# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Artemether/Lumefantrine 20mg/120mg Dispersible Tablets (Glumac® Dispersible)
Artemether/Lumefantrine 40mg/240mg Dispersible Tablets (Glumac® Dispersible)
Artemether/Lumefantrine 60mg/360mg Dispersible Tablets (Glumac® Dispersible)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Glumac® Dispersible Tablet 20mg/120mg contains 20mg Artemether and 120mg Lumefantrine;
Each Glumac® Dispersible Tablet 40mg/240mg contains 40mg Artemether and 240mg Lumefantrine;
Each Glumac® Dispersible Tablet 60mg/360mg contains 60mg Artemether and 360mg Lumefantrine;

This product contains sucralose.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Glumac® Dispersible Tablets 20mg/120mg: Dispersible tablets. Yellow, round tablet, plain on both sides with bevelled edges.
Glumac® Dispersible Tablets 40mg/240mg: Dispersible tablets. Yellow, round tablet, plain on both sides with bevelled edges.
Glumac® Dispersible Tablets 60mg/360mg: Dispersible tablets. Yellow, oval tablets.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Glumac® Dispersible Tablets are 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 Glumac® Dispersible tablets.
Glumac® dispersible tablets 20mg/120mg is used to treat patients weighing 5 to ＜15kg
Glumac® dispersible tablets 40mg/240mg is used to treat patients weighing 15 to ＜25kg
Glumac® dispersible tablets 60mg/360 mg is used to treat patients weighing 25 to ＜35kg

### 4.2 Method of administration and posology

**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.

**Table: Dose administration**

| **Weight range（kg）** | **Strength** | **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 |
| **< 15 kg** | 20mg/120mg | 1 tablet | 1 tablet | 1 tablet | 1 tablet | 1 tablet | 1 tablet |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **15 kg to <25 kg** | 20mg/120mg | 2 tablets | 2 tablets | 2 tablets | 2 tablets | 2 tablets | 2 tablets |
| | 40mg/240mg | 1 tablet | 1 tablet | 1 tablet | 1 tablet | 1 tablet | 1 tablet |
| **25 kg to <35 kg** | 20mg/120mg | 3 tablets | 3 tablets | 3 tablets | 3 tablets | 3 tablets | 3 tablets |
| | 60mg/360mg | 1 tablet | 1 tablet | 1 tablet | 1 tablet | 1 tablet | 1 tablet |
| **≥35 kg (or ≥ 12 years of age)** | 20mg/120mg | 4 tablets | 4 tablets | 4 tablets | 4 tablets | 4 tablets | 4 tablets |
| | 40mg/240mg | 2 tablets | 2 tablets | 2 tablets | 2 tablets | 2 tablets | 2 tablets |

*Patients weighing 35 kg and above:*
Two tablets (80mg/480mg artemether/lumefantrine) should be taken twice a day for three days (total six doses of two tablets each).

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 Glumac® dispersible tablets 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.
*Missed doses*
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.
*Renal or hepatic impairment*
No dose adjustments are necessary in patients with renal or hepatic impairment. However, caution is advised when administering Glumac® dispersible tablets 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, Glumac® dispersible tablets should be taken with food or a milky drink (see section 5.2). If a patient is unable to tolerate food, Glumac® dispersible tablets 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**
Glumac® dispersible tablets 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 drugs 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)
• cisapride
- 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.

**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, Glumac® dispersible tablets should not be given concurrently with any other antimalarial agent due to limited data on safety and efficacy.
If a patient deteriorates while taking Glumac® dispersible tablets 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 Glumac® dispersible tablets (see section 5.1).
If Glumac® dispersible tablets is given after mefloquine, close monitoring of food intake is advised (see section 4.5).
In patients previously treated with halofantrine, Glumac dispersible tablets should not be administered earlier than one month after the last halofantrine dose (see section 4.5).
*Hormonal contraceptives*: Glumac® dispersible tablets 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 Glumac® dispersible tablets 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 form of interaction**

Glumac® dispersible tablets 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*
Glumac dispersible tablets 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 Glumac® dispersible tablets 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*, Glumac® dispersible tablets 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 Cmin by 13% and 3%, and increased Cmax by 7%. Etravirine AUC, Cmin and Cmax 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 with artemether/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 Cmax (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 of CYP3A4.

*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 Glumac dispersible tablets 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.

Glumac® dispersible tablets can be used during the first trimester of pregnancy if no alternative effective antimalarial is available. Glumac® dispersible tablets 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 Glumac® dispersible tablets) for malaria treatment.

