WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO'sPrequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information fromstringent 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

[MA194 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial containsArtesunate powder 120 mg.

Each ampoule of solvent contains: 1 mL of sodium bicarbonate 50 mg/mL solution

Each ampoule of diluent contains: 5 mL of sodium chloride 9 mg/mL solution

Excipients with potential clinical effect

Each 1 mL of Sodium bicarbonate injection contains 50 mg of sodium bicarbonate, equivalent to 13.69 mg (0.595 mmol) sodium.

Each 5 ml of Sodium chloride injection contains 45 mg of sodium chloride, equivalent to 17.71 mg (0.77 mmol) sodium.See section 4-4.

3. PHARMACEUTICAL FORM

Artesunate powder for injection: sterile white powder

Solvent (Sodium bicarbonate solution): clear colourless liquid

Diluent (Sodium chloride solution): clear colourless liquid

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[MA194 trade name], administered intravenously or intramuscularly, is indicated for the treatment of severe malaria caused by *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

Posology

After reconstitution to the appropriate strength, [MA194 trade name] is given by slow intravenous or intramuscular injection for a minimum of 3 doses given over 24 hours. Doses of artesunate depend on body weight and higher proportional doses are recommended in children weighing less than 20 kg, in whom exposure is lower than in adults and older children:

Adults and children weighing 20 kg or more:	2.4 mg/kg
Children weighing less than 20 kg:	3 mg/kg

A dose should be given at admission (0 hours), then at 12 and 24 hours after admission. Further doses may then be given once daily as necessary, until the patient can tolerate oral therapy.

Treatment should then be completed with an oral artemisinin-based combination regimen given for 3 days. The first oral dose should be taken 8 to 12 hours after the last injection of artesunate.

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

Where complete treatment of severe malaria is not possible, but [MA194 trade name] injections are available, adults and children may be given a single intramuscular dose of artesunate before referral to an appropriate facility for further care.

Hepatic and renal impairment

Dose adjustment is not necessary in patients with hepatic or renal impairment (see Sections 4.4 and 5.2).

Method of administration

For instructions on reconstitution of [MA194 trade name] before administration, see section 6.6. The injection solution should be freshly prepared before each dose is given and should not be stored.

[MA194 trade name] injection is given by intravenous bolus injection over 1 to 2 minutes or by slow intramuscular injection into the anterior thigh. If the total volume of solution to be injected intramuscularly is large (more than 2 mL for small children or 5 mL for adults), it may be preferable to divide the volume and inject it at multiple sites, e.g. both thighs.

4.3 Contraindications

[MA194 trade name]is contraindicated in patients with hypersensitivity to artesunate or other artemisininsor to any of the components of the formulation listed in section 6.1.

4.4 Special warnings and precautions for use

Non-falciparum malaria

Artesunate has not been evaluated in the treatment of severe malaria due to *Plasmodium vivax, Plasmodium malariae*or *Plasmodium ovale*(see also section 5.1)

Post-treatment haemolyticanaemia

Delayed haemolyticanaemia following treatment with injectable artesunate has been observed in children in malaria endemic areas and in non-immune travelers presenting with severe falciparum malaria. Onset has typically occurred at least 7 days and sometimes several weeks after starting artesunate treatment. The risk was most pronounced in patients with hyperparasitaemia and in younger children. Some cases have been severe and required blood transfusion.

Vigilance for delayed onset anaemia is therefore advised, particularly in hyperparasitaemic patients and younger children, and prolonged follow-up should be considered (e.g. 14-28 days). The overall benefit-risk ratio remains highly favourable for injectable artesunate in the treatment of severe malaria, and such treatment continues to be recommended.

Reticulocytopenia

The artemisinins have shown direct inhibitory effects on human erythroid precursors in vitro andinhibit bone marrow responses (especially red blood cell precursors) in animal models. Both animalpreclinical data and human data from clinical trials have suggested that reversible reticulocytopeniaoccurs at least commonly in association with treatment with intravenous artesunate (see section 4.8).

The reticulocyte count recovers after cessation of treatment.

Hepatic / renal impairment:

Data regarding artesunate pharmacokinetics in patients with hepatic and/or renal impairment are limited. Based on data from studies in patients with severe malaria, as well as the known metabolism of artesunate (see Section 5.2), dosage adjustment is not considered necessary in patients with hepatic or renal impairment.

