | 24 hours [24, 36] | 145/149 (97.3) |
| 10 to less than 15 kg | 35 hours [24, 36] | 103/107 (96.3) |
| 15 to 25 kg | 24 hours [24, 36] | 41/43 (95.3) |
| Study B2303[CT] | | |
| 5 to less than 10 kg | 36 hours [24, 36] | 65/69 (94.2) |

| | | |
|---|---|---|
| 10 to less than 15 kg | 35 hours [24, 36] | 174/179 (97.2) |
| 15 to less than 25 kg | 35 hours [24, 36] | 134/140 (95.7) |
| 25 to 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 6-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.

## 6.2 Pharmacokinetic properties

*Absorption of* Lumerax Tablets 80/480

No pharmacokinetic data are available for Lumerax Tablets 80/480. A bioequivalence study was conducted with Lumerax Tablets 80/480, which contains 20 mg artemether and 120 mg lumefantrine and is essentially the same as Lumerax Tablets 80/480in qualitative terms and with respect to the ratio of active and other ingredients.

The absorption characteristics of Lumerax Tablets 80/480 have been determined after administration of four (4) tablets in healthy volunteers in the fed state as follows:

| **Pharmacokinetic variable** | **Arithmetic mean ±standard deviation (*)** | |
|---|---|---|
| | **Artemether** | **Lumefantrine** |
| Maximum concentration ($C_{max}$) | 158 ± 92 (134) ng/mL | 5768 ± 2173 (5379) ng/mL |
| Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption | 495 ± 283 ng.h/mL | 98728 ± 40657 (91287) ng.h/mL** |
| Time to attain maximum concentration ($t_{max}$) | 2.60 ± 0.96 h | 5.71 ± 0.58 h |

*geometric mean
**$AUC_{0-72h}$

**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%.<br>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<br>Dihydroartemisinin: about 2 h | 3 – 6 days |
| Mean systemic clearance (Cl/F) | NA* | NA* |
| % of dose excreted in urine | Artemether: NA*<br>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 6 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.

## 6.3 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.

# 7. PHARMACEUTICAL PARTICULARS

## 7.1 List of excipients

Anhydrous lactose
Croscarmellose sodium
Colloidal anhydrous silica
Hypromellose
Polysorbate 80
Purified talc
Magnesium stearate

This medicine is essentially ‘sodium-free’. It contains less than 1 mmol sodium (23 mg) per tablet.

## 7.2 Incompatibilities

Not applicable.

## 7.3 Shelf life

36 months

## 7.4 Special precautions for storage

Do not store above 30°C.

## 7.5 Nature and contents of container

The tablets are packed in Alu-Alu blisters. Each blister card contains 6 tablets.

Presentation:

1) One blister card packed in a carton. Pack size: 1 x 6 tablets.
2) 30 blister cards packed in an outer printed box. Pack size: 30 x 6 tablets.
3) One blister card is packed in a single monocarton. 30 of such monocartons are packed in one outer printed box. Pack size: 30 x 1 x 6 tablets.

### 7.6 Special precautions for disposal and other handling

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

## 8. APPLICANT/HOLDER OF CERTIFICATE OF PRODUCT REGISTRATION

Ipca Pharma Nig Ltd.
No, 3, llupeju Bye Pass,
(Olajire House) llupeju Lagos,
ipcaharma@yahoo.com

## 9. DRUG PRODUCT MANUFACTURER

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Sejavta, Ratlam 457 002
Regd. Off.: 48, Kandivli Ind. Estate,
Mumbai 400 067

## 10. NAFDAC REGISTRATION NUMBER

A4--3867