*Fertility*

There is no information on the effects of Glumac® dispersible tablets 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 Glumac® dispersible tablets 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** | | |
| Arthralgia | 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. Health care 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: Artemisinin and derivatives, ATC code: P01BF01.
Pharmacodynamic effects
Glumac® dispersible tablets 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 ℃ and remained below 37.5 ℃ for at least a further 48 hours (only for patients with temperature >37.5 ℃ 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] | 3-63 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] | N/A | 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 of >37.5 ℃ at baseline only

[4] Only the group data for the 6-dose regimen over 60 hours are 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 pediatric studies**

| **Study No.**<br>**Weight category** | **Median PCT1**<br>**[25th, 75th percentile]** | **PCR-corrected 28-day cure rate2 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 B2303CT | | |
| 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

*Absorption of* Artemether/Lumefantrine dispersible tablets

No pharmacokinetic data are available for Artemether/Lumefantrine dispersible tablets. A

bioequivalence study was conducted with Artemether/Lumefantrine dispersible tablets, which contains 60 mg artemether and 360 mg lumefantrine and is essentially the same as Artemether/Lumefantrine dispersible tablets in qualitative terms and with respect to the ratio of active and other ingredients.
The absorption characteristics of Artemether/Lumefantrine dispersible tablets have been determined after administration of one (1) tablet in healthy volunteers in the fed state as follows:

| **Pharmacokinetic variable** | **Arithmetic mean ±standard deviation** | |
|---|---|---|
| | **Artemether** | **Lumefantrine** |
| Maximum concentration ($C_{max}$) | 141 ± 70 ng/mL | 11.1 ± 3.7 µg/mL |
| Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption | 431 ± 193 ng.h/mL | 198 ± 80* µg.h/mL |
| Time to attain maximum concentration ($t_{max}$) | 3.47 ± 1.11 h | 6.16 ± 1.16 h |

*AUC0-72h

Pharmacokinetics of Artemether and Lumefantrine

| | Artemether | Lumefantrine |
|---|---|---|
| **General** | | |
| **Absorption** | | |
| Absolute bioavailability | -* | -* |
| Oral bioavailability | - | - |
| 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) | -* | -* |
| % of dose excreted in urine | Artemether: NA*<br>Dihydroartemisinin:<0.01% | -* |
| % of dose excreted in faeces | Not detected | Excreted primarily in faeces |
| **Pharmacokinetic linearity** | -* | 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 Cmax (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 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 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.

**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 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 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
Polysorbate
Hypromellose
Croscamellose sodium
Colloidal Silicon Dioxide
Crosspovidone
Orange flavour
Sucralose
Talc
Magnesium Stearate

### 6.2 Incompatibilities
Not applicable.

### 6.3 Self life
24 months

### 6.4 Special precautions for storage
Do not store above 30 ℃. Store tablets in the blisters in the provided carton.

### 6.5 Nature and contents of container
Clear PVC/PVDC-Alu blister packs.
Presentation:
*20/120mg:*
Pack size 1: 6 tablets packaged in a PVC/PVDC and aluminum blister pack, 1 blister/box, 880 boxes/carton.

Pack size 2: 6 tablets packaged in a PVC/PVDC and aluminum blister pack, 2 blisters/box, 300 boxes/carton.
Pack size 3: 6 tablets packaged in a PVC/PVDC and aluminum blister pack, 30 blisters/box, 70 boxes/carton.
*40/240mg:*
Pack size 1: 6 tablets packaged in a PVC/PVDC and aluminum blister pack, 1 blister/box, 880 boxes/carton.
Pack size 2: 6 tablets packaged in a PVC/PVDC and aluminum blister pack, 30 blisters/box, 70 boxes/carton.
*60/360mg:*
Pack size 1: 6 tablets packaged in a PVC/PVDC and aluminum blister pack, 1 blister/box, 640 boxes/carton.
Pack size 2: 6 tablets packaged in a PVC/PVDC and aluminum blister pack, 20 blisters/box, 70 boxes/carton.
Pack size 3: 6 tablets packaged in a PVC/PVDC and aluminum blister pack, 30 blisters/box, 40 boxes/carton.

### 6.6 Special precautions for disposal and other handling

No specific requirements.

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

## 7. Manufacturer

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## 8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

MA153, MA154, MA155

### 9. DATE OF PREQUALIFICATION

13 April 2021

### 11. DATE OF REVISION OF THE TEXT

2 September 2021

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*All weblinks were last accessed in July 2021*

*Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/pqweb/medicines*