# 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/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

# 1. NAME OF THE MEDICINAL PRODUCT

[MA078 trade name]†

# 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains artesunate 25 mg and mefloquine 50 mg

For the full list of excipients, see Section 6.1.

# 3. PHARMACEUTICAL FORM

Film-coated tablets.

Blue, round, smooth, biconvex, film-coated tablets.
The tablets should not be divided.

# 4. CLINICAL PARTICULARS

## 4.1 Therapeutic indications

[MA078 trade name] is indicated for the treatment of uncomplicated malaria. [MA078 trade name] is active against all *Plasmodium* parasites that cause malaria in humans.

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 artesunate/mefloquine is between 2–10 mg of artesunate and 7–11 mg of mefloquine per kg body weight.

[MA078 trade name] is taken once 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.

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

# Formerly known as Cipla Limited

| Patient body weight | Number of tablets | Dose of active substances supplied |
|---|---|---|
| 5 to less than 9 kg | 1 tablet once daily | 25 mg artesunate/50 mg mefloquine once daily |
| 9 to less than 18 kg | 2 tablets once daily | 50 mg artesunate/100 mg mefloquine once daily |
| 18 to less than 30 kg | 4 tablets once daily* | 100 mg artesunate/200 mg mefloquine once daily |
| 30 kg or more | 8 tablets once daily* | 200 mg artesunate/400 mg mefloquine once daily |

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

If a patient gets malaria within 60 days of treatment with [MA078 trade name], a different artemisinin-based combination therapy (ACT) should be used for treatment. Repeating a course of [MA078 trade name] within 60 days is not recommended due to increased risk of neuropsychiatric reactions.

*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 30 minutes of taking the medicine should repeat the dose.

**Special populations**

*Pregnancy*

Treatment with artesunate/mefloquine at standard doses is recommended by WHO to treat uncomplicated malaria during the second and third trimester of pregnancy. The combination may be considered for use in the first trimester where artemether-lumefantrine is not a recommended ACT for uncomplicated malaria or is not available.

*Renal or hepatic impairment*

No dose adjustments are necessary in patients with renal impairment.

In patients with impaired liver function, the elimination of mefloquine may be prolonged, leading to higher plasma levels and a higher risk of adverse reactions. Caution should be exercised when using [MA078 trade name] in patients with impaired liver function. [MA078 trade name] should not be used in patients with severe hepatic impairment.

*Elderly*

No dosage adjustments are necessary in elderly patients.

***Method of administration***

The tablets should be swallowed whole preferably after a meal with plenty of liquid. For patients unable to swallow the tablets, [MA078 trade name] may be crushed and mixed with water. The mixture should be swallowed immediately after preparation.

## 4.3 Contraindications

[MA078 trade name] is contraindicated in:

- patients with known hypersensitivity to artesunate, mefloquine or related compounds (e.g. quinine, quinidine) or to any of the excipients.
- patients with severe malaria according to WHO definition.
- 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);

- halofantrine.

- in patients with a history of blackwater fever, a complication of falciparum malaria with massive intravascular haemolysis causing haemoglobinuria.
- in patients with severe hepatic impairment (see sections 4.4 and 4.8).

## 4.4 Special warnings and precautions for use

*Neuropsychiatric reactions*

Mefloquine can cause psychiatric symptoms, including anxiety, paranoia, depression, hallucinations, and psychosis. Some mental health changes, such as trouble sleeping, strange dreams, intense anxiety, depression, agitation, or confusion, could be warning signs of a more serious problem (see section 4.8). There have also been reports of suicide, suicidal thoughts, and self-harm associated with mefloquine use (see section 4.8).

Malaria may return despite the use of an effective antimalarial treatment and a good initial clinical response. This can occur if the patient has a late treatment failure (i.e. after an initial reduction in parasite counts, they increase again due to failure to achieve complete parasite clearance) or if patients who remain in the malaria endemic region become reinfected. If there is a reappearance of clinical symptoms and signs of malaria, the patient should be immediately evaluated and, if clinically indicated, effective antimalarial treatment should be prescribed. [MA078 trade name] should not be used within two months of a therapeutic dose of mefloquine because of the increased risk of mefloquine-induced neuropsychiatric side effects.

*Eye disorders*

Any patient presenting with a visual disorder should be referred to a physician as certain conditions (such as retinal disorders or optic neuropathy) may require stopping treatment with mefloquine.

