# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

ARTECOR 120 mg IV

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:

Artesunate 120 mg powder.

Each ampoule of solvent contains:

2 mL of sodium bicarbonate 50 mg/mL solution.

Each ampoule of diluent contains:

10 mL of sodium chloride 9 mg/mL solution.

**Excipients with known effect**

Each ampoule of sodium bicarbonate injection contains 27.4 mg (1.2 mmol) sodium.

Each ampoule of sodium chloride injection contains 35.4 mg (1.5 mmol) sodium.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

**Artesunate powder for injection:**
Fine, white, crystalline powder.

**Sodium bicarbonate injection:**
Clear, colourless liquid.

**Sodium chloride injection:**
Clear, colourless liquid.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

ARTECOR 120 mg IV, 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, ARTECOR 120 mg IV 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. Higher proportional doses are recommended in children weighing less than 20 kg, in whom exposure is lower than in adults and older children.

| Patient population | Dose of artesunate |
|---|---|
| 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 ARTECOR 120 mg IV 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 ARTECOR 120 mg IV before administration, see section 6.6.

The injection solution should be freshly prepared before each dose is given and should not be stored.

ARTECOR 120 mg IV 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, i.e. 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

ARTECOR 120 mg IV 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 travellers 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 and 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.

**Excipients**

Each 2 mL of sodium bicarbonate injection contains 100 mg of sodium bicarbonate, equivalent to 27.4 mg (1.2 mmol) sodium.

Each 10 mL of sodium chloride injection contains 90 mg of sodium chloride, equivalent to 35.4 mg (1.5 mmol) sodium.

This medicine contains 27.4 mg sodium (the main component of cooking/table salt) in each ampoule of sodium bicarbonate solution and 35.4 mg sodium in each ampoule of sodium chloride solution. This is equivalent to 3% of the recommended maximum daily dietary intake of sodium for an adult.

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

After intravenous administration, artesunate is rapidly and extensively converted to dihydroartemisinin (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 lactation

### 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.

### Breast-feeding

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 breast-feed, 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 the 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 3,000 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 diarrhoea 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 to < 1/10
- **Uncommon:** ≥ 1/1,000 to < 1/100
- **Rare:** ≥ 1/10,000 to < 1/1,000
- **Very rare:** < 1/10,000
- **Frequency not known:** cannot be estimated from the available data

**Tabulated list of adverse reactions**

| System Organ Class | Frequency | Adverse reaction |
|---|---|---|
| **Blood and lymphatic system 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 |

* Delayed haemolytic anaemia has been observed following treatment with injectable artesunate, particularly in patients with hyperparasitaemia and in younger children. See section 4.4.

**Description of selected adverse reactions**

**Post-treatment haemolytic anaemia**

Cases of delayed haemolytic anaemia have been identified in non-immune travellers following treatment of severe malaria with injectable artesunate. Some cases 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.

The 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**

Healthcare 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via https://pv.pharmacyboardkenya.org

## 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 for 4 days, representing a dose more than 7-fold higher than the highest recommended artesunate dose.

The overdose was associated with pancytopenia, melaena, seizures, multi-organ failure and death.

Treatment of overdose should consist of general supportive measures.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

**Pharmacotherapeutic group:** Antimalarials

**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 haem 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 *Plasmodium falciparum*.

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

**Clinical efficacy and safety**

**SEAQUAMAT**

In the SEAQUAMAT (South East Asian Quinine Artesunate Malaria Trial), an international randomised, open-label, multicentre trial conducted in Bangladesh, India, Indonesia and Myanmar, 1,461 patients with severe malaria, including 1,259 adults, were treated intravenously with either artesunate or quinine.

Artesunate was administered at 2.4 mg/kg IV at 0, 12 and 24 hours and then every 24 hours 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, three 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.

**Paediatric population**

The AQUAMAT (African Quinine Artesunate Malaria Trial) was an international, randomised, open-label, multicentre trial which sought to extend the results of the SEAQUAMAT study by comparing parenteral artesunate versus IV quinine for severe malaria in 5,425 African children (<15 years) in nine African countries: Mozambique, The Gambia, Ghana, Kenya, Tanzania, Nigeria, Uganda, Rwanda, and the 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. Approximately 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 study, post-treatment hypoglycaemia was more common in the quinine-treated group.