Paediatric population

In clinical trials, the efficacy and safety of intravenous and intramuscular artesunate have been similar in adult and paediatric populations.

4.5 Interaction with other medicinal products and other forms of interaction

After intravenous administration, artesunate is rapidly and extensively converted to DHA, largely by plasma and erythrocyte esterases.

DHAis converted to inactive glucuronide conjugates primarily by UGT1A9. DHA elimination is also rapid (half-life approximately 45 minutes) so the potential for drug-drug interactions appears limited. However, co-administration of intravenous artesunate with strong inhibitors of UGT enzymes (e.g. axitinib,vandetanib, imatinib, diclofenac) may increase plasma exposures to DHA.

In vitrodrug-interaction studies have demonstrated minimal effects of artesunate on cytochrome P450 isoenzymes. Few clinical drug-drug interaction studies have been performed but limited data from invitro studies and from clinical drug-drug interaction studies with *oral* artesunateand/or *oral* DHA have indicated that DHA induces CYP3A and inhibits CYP1A2.

An increase in plasma concentrations of artesunate was observed with nevirapine and a reduced plasma concentration of dihydroartemisinin was observed when artesunate was given with ritonavir.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

Severe malaria is especially hazardous during pregnancy, therefore full dose parenteral artesunate treatment should be administered at any stage of pregnancy without delay.

In animal studies, artesunate has been associated with fetal toxicity during the first trimester of pregnancy. Limited clinical experience with the use of artesunate in the first trimester of pregnancy as well as clinical data from more than 4,000 pregnant women, treated with artemisinin derivatives in the second and third trimester, do not indicate adverse effects of artesunate on pregnancy or on the health of the fetus/newborn child.

Breastfeeding

Limited information indicates that dihydroartemisinin, the active metabolite of artesunate, is present at low levels in breast milk. Patients with severe malaria may be too ill to breastfeed, but in any case the levels of metabolite present in breast milk are not expected to cause any adverse effects in breastfed infants. The amount of drug present in breast milk does not protect the infant from malaria.

Fertility

No specific studies with artesunate in humans have been conducted to evaluate effects on fertility. In a reproduction toxicity study in rats, testicular and epididymal lesions were seen, but there were no effects on fertility (see section 5.3). The relevance of this finding for humans is unknown.

4.7 Effects on ability to drive and use machines

There is no information on the effect of artesunate on the ability to drive or use machines. The patient's clinical status should be considered when assessing ability to drive or operate machinery.

4.8 Undesirable effects

The most important reported side effect of artesunate is a rare severe allergic reaction (estimated risk approximately 1 in 3000 patients), which has involved urticarial rash as well as other symptoms, including hypotension, pruritus, oedema, and/or dyspnoea.

More common minor side effects associated with IV administration have included dizziness, light-headedness, rash, and taste alteration (metallic/ bitter taste). Nausea, vomiting, anorexia and diarrhea have also been reported, however it is uncertain whether such events have been symptoms of severe malaria.

Adverse events considered at least possibly related to 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), and very rare (< 1/10 000).

Blood and lymphatic systems disorders

Common	post-treatment haemolytic anaemia*, mild and transient decrease in reticulocyte count
Uncommon	neutropenia and anaemia (both occasionally severe), thrombocytopenia
Very rare	pure red cell aplasia

Nervous system disorders

Common	dizziness, light-headedness, headache, insomnia, tinnitus (with or without decrease in auditory function)
Very rare	peripheral neuropathy (or paraesthesia)

Cardiac disorders

Common	bradycardia
Frequency not known	QT prolongation

Vascular disorders

Common	hypotension, phlebitis
Uncommon	flushing

Respiratory disorders

Common	cough, nasal symptoms

Gastrointestinal disorders

Common	altered taste, nausea, vomiting, abdominal pain or cramps, diarrhoea
Uncommon	constipation
Rare	raised serum amylase, pancreatitis

Hepatobiliary disorders

Common	transient rises in liver transaminases (AST, ALT), hyperbilirubinaemia, jaundice
Rare	hepatitis

Skin and subcutaneous tissue disorders

Common	rash, alopecia
Uncommon	Stevens-Johnson syndrome, pruritus, urticaria

Musculoskeletal and connective tissuedisorders

Common	arthralgia, muscle disorders

General disorders and administration site conditions

Common	fatigue, malaise, fever, pain at injection site

Immune systemdisorders

Uncommon	hypersensitivity

**Post-treatment anaemia*

Cases of delayed haemolytic anaemia have been identified in non-immune travelers following treatment of severe malaria with injectable artesunate. Some were severe and required blood transfusions. In a study in African children aged 6 months to 10 years of age in malaria endemic areas, 5 out of 72 children (7%) experienced delayed haemolytic anaemia following treatment with injectable artesunate, and one child required transfusion. Risk was increased with hyperparasitaemia in all age groups and with younger age in children. Onset of haemolysis and anaemia was evident by 14-28 days after artesunate treatment. Vigilance for this adverse event is advised.