*Cardiac toxicity*
Patients with underlying cardiac conduction defects or known cardiac arrhythmias: In rare cases, treatment and prophylaxis with mefloquine have been associated with clinically significant adverse events related to cardiac conduction. The risk of QTc prolongation should be considered when co-administering [MA078 trade name] with certain medicines (see section 4.5).

*Seizure disorders*
In patients with a history of seizures, [MA078 trade name] may increase the risk of convulsions.

*Renal impairment*
Patients with renal impairment as there is limited data on use in renal impairment

*Inhibitors and Inducers of CYP3A4*
Patients taking inhibitors and inducers of the isoenzyme CYP3A4 may modify the pharmacokinetics/metabolism of mefloquine, leading to an increase or decrease in mefloquine plasma concentrations (see section 4.5).

*Impaired liver function*

In patients with impaired liver function the elimination of mefloquine may be prolonged, leading to higher plasma levels and a higher risk of adverse reactions.

*Neuropathy*

Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients receiving mefloquine.

Mefloquine should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see section 4.8).

*Blood and lymphatic system disorders*

Cases of agranulocytosis and aplastic anaemia have been reported during mefloquine therapy (see section 4.8).

*Pneumonitis*

Pneumonitis of possible allergic etiology has been reported in patients receiving mefloquine (see section 4.8). Patients who develop signs of dyspnoea, dry cough or fever etc. while receiving mefloquine should be advised to contact a doctor to undergo medical evaluation.

*Interaction with vaccines*

When mefloquine is taken concurrently with oral live typhoid vaccines, attenuation of immunisation cannot be excluded. Vaccinations with oral attenuated live bacteria should therefore be completed at least 3 days before the first dose of mefloquine (see section 4.5).

*Hypoglycaemia*

The possibility of hypoglycaemia in patients with congenital hyperinsulinaemic hypoglycaemia should be considered.

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

Co-administration of [MA078 trade name] with halofantrine is contraindicated due to the additive effects on QT-interval and the increased risk of cardiac arrhythmia. See table below.

[MA078 trade name] should be used with caution in patients taking other medicines that are known to prolong the QTc interval (such as class IA and III antiarrhythmics, some tricyclic antidepressants, and certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal agents).

[MA078 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 [MA078 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.

*Interactions with particular medicines*

Whenever co-prescribing any drug together with [MA078 trade name], the possibility of a drug-drug interaction should be considered. The following list of drug interactions with [MA078 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 | Co-administration is contraindicated.<br>[MA078 trade name] should not be given until at least 15 weeks after the last halofantrine dose due to the long elimination half-life of halofantrine. |
| Quinine | Risk of QTc prolongation associated with concurrent use of quinine and mefloquine | Use with caution and appropriate monitoring. |

| **Drugs** (grouped by therapeutic area) | **Interaction** | **Recommendation on co-administration** |
|---|---|---|
| **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 | Co-administration has not been studied. Mefloquine is metabolized by CYP3A4. | Efavirenz could potentially decrease artesunate and mefloquine exposure which may impair efficacy. |
| Etravirine | Co-administration has not been studied. Mefloquine is metabolized by CYP3A4. | Etravirine could potentially decrease artesunate and mefloquine exposure which may impair efficacy. |
| Nevirapine | Co-administration has not been studied. Mefloquine is metabolized by CYP3A4. | Nevirapine could potentially decrease artesunate and mefloquine exposure which may impair efficacy. |
| 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. |
| Doravirine | Co-administration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. | No additional measures needed. |
| *HIV protease inhibitors* | | |
| Atazanavir | Coadministration has not been studied but atazanavir may increase plasma levels of artemisinins and mefloquine. | Caution is required since both mefloquine and atazanavir may prolong the QT-interval. |
| Darunavir | Coadministration has not been studied but darunavir may increase plasma levels of mefloquine. | Use with caution due to the potential increase in mefloquine exposure. |
| Lopinavir/ritonavir | Lopinavir $C_{max}$ ↓ 23% AUC ↓ 22%<br>artesunate $C_{max}$ ↑ 59% AUC ↑ 52%<br>dihydroartemisinin $C_{max}$ ↓ 37% AUC ↓ 49%<br>mefloquine $C_{max}$ ↓ 13% AUC ↓ 28% | The reduction in drug exposure raises concerns for an increased risk of treatment failure for malaria and HIV. In addition, caution is required since both mefloquine and lopinavir can prolong the QT-interval. |
| *Integrase strand transfer inhibitors (INSTIs)* | | |
| Elvitegravir/Cobicistat | Co-administration has not been studied. Elvitegravir/cobicistat may increase concentrations of artemisinins and mefloquine. | Monitor patients for side effects if co-administration is required. |

