

MODULE-1	ADMINISTRATIVE INFORMATION & PRODUCT INFORMATION
BRAND NAME:	SANGART 120
GENERIC NAME:	Combi Pack of Artesunate For Injection, Sodium Bicarbonate Injection BP and Sodium Chloride Injection BP

1.3 PRODUCT INFORMATION

1.3.1 Summary of Product Characteristics (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

1.1 Name of the Medicinal Product

SANGART 120

(Combi Pack of Artesunate For Injection, Sodium Bicarbonate Injection BP and Sodium Chloride Injection BP)

1.2 Strength

Each vial contains:

Artesunate 120 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:

Artesunate 120 mg

Each ampoule of diluent contains: Sodium Bicarbonate Injection BP 5.0% w/v

Each ampoule of diluent contains: Sodium Chloride Injection BP 0.9% w/v

3. PHARMACEUTICAL FORM

Powder for injection

4. Clinical particulars

4.1 Therapeutic indications

SANGART 120, administered intravenously or intramuscularly, is indicated for the treatment of severe malaria caused by *Plasmodium falciparum*, in adults and children

4.2 Posology and method of administration

Route of administration

Intravenous or Intramuscular injection

Dose:

Adults and children: SANGART 120 is administered at a dose of 2.4 mg of artesunate / kg body weight, by intravenous (IV) or intramuscular (IM) injection, at 0, 12 and 24 hours, then once daily until oral treatment can be substituted.

SANGART 120 should be administered for a minimum of 24 hours (3 doses), regardless of the patient's ability to tolerate oral medication earlier. After at least 24 hours of SANGART 120, and when able to tolerate oral medication, the patient should be switched to a complete treatment course of an oral combination antimalarial regimen. Relevant treatment guidelines should be consulted when selecting an appropriate regimen

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Preparation

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) 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 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 artesunate solution should always be used immediately, and discarded if not used within one hour.

Following reconstitution the solution must be diluted according to the method of injection, as described below.

For intravenous (IV) injection (10 mg/ml)

Using a syringe, add 10 ml of sodium chloride 0.9% for injection to the vial containing the reconstituted artesunate solution. This will yield 12 ml of a solution containing artesunate 10 mg/ml. Shake to mix well, ensuring that the resulting solution is still clear. If the solution appears cloudy or a precipitate is present, it should be discarded. The volume of the solution required (ml) will be:

$$\text{Volume (ml)} = [\text{dose (mg)}] \div 10$$

Withdraw the required volume of artesunate solution from the vial with a syringe and then inject slowly intravenously, over 1-2 minutes.

SANGART 120 should NOT be administered as an intravenous drip.

For intramuscular (IM) injection (20 mg/ml)

Using a syringe, add 4 ml of sodium chloride 0.9% for injection to the vial containing the reconstituted artesunate solution. This will yield 6 ml of a solution containing artesunate 20 mg/ml. Shake to mix well, ensuring that the resulting solution is still clear. If the solution appears cloudy or a precipitate is present, it should be discarded. The volume of the solution required (ml) will be:

$$\text{Volume (ml)} = [\text{dose (mg)}] \div 20$$

Withdraw the required volume of artesunate solution from the vial with a syringe and then inject intramuscularly; the anterior thigh is usually the preferred site for injection. If the total volume of solution to be injected intramuscularly is large, it may be preferable to divide the volume and inject it at several sites, e.g. both thighs.

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

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Hepatic and renal impairment:

Dose adjustment is not necessary in patients with hepatic or renal impairment.

4.3 Contraindications

SANGART 120 is contraindicated in patients with hypersensitivity to artesunate or other artemisinins.

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.

Switching to oral treatment regimen

Acute treatment of severe falciparum malaria with SANGART 120 should always be followed by a complete treatment course of an appropriate oral combination antimalarial regimen

Resistance to antimalarials

Local information on the prevalence of resistance to antimalarials should be considered in choosing the appropriate combination antimalarial regimen for use with SANGART 120.

Post-treatment anaemia

Despite transient decreases in reticulocyte counts, clinically significant anaemia associated with IV artesunate has not been common in clinical trials. However, occasional cases of post-treatment haemolytic anaemia severe enough to require transfusion have been reported.

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, 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

Artesunate is rapidly and extensively converted to dihydroartemisinin (DHA), the active metabolite, primarily by plasma and erythrocyte esterases.

DHA elimination is also rapid (half-life approximately 45 min) and the potential for drug-drug interactions appears limited. In vitro drug-interaction studies have demonstrated minimal effects of artesunate on cytochrome P450 isoenzymes. Few clinical drug-drug interaction studies have been performed, however no clinically significant interactions have been identified.

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4.6 Fertility, pregnancy and lactation

Pregnancy

Severe malaria is especially hazardous during pregnancy, therefore full dose parenteral antimalarial treatment should be administered without delay.

There has been limited clinical experience with the use of artesunate in pregnancy. In animal studies, artesunate has been associated with foetal toxicity during the first trimester of pregnancy. To date, clinical data regarding safety in the first trimester have not indicated an increased risk of foetal harm. Treatment with artesunate should not be withheld during the first trimester if it is potentially life-saving for the mother. As in other populations, the evidence that artesunate reduces the risk of death from severe malaria compared to other treatments should be borne in mind.

Breastfeeding / lactation

Limited information indicates that dihydroartemisinin, the active metabolite of artesunate, is present at low levels in breast milk. The drug levels 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.

