WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[MA099 trade name][†]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg artemether and 120 mg lumefantrine

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet.

A yellow, round, flat-faced, beveled edge tablet debossed with 'M' on one side of the tablet and 'AL' above the score and '1' below the score on the other side.

The break line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[MA099 trade name] 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.

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

The recommended daily dose range of artemether/lumefantrine is between 4–24 mg of artemether and 24–144 mg of lumefantrine per kg body weight.

[MA099 trade name] is taken twice daily for 3 days as indicated in the table below. It is important to ensure that the number of tablets (packs) supplied to the patient is sufficient for a full 3-day treatment course.

Patient body weight	Number of tablets	Dose of active substances supplied
5 to less than 15 kg	1 tablet twice daily	20 mg artemether/120 mg lumefantrine twice daily
15 to less than 25 kg*	2 tablets twice daily	40 mg artemether/240 mg lumefantrine twice daily
25 to less than 35 kg*	3 tablets twice daily	60 mg artemether/360 mg lumefantrine twice daily
35 kg or more*	4 tablets twice daily	80 mg artemether/480 mg lumefantrine twice daily

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

The first and second doses should be given 8 hours apart. Subsequent doses of [MA099 trade name] should be given 12 hours apart, in the morning and evening.

Missed dose and vomiting after a dose

[†] Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

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 medicine 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 [MA099 trade name] to 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, [MA099 trade name] should be taken with food or a milky drink (see section 5.2). If a patient is unable to tolerate food, [MA099 trade name] should 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.

4.3 Contraindications

[MA099 trade name] 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.

4.4 Special warnings and precautions for use

To improve absorption, [MA099 trade name] 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 [MA099 trade name] 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*.

4.5 Interaction with other medicinal products and other forms of interaction

[MA099 trade name] 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.

[MA099 trade name] should 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 [MA099 trade name] to 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 [MA099 trade name], the possibility of a drug-drug interaction should be considered. The following list of drug interactions with [MA099 trade name] is 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	[MA099 trade name] should 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% 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 [MA099 trade name] with food, to compensate for the decrease in bioavailability.
Quinine	risk of QTc prolongation associated with i.v. quinine was enhanced by prior administration of artemether/lumefantrine	Use with caution and appropriate monitoring.

Drugs (grouped by therapeutic area)	**Interaction**	**Recommendation on co-administration**
HIV antiretrovirals		
Nucleoside/nucleotide transcriptase inhibitors		
Abacavir Emtricitabine Lamivudine Tenofovir disoproxil or alafenamide 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% dihydroartemsisin AUC ↓ 45-75% lumefantrine AUC ↓ 20-55% No significant effect on efavirenz exposure	[MA099 trade name] should be used with caution in patients receiving efavirenz, as antimalarial efficacy may be decreased.
Etravirine	artemether AUC ↓ dihydroartemsisin AUC ↓ lumefantrine AUC ↓ 13%, C_{min} ↓ 3% 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. No dose adjustment is needed for etravirine.
Nevirapine	artemether AUC ↓ 72% dihydroartemisinin AUC ↓ 37% lumefantrine AUC ↓ 20% 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} ↑ lumefantrine C_{max} ↑	Caution is required since both lumefantrine and atazanavir may prolong the QT-interval.
Darunavir	artemether AUC ↓ 16% lumefantrine AUC ↑ 175% lumefantrine C_{min} ↑ 126% lumefantrine C_{max} ↑ 65%	Use with caution due to the increase in lumefantrine exposure.

Drugs (grouped by therapeutic area)	**Interaction**	**Recommendation on co-administration**
Lopinavir/ritonavir	dihydroartemisinin AUC ↓ 40-60% 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 Raltegravir Bictegravir 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 ↑ Lumefantrine is a substrate of CYP3A4, which is inhibited by ritonavir.	Co-administration is not recommended unless there is no alternative. If unavoidable, patients should be closely monitored.
Antifungals		
Ketoconazole Itraconazole Voriconazole	Modest increase (2 fold or less) in artemether, DHA and lumefantrine exposure	No dose adjustment required but use with caution.
Hormonal contraceptives		
Ethinylestradiol 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 [MA099 trade name] 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 breast-feeding

Pregnancy

[MA099 trade name] is recommended by WHO to treat uncomplicated falciparum malaria during the first trimester of pregnancy. [MA099 trade name] can 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 [MA099 trade name]) for malaria treatment.

Fertility

There is no information on the effects of [MA099 trade name] 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 [MA099 trade name] 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 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.

For reporting of adverse events and PV related queries please write to Email: ProductSafety@viatris.com

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

[MA099 trade name] 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 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 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 table below.

Clinical efficacy by weight for paediatric 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 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.

5.2 Pharmacokinetic properties

Absorption of [MA099 trade name]

The absorption characteristics of [MA099 trade name] have been determined after administration of four (4) tablets in healthy volunteers in the fed state as follows:

Pharmacokinetic variable	**Arithmetic mean value (± standard deviation)**		
	Artemether	**Dihydroartemisinin**	**Lumefantrine**
Maximum concentration (C_{max})	156 ± 66 ng/mL	120 (± 32) ng/mL	4.39 ± 2.14 µg /mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	471 ± 202 ng·h/mL	379 (± 97) ng·h/mL	71.3 ± 40.4 µg·h/mL*
Time to attain maximum concentration (t_{max})#	2.67 (0.67 - 4.50) hours	3.00 (1.33-4.50) hours	6.00 (5.00 – 8.00) hours

* AUC_{0-72h} ; # median (range)

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 exposureless 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 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.

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

Colloidal silicon dioxide,

Croscarmellose sodium,

Crospovidone,

Hypromellose,

Magnesium stearate,

Microcrystalline cellulose,

Polysorbate 80

Talc

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

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

Special precautions for storage

Do not store above 30ºC. Store in original container.

6.4 Nature and contents of container

Blisters

The tablets are provided in Alu-Alu (desiccant-embedded) blisters, Alu-Alu blisters, Alu-PVC/Aclar blisters and Alu-PVC/PE/PVDC blisters

1, 2, 3 or 4 blister cards of 6 tablets contained in a carton. Pack sizes: 6x1, 6x2, 6x3 and 6x4

1 blister card of 18 or 24 tablets contained in a carton. Pack sizes: 18x1 and 24x1

10 blister cards of 18 or 24 tablets contained in a carton. Pack sizes: 18x10 and 24x10

30 blister cards of 18 or 24 tablets contained in a carton. Pack sizes: 30x18 and 30x24

6.5 Special precautions for disposal and other handling

No special requirements.

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

7. SUPPLIER

Mylan Laboratories Limited

Plot No. 564/A/22

Road No.92, Jubilee Hills

Hyderabad - 500096, Telangana, India

Email: ProductSafety@viatris.com

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

MA099

9. DATE OF PREQUALIFICATION

16 May 2014

10. DATE OF REVISION OF THE TEXT

March 2023
Section 6 was updated in October 2025.

References

General reference sources for this SmPC include:

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Section 4.5

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https://www.hiv-druginteractions.org/
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Section 4.6 and others (information related to use in pregnancy)

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Saito M, McGready R, Tinto H, et al. Pregnancy outcomes after first-trimester treatment with artemisinin derivatives versus non-artemisinin antimalarials: a systematic review and individual patient data meta-analysis. Lancet 2022 (in press). Available at: https://doi.org/10.1016/S0140-6736(22)01881-5

All weblinks were last accessed on 19 March 2023.

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