| **Drugs** (grouped by therapeutic area) | **Interaction** | **Recommendation on co-administration** |
|---|---|---|
| *Pharmacokinetic enhancers* | | |
| Ritonavir | Co-administration may decrease dihydroartemisinin exposure. | Caution is recommended in co-administration. |
| Cobicistat | Co-administration has not been studied. Cobicistat may increase concentrations of artemisinins and mefloquine by inhibition of CYP3A4. | Monitor patients for side effects if co-administration is required. |
| **Antivirals for hepatitis B/C** | | |
| Ombitasvir/paritaprevir/ritonavir | Mefloquine exposure may ↑<br>Mefloquine is a substrate of CYP3A4. | Co-administration of mefloquine with is not recommended unless the benefit outweighs the risk due to QTc prolongation.<br>If unavoidable, patients should be closely monitored. |
| Daclatasvir | Co-administration has not been studied. Mefloquine and daclatasvir are substrates and inhibitors of P-glycoprotein and concentrations of both drugs may increase. | Clinical relevance of increases via this mechanism is uncertain. |
| **Antifungals** | | |
| Ketoconazole | Mefloquine $C_{max}$ ↑ 64% AUC ↑ 79% | Co-administration is contraindicated due to increased risk of QTc prolongation when ketoconazole is taken with mefloquine. |
| **Antiepileptics** | | |
| Carbamazepine<br>Phenytoin | Concomitant use of strong inducers of CYP3A4 such as carbamazepine and phenytoin may decrease dihydroartemisinin exposure, leading to a reduction in, or loss of, efficacy. In addition, concomitant administration of mefloquine and anticonvulsants (e.g. carbamazepine or phenytoin) may reduce seizure control by lowering the plasma levels of anticonvulsant. | Co-administration should be avoided. |
| **Antituberculars** | | |
| Rifampicin | Concomitant use of rifampicin may decrease dihydroartemisinin and mefloquine exposure, leading to a reduction in, or loss of, efficacy. Patients taking this drug should be followed up carefully to identify treatment failures. | Co-administration should be avoided. |

| **Drugs** (grouped by therapeutic area) | **Interaction** | **Recommendation on co-administration** |
|---|---|---|
| **Anticancers** | | |
| Axitinib<br>Vandetanib<br>Imatinib | These agents may increase dihydroartemisinin exposure due to UGT enzyme inhibition, leading to a reduction in, or loss of, efficacy. | Co-administration should be avoided if possible. |
| **Other** | | |
| Diclofenac | Diclofenac may increase dihydroartemisinin exposure due to UGT enzyme inhibition, leading to a reduction in, or loss of, efficacy | Co-administration should be avoided if possible. |
| Tramadol | Co-administration may increase risk of convulsions | Caution recommended in co-administration |

## 4.6 Fertility, pregnancy and breastfeeding

*Pregnancy*

[MA078 trade name] can be used during the second and third trimester of pregnancy.

[MA078 trade name] may be used during the first trimester of pregnancy when the first-line option (artemether-lumefantrine) is not suitable or available.

*Breastfeeding*

Animal data suggest excretion of [MA078 trade name] into breast milk, but the amounts that enter breast milk and are consumed by breastfeeding infants are expected to be relatively small. In line with WHO guidelines, [MA078 trade name] can be used in breastfeeding women.

*Fertility*

There is no information on the effects of [MA078 trade name] on fertility in humans.

## 4.7 Effects on ability to drive and use machines

[MA078 trade name] is unlikely to affect the ability to drive or operate machinery.

However, patients should be advised to consider if their clinical status, including any undesirable effects of the medicine, allows them to perform skilled tasks safely.

No studies on the effects on the ability to drive and use machines have been performed. Patients receiving [MA078 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

Adverse events considered at least possibly related to mefloquine and artesunate are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (≥ 1/10), common (1/100 – 1/10), uncommon (1/1000 – 1/100), rare (1/10 000 – 1/1000), very rare (< 1/10 000) or not known (frequency cannot be estimated from available data).