Paediatric population:

The safety profile of injectable artesunate is similar in children and adults.

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

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimalaria, ATC code: P01BE03

Mechanism of action

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.

Clinical efficacy and safety

In the SEAQUAMAT (South East Asian Quinine Artesunate Malaria Trial), an international randomised,

open-label, multicenter trial conducted in Bangladesh, India, Indonesia and Myanmar, 1461 patients with severe malaria (including 1259 adults) were treated intravenously with either artesunate or quinine. Artesunate was administered at 2.4 mg/kg IV at 0, 12 and 24 h and then every 24 h until the patient could tolerate oral medication. Quinine was given IV at 20 mg/kg over 4 hours, followed by 10 mg/kg over 2-8 hours, 3 times daily until oral therapy could be started. Mortality in the artesunate group was 15% versus 22% in the quinine group, for a reduction in risk of death of 34.7% (p=0.0002). Subgroup analysis suggested a greater benefit of artesunate versus quinine in patients with parasitaemia>10%. The reduction in mortality observed in the 202 paediatric patients (<15 years of age) appeared consistent with the overall results, however the number of children was too small to demonstrate statistical significance. Post-treatment hypoglycaemia was more common in the quinine-treated group.

Paediatrics

The AQUAMAT (African Quinine Artesunate Malaria Trial) was an international, randomized open-label multicenter trial which sought to extend the results of the SEAQUAMAT study by comparing parenteral artesunate versus IV quinine for severe malaria in 5425 African children (< 15 years) in 9 African countries (Mozambique, The Gambia, Ghana, Kenya, Tanzania, Nigeria, Uganda, Rwanda, and Democratic Republic of the Congo). Dosing was similar to SEAQUAMAT, except that both artesunate and quinine could be administered either intravenously or intramuscularly, using the same doses for IM and IV administration for each drug. Roughly one third of patients received study drug by intramuscular injection. Mortality in the artesunate group was 8.5% compared to 10.9% in the quinine group, resulting in a relative risk reduction for death of 22.5% (p=0.0022); the risk reduction was similar for IV and IM administration. In addition, although the risk of neurological sequelae in survivors in both groups did not differ significantly by 28 days following treatment, in-hospital coma, convulsions, and deterioration of coma were all less frequent in the artesunate-treated patients. As in the SEAQUAMAT, post-treatment hypoglycaemia was more common in the quinine-treated group.

5.2 Pharmacokinetic properties

No bioequivalence study was required due to the pharmaceutical formulation of [MA194 trade name]. Therefore, no pharmacokinetic data are available for this product.

Pharmacokinetics of Artesunate

Absorption	
Oral bioavailability	Not applicable
Food effect	Not applicable
Distribution	
Volume of distribution (mean)	Artesunate:15 L/kg Dihydroartemisinin: 1.6-2.6 L/kg
Plasma proteinbinding in vitro	Artesunate: 75% Dihydroartemisinin: 80-90%with decreased binding at higher concentrations
Tissue distribution	Dihydroartemisinin accumulates substantially in *P.falciparum*-infectederythrocytes
Metabolism	
	Extensively hydrolysed by plasma esterases and perhaps also by CYP2A6.
Active metabolite(s)	Dihydroartemisinin is further metabolised through glucuronidation
Elimination	
Elimination half life	Artesunate: 3–29 minutes Dihydroartemisinin: 40–95 minutes

Mean systemic clearance (Cl/F)	Artesunate: 20 L/kg/h Dihydroartemisinin: 1.4 – 2.7 L/kg/h
% of dose excreted in urine	NA*
% of dose excreted in faeces	NA*

*Information not available.