**Paediatric population**

The efficacy and safety of parenteral artesunate in children with severe malaria have been demonstrated in clinical trials, including the AQUAMAT trial. The efficacy of artesunate was similar when administered intravenously or intramuscularly.

The recommended dose in children weighing less than 20 kg is 3 mg/kg, while adults and children weighing 20 kg or more should receive 2.4 mg/kg.

## 5.2 Pharmacokinetic properties

**Pharmacokinetics of ARTECOR 120 mg IV**

No bioequivalence study was required due to the pharmaceutical formulation of ARTECOR 120 mg IV. Therefore, no pharmacokinetic data are available for this product.

**Pharmacokinetics of artesunate**

**Absorption**

| Parameter | Artesunate |
|---|---|
| Oral bioavailability | Not applicable |
| Food effect | Not applicable |

**Distribution**

| Parameter | Pharmacokinetic data |
|---|---|
| Volume of distribution (mean) | Artesunate: 15 L/kg; Dihydroartemisinin: 1.6–2.6 L/kg |
| Plasma protein | Artesunate: 75%; Dihydroartemisinin: 80–90%, with |

| Parameter | Pharmacokinetic data |
|---|---|
| binding *in vitro* | decreased binding at higher concentrations |
| Tissue distribution | Dihydroartemisinin accumulates substantially in *P. falciparum*-infected erythrocytes |

**Metabolism**

Artesunate is extensively hydrolysed by plasma esterases and perhaps also by CYP2A6.

**Active metabolite(s):**

Dihydroartemisinin is further metabolised through glucuronidation.

**Elimination**

| Parameter | Pharmacokinetic data |
|---|---|
| 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 |
| Percentage of dose excreted in urine | Not available* |
| Percentage of dose excreted in faeces | Not available* |

* 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 humans, evidence of toxicity was observed in the haematopoietic organs, the immune system and immune response, the liver and kidneys.

**Genotoxicity**

Artesunate did not show any mutagenic or clastogenic potential in *in vitro* and *in vivo* tests, including the Ames test and mouse micronucleus test.

**Carcinogenicity**

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 following 3- and 7-day exposures and the no or low adverse effects level was 5–7 mg/kg in pregnant rats or rabbits following 12-day exposures.

These doses 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 in mice, 450 mg/kg in rats, rabbits and dogs, and following a single oral dose 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 powder for injection:**
No excipients.

**Solvent:**
Sodium bicarbonate and water for injection.

**Diluent:**
Sodium chloride and water for injection.

## 6.2 Incompatibilities

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

## 6.3 Shelf life

36 months.

## 6.4 Special precautions for storage

Store below 30 °C.

Protect from light.

The reconstituted solution should be stored below 30 °C and should be used within 1 hour.

## 6.5 Nature and contents of container

**Artesunate for injection**

The primary packs are colourless 7 mL Type I glass vials with grey-coloured Type I rubber stoppers, crimped with an aluminium-plastic cap.

Solvent — sodium bicarbonate injection 50 mg/mL

The primary packs are colourless Type I glass ampoules of 2 mL.

Diluent — sodium chloride injection 9 mg/mL

The primary packs are colourless Type I glass ampoules of 10 mL.

**Pack size**

A small box containing:

- one vial of artesunate for injection;
- one ampoule of sodium bicarbonate injection (solvent); and
- one ampoule of sodium chloride injection (diluent).

## 6.6 Special precautions for disposal and other handling

No special precautions.

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

## 7. Marketing Authorization Holder

Signature Healthcare Ltd.

Cape Business Park,

Thika Super Highway

Postal Address: P.O Box 66172, Nairobi 00800.

## 8. Marketing Authorisation Number

H2022/CTD9134/20226

## 9. Date of First Authorisation/Renewal of The Authorisation

2023 September 18

## 10. Date of Revision of The Text

2023 September 18