**Blood and lymphatic systems disorders**

| | **Artesunate*** | **Mefloquine** |
|---|---|---|
| *Very common* | anaemia, post-treatment delayed haemolysis, mild and transient decrease in reticulocyte count | |

| | | |
|---|---|---|
| *Not known* | immune haemolytic anaemia | agranulocytosis, aplastic anaemia, leukopenia, leukocytosis, thrombocytopenia |

**Immune system disorders**

| | | |
|---|---|---|
| *Not known* | anaphylaxis | hypersensitivity from mild cutaneous events to anaphylaxis |

**Metabolism and nutrition disorders**

| | | |
|---|---|---|
| *Uncommon* | anorexia | |
| *Not known* | | decreased appetite |

**Psychiatric disorders**

| | | |
|---|---|---|
| *Very common* | | abnormal dreams, insomnia |
| *Common* | | depression, anxiety |
| *Not known* | | suicide, attempted suicide, suicidal ideation and self-endangering behavior, bipolar disorder, psychotic disorder including e.g. delusional disorder, depersonalization, mania, and schizophrenia/schizophreniform disorder, paranoia, panic attacks, confusional state, hallucinations, aggression, agitation, restlessness, mood swings, disturbance in attention |

**Nervous system disorders**

| | | |
|---|---|---|
| *Common* | dizziness, headache | dizziness, headache |
| *Not known* | | encephalopathy, cranial nerve paralysis, convulsions, amnesia (sometimes long lasting for more than 3 months), syncope, speech disorder, memory impairment, balance disorder, gait disturbance, peripheral motor neuropathy (including paraesthesia, tremor and ataxia), peripheral sensory neuropathy, somnolence |

**Eye disorders**

| | | |
|---|---|---|
| *Common* | | visual impairment |
| *Not known* | | cataract, retinal disorders and optic neuropathy which may occur with latency during or after treatment, vision blurred |

**Ear and labyrinth disorders**

| | | |
|---|---|---|
| *Common* | | vertigo |
| *Not known* | | vestibular disorders including tinnitus, partial deafness (sometimes prolonged), hearing impaired, hyperacusis |

**Cardiac disorders**

| | | |
|---|---|---|
| *Common* | bradycardia | |
| *Not known* | QT prolongation | AV block, tachycardia, palpitation, bradycardia, irregular heart rate, extrasystoles, other transient conduction disorder |

**Vascular disorders**

| | | |
|---|---|---|
| *Common*<br>*Uncommon*<br>*Not known* | hypotension, phlebitis<br>flushing | <br><br>cardiovascular disorders (hypotension, hypertension, flushing) |

**Respiratory, thoracic and mediastinal disorders**

| | | |
|---|---|---|
| *Common* | cough, nasal symptoms | |
| *Not known* | | pneumonia, pneumonitis of possible allergic etiology, dyspnoea |

**Gastrointestinal disorders**

| | | |
|---|---|---|
| *Common* | altered taste, vomiting, diarrhoea, abdominal pain or cramps | nausea, diarrhoea, abdominal pain, vomiting |
| *Uncommon* | nausea, constipation | |
| *Not known* | | pancreatitis, dyspepsia |

**Hepatobiliary disorders**

| | | |
|---|---|---|
| *Common* | transient rises in liver transaminases (AST, ALT), hyperbilirubinaemia, jaundice | |
| *Not known* | | hepatic failure, hepatitis, jaundice, asymptomatic transient transaminase (ALT, AST, GGT) increased |

**Skin and subcutaneous tissue disorders**

| | | |
|---|---|---|
| *Common*<br>*Uncommon* | <br>Stevens-Johnson syndrome, pruritus, rash, urticaria | pruritus |
| *Not known* | | Stevens-Johnson syndrome, erythema multiforme, rash, erythema, urticaria, alopecia, hyperhidrosis |

**Musculoskeletal and connective tissue disorders**

| | | |
|---|---|---|
| *Common* | arthralgia, muscle disorders | |
| *Not known* | | muscular weakness, muscle spasms, myalgia, arthralgia |

**General disorders and administration site conditions**

| | | |
|---|---|---|
| *Common*<br>*Uncommon* | fever<br>fatigue | |
| *Not known* | | oedema, chest pain, asthenia, chills, pyrexia, malaise, fatigue |

**Renal and urinary disorder**

| | | |
|---|---|---|
| *Not known* | | renal failure acute, nephritis, blood creatinine increased |

***Abnormal dreams/nightmares***

Abnormal dreams and insomnia are very common adverse reactions with mefloquine, therefore their significance should be considered in the overall evaluation of patients reporting reactions or changes to their mental state with mefloquine (see warning section 4.4).

