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

[MA168 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 60 mg of artesunate.

Each ampoule is filled with 3mL of solvent containing 8.4 mg of sodium bicarbonate and 20 mg of arginine per mL of solution.

For the list of excipients, see section 6-1.

3. PHARMACEUTICAL FORM

Artesunate 60 mg powder for solution for injection:
White crystalline powder.

Sodium bicarbonate 8.4 mg/mL and arginine injection 20 mg/mL solution for dilution:
Clear, colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[MA168 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, [MA168 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.

Where complete treatment of severe malaria is not possible, but [MA168 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.

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

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 [MA168 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.

[MA168 trade name] is given by slow intravenous or intramuscular injection over 1 to 2 minutes 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.

Instructions for reconstitution

When reconstituted correctly, one vial of [MA168 trade name] will yield 3 mL of a solution for intravenous or intramuscular administration (20 mg/mL).

For patients weighing over 25 kg, more than 1 vial of [MA168 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 (60 mg) needed
up to 25 kg	1
26 to 50 kg	2
51 to 75 kg	3
76 to 100 kg	4

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

4.3 Contraindications

[MA168 trade name] is contraindicated in patients with hypersensitivity to artesunate or other artemisinins or 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 haemolytic anaemia

Delayed haemolytic anaemia 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 and inhibit bone marrow responses (especially red blood cell precursors) in animal models. Both animal preclinical data and human data from clinical trials have suggested that reversible reticulocytopenia occurs 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.

DHA is 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 vitro drug-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 in vitro studies and from clinical drug-drug interaction studies with *oral* artesunate and/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 tissue disorders

Common	arthralgia, muscle disorders

General disorders and administration site conditions

Common	fatigue, malaise, fever, pain at injection site

Immune system disorders

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

Absorption of [MA168 trade name]

The absorption characteristics of [MA168 trade name] have been determined after intravenous and intramuscular administration of a 20 mg/mL solution of artesunate at a dose of 2.4 mg/kg, in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	**Mean value* (± standard deviation)**	
	Artesunate (intravenous administration)	**Artesunate (intramuscular administration)**
Maximum concentration (C_{max})	5934 ± 2191 ng/mL	1393 ± 347 ng/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	654 ± 216 ng·hour/mL	1046 ± 188 ng·hour/mL
Time to attain maximum concentration (t_{max})	0.080 ± 0.001 h	0.24 ± 0.12 h
* arithmetic mean		

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*-infected erythrocytes
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 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.

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. 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.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Artesunate 60 mg powder for solution for injection:
None

Sodium bicarbonate 8.4 mg/mL and arginine injection 20 mg/mL solution for dilution:
Sodium bicarbonate
Arginine
Phosphoric acid (for pH adjustment)
Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with or diluted with other medicinal products except those mentioned under section 6.6.

6.3 Shelf life

Unopened product
24 months

In-use shelf life:
The reconstituted solution should be used within one hour. See section 6-6

6.4 Special precautions for storage

Store below 30^{o}C.
Keep the vial and ampoule in the provided carton to protect from light.
Do not refrigerate or freeze.

The reconstituted solution should be stored below 30^{o}C and should be used within one hour. See section 6-6.

6.5 Nature and contents of container

Artesunate 60 mg powder for solution for injection is filled in a colourless, transparent type I glass vial (5 mL) with a type I grey halogenated butyl rubber stopper, crimped with a blue aluminium-plastic cap.

Sodium bicarbonate 8.4 mg-mL and arginine injection 20 mg/mL solution for dilution is filled in a colourless, transparent type I glass ampoule.

Outer pack: A plastic tray containing one vial of artesunate 60 mg powder for solution for injection and one ampoule of sodium bicarbonate 8.4 mg-mL and arginine injection 20 mg/mL solution for dilution. The tray is packed in an outer carton.

6.6 Special precautions for disposal and other handling

Disposal

Discard unused portion in accordance with local requirements. No other special requirements.

Preparation and administration

Because of the instability of artesunate in aqueous solutions, the reconstituted solution must be used within one hour of preparation. Therefore, the required dose of artesunate should be calculated (dose in mg = patient's weight in kg x 2.4 for patients weighing more than 20 kg; or dose in mg = patient's weight in kg x 3 for children weighing less than 20 kg) and the number of vials of artesunate needed should be determined prior to reconstituting the artesunate powder.

Reconstitution of the artesunate solution

Using a syringe, withdraw 3 ml of the sodium bicarbonate and arginine solvent and inject this into the vial containing the artesunate powder. Gently shake the vial 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 artesunate solution should always be used immediately and discarded if not used within one hour. The end concentration of the solution will be 20 mg artesunate per ml of solvent. Thus, the volume in ml for administration to the patient will be equal to: (desired dose in mg)/20.

Withdraw the required volume of artesunate solution from the vial with a syringe and then administer to the patient by slow intravenous or intramuscular injection over 1-2 minutes.

[MA168 trade name] should **NOT** be administered as an intravenous drip.

Reconstituted vials of artesunate injection and ampoules of the sodium bicarbonate and arginine injection are for single use only. Discard unused portions.

Do not use water for injection for reconstitution of the artesunate powder or for dilution of the resulting solution prior to injection.

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

MA168

9. DATE OF PREQUALIFICATION

27 June 2023

10. DATE OF REVISION OF THE TEXT

September 2023

References

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4.4 Special warnings and precautions for use

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4.6 Pregnancy and lactation

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4.9 Overdose

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