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 ($\geq 1/10$), 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

Uncommon: Neutropenia and anaemia (both occasionally severe),
thrombocytopenia Very rare: Pure red cell aplasia
Frequency unknown: Post-treatment anaemia (see below), mild and transient
decrease in reticulocyte count

Nervous system disorders

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

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Respiratory disorders

Common: Cough, nasal symptoms

Gastrointestinal disorders

Common: Altered taste, nausea, vomiting, abdominal pain or cramps, diarrhoea
Rare: Raised serum amylase, pancreatitis

Hepatobiliary disorders

Uncommon: Transient rises in liver transaminases (AST, ALT)
Rare: Hepatitis

Skin and subcutaneous tissue disorders

Common: Rash, alopecia

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

In general, despite transient decreases in reticulocyte counts, clinically significant anaemia attributed to IV artesunate has not been common in clinical trials in severe malaria. However, in a case-series of 25 patients in Europe who were treated with IV artesunate for severe malaria acquired in an endemic area, 6 patients developed significant post-treatment haemolytic anaemia, presenting as late as 3 weeks after treatment, and 5 of them required transfusion. The aetiology of the haemolysis remains unknown.

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, multiorgan failure and death. Treatment of overdose should consist of general supportive measures.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimalarial , ATC code: P01BE03

Mechanism of action

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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 parasitemia $>10\%$. 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. IV artesunate was well tolerated, while quinine was associated with a substantially increased risk of hypoglycaemia.

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Paediatrics

The AQUAMAT (African Quinine Artesunate Malaria Trial) was an international, randomized open-label multicenter trial which sought to extend the results of the SEQUAMAT study by comparing parenteral artesunate versus IV quinine for severe malaria in 5425 African children (< 15 years) in 9 African countries. Dosing was similar to SEQUAMAT, 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 SEQUAMAT, post-treatment hypoglycaemia was more common in the quinine-treated group.

5.2 Pharmacokinetic properties

Intravenous

After intravenous injection artesunate is very rapidly biotransformed to its active metabolite, dihydroartemisinin (DHA). Consequently, artesunate half-life ($t_{1/2}$) is estimated to be less than 5 minutes. Following a single IV dose of 2.4 mg/kg, maximum artesunate plasma concentrations (C_{max}) were estimated to be 77 $\mu\text{mol/L}$ in a study in Gabonese children with severe malaria, and 42 and 36 $\mu\text{mol/L}$ in two studies in Vietnamese adults with uncomplicated malaria.

High concentrations of DHA are observed within 5 minutes of artesunate IV administration. In the above studies (adult and paediatric), the ranges of values for the estimated time to maximum concentration (t_{max}) and $t_{1/2}$ for DHA were 0.5-15 minutes and 21-64 minutes, respectively, while DHA C_{max} values ranged from 5.3-10.6 $\mu\text{mol/L}$.

Intramuscular

Artesunate is rapidly absorbed following intramuscular injection, and peak plasma levels are generally achieved within 30 minutes of administration. Thus, after IM injection of 2.4 mg/kg of artesunate, absorption was rapid in Gabonese children and Vietnamese adults, with T_{max} values of 8 and 12 minutes, respectively. The corresponding artesunate $t_{1/2}$ values were estimated to be 48 minutes in children and 41 minutes in adults, and C_{max} values were 1.7 and 2.3 $\mu\text{mol/L}$, for children and adults, respectively.

After IM injection artesunate C_{max} values were therefore lower by roughly 45-fold in children and 20-fold in adults when compared to IV injection. However, rates of artesunate elimination in children and adults were 32-fold and 13-fold slower, respectively, following IM injection, compared to IV administration.

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Distribution

DHA has been shown to substantially accumulate in *P. falciparum*-infected erythrocytes. Plasma protein binding of dihydroartemisinin was determined to be 93% in patients and 88% in healthy volunteers

Metabolism and elimination

Artesunate is extensively and rapidly hydrolysed by plasma esterases, with possible minimal contribution by CYP2A6. The main metabolite, dihydroartemisinin, accounts for most of the *in vivo* antimalarial activity of oral artesunate, however, following IV administration, artesunate may contribute more significantly. DHA is further metabolized in the liver via glucuronidation and is excreted in the urine; α -dihydroartemisinin- β -glucuronide has been identified as the major urinary product in patients with *falciparum* malaria.

Special population:

No pharmacokinetic data are available for patients with impaired renal or hepatic function. However, based on the known mechanisms of metabolism and elimination of artesunate, combined with clinical data from patients with severe malaria and accompanying renal and/or hepatic compromise of various degrees, no dose modifications are considered necessary in renal or hepatic impairment.

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

6. Pharmaceutical particulars

6.1 List of excipients

Solvent: Sodium bicarbonate
Sodium chloride

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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 10 ml moulded glass vials with 20 mm bromo butyl RFU rubber stopper and 20 mm flip-off seal.

Diluent (Sodium bicarbonate injection BP 5.0% w/v and Sodium chloride injection BP 0.9 % w/v): The primary packs are colourless type I glass ampoules of 2 ml and 10 mL respectively.

Pack size: A carton box containing one vial of artesunate for injection and one ampoule of the sodium bicarbonate injection BP 5.0% w/v and one ampoule of sodium chloride injection BP 0.9% w/v packed in a tray.

6.6 Special precautions for disposal and other handling

No special requirements

7. Marketing Authorization Holder

SANGHARSH LIFECARE PVT. LTD.

A-503, Solitaire Corporate Park,
Nr. Divya Bhaskar, S.G.Highway, Makarba,
Ahmedabad-380015

8. Marketing Authorization Number

Not Applicable.

9. Date of First Authorization/Renewal of the Authorization

Not Applicable.

10. Date of Revision of the Text

Not Applicable.