***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.

### 4.9 Overdose

***Artesunate***

Experience of acute overdose with artesunate is limited. A case of overdose has been documented in a 5 year-old child who was inadvertently administered rectal artesunate at a dose of 88 mg/kg/day over 4 days, representing a dose more than 7-fold higher than the highest recommended artesunate dose. The overdose was associated with pancytopenia, melena, seizures, multi-organ failure and death.

Treatment of overdose should consist of general supportive measures.

***Mefloquine***

In cases of overdosage with mefloquine, the symptoms mentioned under section 4.8 may be more pronounced.

Patients should be managed by symptomatic and supportive care following mefloquine overdose. There are no specific antidotes. The use of oral activated charcoal to limit mefloquine absorption may be considered within one hour of ingestion of an overdose. Monitor cardiac function (if possible by ECG) and neuropsychiatric status for at least 24 hours. Provide symptomatic and intensive supportive treatment as required, particularly for cardiovascular disorders. Elimination of mefloquine and its metabolites is limited by haemodialysis**.**

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimalarials; Artemisinin and derivatives, combinations, ATC code: P01BF02

*Mechanism of action*

*Artesunate*

Artesunate is a hemisuccinate derivative of dihydroartemisinin, which is itself formed by the reduction of artemisinin. Artemisinin is a sesquiterpene lactone endoperoxide extracted from qinghao (sweet wormwood, *Artemisia annua L.*), a plant which has been used for centuries in traditional Chinese medicine.

The mechanism of action of the artemisinins likely involves cleavage of the internal endoperoxide bridge through reaction with haeme within the infected erythrocyte, thereby generating free radicals which alkylate vital parasite proteins. However, artemisinins have also been reported to inhibit an essential parasite calcium adenosine triphosphatase.

The artemisinins are distinguished from other antimalarials by their ability to kill all erythrocytic stages of the malaria parasite, including the relatively inactive ring stage and late schizonts, as well as the gametocytes responsible for malaria transmission. Artesunate and the artemisinins are the most rapid acting of the antimalarials, and they have also been shown to enhance splenic clearance of infected erythrocytes by reducing cytoadherence.

In vitro, dihydroartemisinin (DHA), the active metabolite of artesunate, exhibits similar potency against chloroquine-resistant and chloroquine-sensitive clones of *P. falciparum.*

Artesunate and the other artemisinins are essentially inactive against extra-erythrocytic forms, sporozoites, liver schizontes or merozoites.

*Mefloquine*

Mefloquine acts on and destroys the asexual intraerythocytic forms of the human malaria parasites: *Plasmodium falciparum, P. vivax. P. malariae* and *P. ovale.* It is effective in the treatment and prophylaxis of malaria. Mefloquine is also effective against malarial parasites resistant to other antimalarials such as chloroquine and other 4-aminoquinoline derivatives, proguanil, pyrimethamine and pyrimethamine-sulphonamide combinations.

*Clinical efficacy and safety*

The efficacy of [MA078 trade name] will depend on the drug sensitivities of the local malaria parasites. Resistance has been evidenced by a decline in cure rates of artesunate plus mefloquine given as separate tablets in Western Cambodia and a slowing of parasite clearance in North-Western Thailand.

An open-label clinical study in 500 patients (adults and children) was conducted in North-Western Thailand. Patients treated with artesunate/mefloquine 100/200mg fixed dose combination experienced a Day 63 PCR-corrected cure rate of 91.9% (95% CI 88.2, 95.6), while those treated with the standard loose tablet regimen of artesunate and mefloquine displayed a Day 63 PCR-corrected cure rate of 89.2% (95% CI 85.0, 93.4; Kaplan-Meier analysis, log-rank test for significance).

In an additional, randomized open-label study in 50 adult patients with acute, *uncomplicated P. falciparum* malaria conducted in Thailand, 22/24 patients (91.7%) patients treated with Artesunate/Mefloquine 100/200mg fixed dose combination had parasitological cure at day 28, compared to 24/24 (100%) patients administered artesunate and mefloquine as separate tablets.

An open-label, single-arm study with Artesunate/Mefloquine 100/200mg fixed dose combination in 77 adult patients with acute, uncomplicated *P. falciparum* malaria conducted in India reported 63-day parasitological cure rates of 100%.

