SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SUNAT 120mg INJECTION

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

A) Artesunate powder for Injection

Ingredient	**Quantity per vial in mg**
Artesunate IH	120 mg

B) Sodium Bicarbonate Injection USP 5% w/v - (Solvent)

Ingredient	**Quantity per ml in mg**
Sodium Bicarbonate USP	50 mg
Water for Injection USP	Q. S.

C) Sodium Chloride Injection USP 0.9% w/v – (Diluent)

Ingredient	**Quantity per ml in mg**
Sodium Chloride USP	9 mg
Water for Injection USP	Q. S.

Defination: **USP** =United State Pharmacopoeia

IH = In House Specifications

3. PHARMACEUTICAL FORM

Artesunate 120mg powder for injection: - A white crystalline powder.

Sodium Bicarbonate Injection USP: - A clear colourless solution

Sodium Chloride Injection USP: - A clear colourless solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sunat 120 Injection is indicated for severe malaria caused by Plasmodium falciparum, in both children and adults.

4.2 Posology and method of administration

Dose: For children < 20 kg: 3.0 mg of artesunate/kg body weight per dose; and Children > 20 kg and adults: 2.4 mg of artesunate / kg body weight per dose, by intravenous (IV) or intramuscular (IM) injection, at 0, 12 and 24 hours, then once daily until oral treatment can be substituted.

Sunat 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 Sunat, and when able to tolerate oral medication, the patient should be switched to a full 3-day course of recommended first line oral Artemisinin Combination therapy (ACT). The first dose of ACT should be taken between 8 and 12 hours after the last injection of artesunate. Relevant treatment guidelines should be consulted when selecting an appropriate regimen (e.g. those of the WHO: http://www.who.int/malaria/en/) medication.

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 (For children < 20 kg: dose in mg = patient's weight in kg x 3; and for Children > 20 kg and adults: 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: Using a syringe, add 5 ml of either 5% glucose for injection or sodium chloride 0.9% for injection to the vial containing the reconstituted artesunate solution. This will yield 6 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 (ml) required will be equal to: (desired dose in mg)/10. Withdraw the required volume of artesunate solution from the vial with a syringe and then inject slowly intravenously, 3 – 4 ml per minute. . Sunat should NOT be administered as an intravenous drip.

For intramuscular (IM) injection: Using a syringe, add 2ml of either 5% glucose for injection or sodium chloride 0.9% for injection to the vial containing the reconstituted artesunate solution. This will yield 3ml of a solution containing artesunate 20mg/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 (ml) required will be equal to: (desired dose in mg) /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 (2 ml for babies and 5 ml for adults), 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. Hepatic and renal impairment: Dose adjustment is not necessary in patients with hepatic or renal impairment.

Method of administration: IM/IV

4.3 Contraindications

Sunat 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 Sunat 30 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 Sunat 30. Relevant treatment guidelines should be consulted (e.g. those of the WHO: http://www.who.int/malaria/en/).

Post-treatment anaemia: Occasional cases of post-treatment haemolytic anaemia severe enough to require transfusion have been reported.

Hepatic / renal impairment: 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

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.

4.6 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. Treatment with artesunate should not be withheld during the first trimester if it is potentially lifesaving 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/Lactaction: 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.

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 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 (1/100–1/10), 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).

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological category: Artemisinin group of antimalarial drug with ATC code P01BE03.

Mechanism of action: Artesunate is a hemisuccinate derivative of dihydroartemisinin, which is itself formed by the reduction of artemisinin. 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.

5.2 Pharmacokinetic properties

Intravenous: After intravenous injection artesunate is very rapidly biotransformed to its active metabolite, dihydroartemisinin (DHA). Consequently, artesunate half-life (t½) is estimated to be less than 5 minutes. Following a single IV dose of 2.4 mg/kg, maximum artesunate plasma concentrations (Cmax) were estimated to be 77 µmol/L in a study in Gabonese children with severe malaria, and 42 and 36 µmol/L in two studies in Vietnamese adults with uncomplicated malaria. High concentrations of DHA are observed within 5 minutes of artesunate IV administration.

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 Tmax values of 8 and 12 minutes, respectively. The corresponding artesunate t1/2 values were estimated to be 48 minutes in children and 41 minutes in adults, and Cmax values were 1.7 and 2.3µmol/L, for children and adults, respectively.

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.

5.3 Preclinical Saftey 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, rare occurrences of moderate hepatotoxicity (4%) were reported, with regression in 100% of cases without sequelae. Hematopoietic toxicity on the red and white line is responsible

for reticulocytopenia and leucopenia of central origin. The toxicity appears to be on the progenitors of the erythroid lineage. There is also a negative effect on the phagocytosis capacities of neutrophils and inhibition of lymphocyte proliferation (in vitro).

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 foetal toxicity in rats, rabbits and monkeys, resulting in foetal 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, 50, 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.

Reference: Artesunate 120mg powder for injection / (Guilin Pharmaceutical Co., Ltd.), MA090/WHOPAR part 4/November 2015

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

Not applicable

6.3 Shelf life

3 Years

6.4 Special precautions for storage

Do not store above 30°C. Protect from sunlight. Keep out of reach of children. Store in the original package. The reconstituted solution should be stored below 30°C and should be used within 1 hour.

6.5 Nature and contents of container

Each combipack contains: One glass vial containing Artesunate Injection 120mg along with 2 glass ampoules, one 2ml ampoule containing Sodium Bicarbonate Injection 5%w/v and another containing 10ml ampoule containing Sodium Chloride Injection 0.9%w/v.

6.6 Special precautions for disposal and other handling

No special requirement.

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES

Manufactured for:

SHALINA LABORATORIES PVT.LTD.

96, Maker Chambers VI, Nariman Point, Mumbai-India. www.shalina.com

Email: regulatory@shalina.com

Manufactured by:

SAMRUDH PHARMACEUTICALS PVT. LTD

J-174, J-168 & J-168/1, M.I.D.C, Tarapur,

Boisar, Thane – 401 506, Maharashtra, India

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8. MARKETING AUTHORIZATION NUMBER

FDA/SD.243-101959

9. DATE OF FIRST AUTHORIZATION OR RENEWAL

October/2024

8. DATE OF REVISION OF THE TEXT

14/07/2025