5.3 Preclinical safety data

General toxicity

Artesunate presents low acute toxicity. After repeated administration of 50 mg/kg/day in rats and82.5 mg/kg/day in dogs, i.e. approximately 10 and 17 times the proposed maximal therapeutic dose inman, evidence of toxicity was observed in the haematopoietic organs, the immune system andresponse, the liver and kidneys.

Genotoxicity

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

Carcinogenesis

No studies of the carcinogenic potential of artesunate 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. Theno-observed-adverse-effect-level (NOAEL) was 12 mg/kg in pregnant monkeys (3- and 7-dayexposures) and the no or low adverse effects level was 5-7 mg/kg in pregnant rats or rabbits (12-dayexposures), both of which are above the therapeutic dose range (2.4-4.8 mg/kg) and expected durationof exposure for treatment of severe malaria in humans. In rats, the embryo-fetuses were most sensitivefrom gestational days 9-14; at other times embryotoxicity was significantly reduced. A study ofartesunate 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.

Safety pharmacology studies

A slight sedative effect, decrease in body temperature, mild natriuretic effect, and a decrease increatinine 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. Beagledogs administered IV artesunate at 10, 20 and 50 mg/kg for 14 days did not display significantclinical effects, including any signs of neurotoxicity, effects on body weight, ECG abnormalities (including QT interval changes), heart rate, blood pressure, or respiratory rate.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Artesunatepowder for injection: No excipient

Solvent: Sodium bicarbonate,
Disodiumedetate, and
Water for injection

Diluent: Sodium chloride, and
Water for injection

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

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with othermedicinal products

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25^0C, store in a dry place. Keep the vial and ampoules in the provided carton to protect the products from light. Do not refrigerate or freeze.

*Reconstituted/diluted solution:*The reconstituted and diluted solutions should be stored below 25^0C and the total in-use period should not exceed 1 hour.

6.5 Nature and contents of container

Artesunate powder for injection is a sterile white powder

120 mg of artesunate powder for injection is filled in a 15mL clear glass vial (USP Type III.) The filled vial is closed with 20mm grey bromobutyl rubber plug and sealed with 20mm dark green flip off aluminium seal.

Solvent (Sodium bicarbonate injection) is a clear colourless liquid

1 mL of Sodium bicarbonate is filled in a 1mL clear glass ampoule (USP Type I) with a green snap off ring.

Diluent (Sodium chloride injection) is a clear colourless liquid

It is filled in a 5mL clear glass ampoule (USP Type I)

*Pack size:*A carton box containing one vial of artesunate powder for injection, two ampoules of sodium bicarbonate injection, and two ampoules of sodium chloride injection placed in a plastic tray along with a package insert.

6.6 Special precautions for disposal and other handling

Instructions for reconstitution

When reconstituted correctly, one vial of [MA194 trade name] will yield 12 mL of a solution for intravenous administration (10 mg/mL) or 6 mL of a solution for intramuscular administration (20 mg/mL).

For patients weighing over 50 kg, more than 1 vial of [MA194 trade name] will be needed for each dose. The required number of product packs should be determined as follows.

Patient weight	Number of vials of artesunate (120 mg) needed
up to 50 kg	1
51 to 100 kg	2

- Using a syringe, withdraw 1 mL of the supplied sodium bicarbonate solvent from the ampoule and inject into the vial containing the artesunate powder.
- Shake the vial for several minutes to mix well until the powder is completely dissolved and the solution is clear. If the solution appears cloudy or a precipitate is present, it should be discarded.
- The reconstituted solution should then be diluted using the appropriate amount of supplied diluent (sodium chloride 0.9% for injection) according to the intended route of administration, as follows:

	For intravenous use	For intramuscular use
Volume of bicarbonate solvent	2 mL	2 mL
Volume of sodium chloride diluent	10 mL	4 mL
Total volume	12 mL	6 mL
Concentration of final artesunate solution	10 mg/mL	20 mg/mL

Once reconstituted, the artesunate solution must be used within one hour.

7. SUPPLIER

Macleods Pharmaceuticals Limited
304 Atlanta Arcade
Marol Church Road
Andheri (East), Mumbai
400 059, India
Tel: +91-22-66762800
Fax: +91 -22-28216599
Email: exports@macleodsphara.com, vijay@macleodspharma.com
sjadhav@macleodspharma.com

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

MA194

9. DATE OF PREQUALIFICATION

29 May 2024

10. DATE OF REVISION OF THE TEXT

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Section 6 was updated in August 2025.

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