## 5.2 Pharmacokinetic properties

The absorption characteristics of [MA078 trade name] have been determined after administration of two tablets in healthy volunteers in the fasting state as follows

| **Pharmacokinetic variable** | **Arithmetic mean ± standard deviation** | |
|---|---|---|
| | **Artesunate** | **Mefloquine** |
| Maximum concentration ($C_{max}$) | 138 ± 56 ng/mL | 716 ± 217 ng/mL |
| Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption | 182 ± 144 ng·h/mL | 378 ± 124 µg/mL |
| Time to attain maximum concentration (Tmax) | 0.6 ± 0.8 h | 24 ± 25 h |

The absorption characteristics have also been determined after administration of two tablets once daily for 3 days in patients with P. falciparum malaria as follows

| **Pharmacokinetic variable** | **Arithmetic mean ± standard deviation** | |
|---|---|---|
| | **Artesunate** | **Mefloquine** |
| Maximum concentration ($C_{max}$) | 249 ± 266 ng/mL | 3279 ± 1252 ng/mL |

| | | |
|---|---|---|
| Area under the curve (AUC0-∞), a measure of the extent of absorption | 780 ± 675 ngh/mL | 1193 ± 634 µg/mL |
| Time to attain maximum concentration (Tmax) | 0.8 ± 0.7 h | 72 ± 19 h |

*Pharmacokinetics of artesunate and mefloquine*

| | Artesunate | Mefloquine |
|---|---|---|
| **General** | | |
| | In patients with malaria, single PK parameters may differ from those in healthy subjects. | |
| **Absorption** | | |
| Absolute bioavailability | NA* | NA* |
| Oral bioavailability | After absorption, artesunate is rapidly and extensively metabolised to its main active metabolite dihydroartemisinin. | The bioavailability of tablets compared with the oral solution of mefloquine is over 85%. |
| Food effect | Exposure increased by 43% with a high fat/high calorie meal | Food significantly increases absorption and increases bioavailability by 40% |
| **Distribution** | | |
| Volume of distribution | Artesunate: 15 L/kg<br>Dihydroartemisinin: 1.6-2.6 L/kg | 20 L/kg |
| Plasma protein binding *in vitro* | Artesunate: 75%<br>Dihydroartemisinin: 47 – 76% | 98% |
| Tissue distribution[1] | Dihydroartemisinin accumulates substantially in *P. falciparum*-infected erythrocytes | Distributed to blood, urine, CSF, and tissues; concentrated in erythrocytes, with concentrations almost twice as high as plasma concentrations.<br>Mefloquine crosses the placenta. Excretion into breast milk appears to be minimal. |
| **Metabolism** | | |
| | Extensively hydrolysed by plasma esterases and perhaps also by CYP2A6. | Extensively metabolised in the liver by CYP3A4. |
| Active metabolites | Dihydroartemisinin is further metabolised through glucuronidation | NA* |
| **Elimination** | | |
| Elimination half life | Artesunate: 3–29 minutes<br>Dihydroartemisinin: About 2 hours | 21 days in healthy subjects; 14 days in malaria patients |
| Mean systemic clearance (Cl/F) | Artesunate: 20 L/kg/h<br>Dihydroartemisinin: 1.4 – 2.7 L/h/kg | 0.022 to 0.073 L/h/kg |
| **Pharmacokinetic linearity** | NA* | NA* |

*Information not available

***Special populations***

*Renal impairment*

No specific recommendations available regarding need for dosage adjustment in individuals with renal impairment.

*Hepatic impairment*

In patients with impaired liver function, the elimination of mefloquine may be prolonged, leading to higher plasma concentrations.

*Pregnant women*

Clearance of mefloquine may increase in late pregnancy, however, in general, pregnancy has no clinically relevant effect on the pharmacokinetics of mefloquine.

## 5.3 Preclinical safety data

*General toxicity*

Artesunate presents low acute toxicity. After repeated administration of 50 mg/kg/day in rats and 82.5 mg/kg/day in dogs, i.e. approximately 10 and 17 times the proposed maximal therapeutic dose in man, evidence of toxicity was observed in the haematopoietic organs, the immune system and response, the liver and kidneys.

Similar to artesunate, mefloquine has a higher tolerance compared to therapeutic doses. However, exceeding recommended dosages can lead to toxicity. Studies in rats and dogs administered repeated doses of mefloquine have shown toxicity at levels exceeding the proposed human therapeutic dose. The specific effects vary depending on the species and dose, but some reported findings include central nervous system (CNS) effects, gastrointestinal effects as well as effects on the liver and kidneys. Effects on the heart, blood cells, and reproductive system have also been reported in some studies with high-dose mefloquine administration in rats and dogs.

*Genotoxicity*

Artesunate did not show any mutagenic or clastogenic potential in in vitro and in vivo tests (Ames, mouse micronucleus).

Mutagenicity tests indicated that activation of mefloquine hydrochloride produced mutagenic products that mediated base-pair substitution mutation in the E. coli WP2 trp (pEB017) tester strains. The *S. typhimurium his* TA97 strains also mediated a weak frameshift mutation but mefloquine mutagenicity potential was most remarkable as a base pair substitutions mutagen. Mefloquine hydrochloride exhibits base-pair substitution mutagenesis and is not strictly genotoxic.

*Carcinogenesis*

No studies of the carcinogenic potential of artesunate and mefloquine have been conducted.

*Reproductive toxicology studies*

Oral artesunate caused dose-dependent fetal toxicity in rats, rabbits, and monkeys, resulting in fetal resorption and abortion, as well as a low incidence of cardiac and skeletal defects. The no-observed-adverse-effect-level (NOAEL) was 12 mg/kg in pregnant monkeys (3- and 7-day exposures) and the no or low adverse effects level was 5-7 mg/kg in pregnant rats or rabbits (12-day exposures), both of which are above the therapeutic dose range (2.4-4.8 mg/kg) and expected duration of exposure for treatment of severe malaria in humans. In rats, the embryo-fetuses were most sensitive from gestational days 9-14; at other times embryotoxicity was significantly reduced. A study of artesunate administered to male rats daily for 6 weeks noted testicular and epididymal lesions, although these lesions did not affect fertility. The lesions were reversible after cessation of treatment.

Mefloquine was teratogenic in mice and rats and embryotoxic in rabbits; however, large clinical experience with mefloquine as prophylactic treatment has not revealed an embryotoxic or teratogenic effect. Data from a limited number of exposed pregnancies indicate no adverse effects of mefloquine on pregnancy or on the health of the foetus/newborn child. To date, no other relevant epidemiological data are available. Mefloquine is also secreted into breast milk in small amounts.

*Safety pharmacology studies*

A slight sedative effect, decrease in body temperature, mild natriuretic effect, and a decrease in creatinine clearance were observed with artesunate after single intravenous doses of 200 mg/kg (mice), 450 mg/kg (rats, rabbits and dogs), and following single oral doses of 180 mg/kg in male rats. Beagle dogs administered IV artesunate at 10, 20 and 50 mg/kg for 14 days did not display significant clinical effects, including any signs of neurotoxicity, effects on body weight, ECG abnormalities (including QT interval changes), heart rate, blood pressure, or respiratory rate.

In vitro, mefloquine blocks preferentially the slow ($I_{Ks}$ ) component of the delayed rectifier potassium ($K^+$) channel in cardiac muscle and, therefore theoretically has the potential to exacerbate the QTc prolongation produced by other drugs.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

*Core tablet:* croscarmellose sodium,
magnesium stearate and
microcrystalline cellulose.

*Film coat*: Indigo carmine aluminium lake (FD & C Blue #2),
hypromellose,
macrogol,
polysorbate 80 and
titanium dioxide.

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

## 6.2 Incompatibilities

None

## 6.3 Shelf life

36 months

## 6.4 Special precautions for storage

Do not store above 30°C

## 6.5 Nature and contents of container

Primary packing: Aluminium-aluminium blister strip with 3 tablets.

Secondary packing**:** Carton having one strip of 3 tablets and carton having 2 strips of 3 tablets.

## 6.6 Special precautions for disposal and other handling

Not applicable

## 7. SUPPLIER

Cipla Limited
Cipla House,
Peninsula Business Park,
Ganpatrao Kadam Marg,
Lower Parel, Mumbai– 400013
India.
Phone: (+9122) 24826000
Fax: (+9122) 24826120
Email: globalra@cipla.com

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

MA078

## 9. DATE OF PREQUALIFICATION

12 September 2012

## 10. DATE OF REVISION OF THE TEXT

May 2025

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*All weblinks were last accessed on 22 June 2025.*

*Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products*