Summary of Product Characteristics (SPC)

1. NAME OF THE MEDICINAL PRODUCT

SUNAT 120 INJECTION

1.1 (INVENTED) NAME OF THE MEDICINAL PRODUCT

Sunat 120 (Artesunate Injection 120 mg [Combipack])

1.2 STRENGTH

Each combipack contains:
Artesunate Injection 120 mg
Each vial contains:

Sodium Bicarbonate Injection USP (2ml)
Each ampoule contains:

Sodium Bicarbonate USP.....5% w/v
Water for Injection USP..... q.s.

Sodium Chloride Injection USP (10ml)
Each ampoule contains:

Sodium Chloride USP..... 0.9% wiv
Water for Injection USP..... q-s.

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.

Note: USP = United State Pharmacopoeia
IH = In House Specifications

3. PHARMACEUTICAL FORM

Powder for Injection

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
It is recommended that Artesunate Amivas should be used to treat patients with severe malaria only after consultation with a physician with appropriate experience in the management of malaria.

Posology

Initial treatment of severe malaria with artesunate should always be followed by a complete treatment course with appropriate oral antimalarial therapy.

Adults and children (birth to less than 18 years)
The recommended dose is 2.4 mg/kg (0.24 mL of reconstituted solution for injection per kg body weight) by intravenous (IV) injection at 0, 12 and 24 hours.

After at least 24 hours (3 doses) treatment with Artesunate, patients unable to tolerate oral treatment may continue to receive intravenous treatment with 2.4 mg/kg once every 24 hours (from 48 hours after start of treatment).

Treatment with Artesunate should be stopped when patients can tolerate oral treatment. After stopping Artesunate, all patients should receive a complete treatment course of an appropriate oral combination antimalarial regimen.

Elderly
No dose adjustment is required.

Renal impairment
No dose adjustment is required.

Hepatic impairment
No dose adjustment is required.

Paediatric population
No dose adjustment is recommended based on age or weight.

Method of administration:

Artesunate is for IV administration only. The reconstituted solution should be administered as a slow bolus injection over 1-2 minutes.

Artesunate must be reconstituted with the supplied solvent prior to administration. Because of the instability of artesunate in aqueous solutions the reconstituted solution must be used within 1.5 hours 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

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 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 bore 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 Symptoms of Overdosage & Treatment

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 PO1BE03.

Pharmacological 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.

Artemisinin resistance: Decreased susceptibility to artesunate and other artemisinins, manifesting clinically as slower rates of parasite clearance is associated with mutation in the K13 gene, which encodes the parasite's Kelch propeller protein Kelch13.

Clinical Efficacy: Artemisinin resistance Decreased susceptibility to artesunate and other artemisinins, manifesting clinically as slower rates of parasite clearance is associated with mutation in the K13 gene, which encodes the parasite's Kelch propeller protein Kelch13. Clinical efficacy In SEAQUAMAT (South East Asian

Quinine Artesunate Malaria Trial), an open-label, multicentre trial conducted in Bangladesh, India, Indonesia and Myanmar, 1461 patients (1259 adults and 202 children < 15 years (n=5425) with severe falciparum malaria were randomised to parenteral artesunate or parenteral quinine using the same dose as in SEAQUAMAT. Mortality in the intent to treat population was 8.5% (230 of 2712) in the artesunate group compared to 10.9% (297 of 2713) in the quinine group, a reduction in the odds of death adjusted by study site of 25% (95% CI: 10%, 37%; p=0.0022). Mortality in children with severe malaria in the artesunate group was 9.9% (226 of 2280) compared to 12.4% (291 of 2338) in the quinine group, a reduction in the odds of death adjusted by study site of 23% (95% CI: 7%, 36%; (p=0.0055)

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 (Cmax) were estimated to be 77 mol/L in a study in Gabonese children with severe malaria, and 42 and 36 umol/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 $t^{1/2}$ values were estimated to be 48 minutes in children and 41 minutes in adults, and Cmax values were 1.7 and 2.3umol/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.

Special Populations:

Elderly: There are no pharmacokinetic data available after intravenous artesunate dosing in patients aged 65 years or older with severe malaria. Renal impairment No pharmacokinetic data are available for patients with impaired renal function. Clinical trial data from patients with severe malaria and accompanying renal impairment at start of treatment indicate that no dose modifications are necessary.

Hepatic impairment: No pharmacokinetic data are available for patients with impaired hepatic function. Clinical trial data from patients with severe malaria and accompanying hepatic impairment at start of treatment indicate that no dose modifications are necessary.

Paediatric population: There are limited PK data on the use of IV artesunate in neonates and infants. Physiologically-based PK modelling and simulations predict that plasma exposures are likely to be higher in infants below 6 months of age compared to infants aged more than 6 months.

5.3 Preclinical safety data

Artesunate was negative in an in vitro bacterial reverse mutation assay, an in vitro Chinese hamster ovary chromosome aberration assay, and an in vivo mouse bone marrow micronucleus assays. Carcinogenicity studies have not been conducted with artesunate. Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

Reproductive and developmental toxicity Animal reproduction studies show a single IV administration of artesunate to rats early in gestation results in embryolethality. Oral administration of artesunate during organogenesis in rats, rabbits, and monkeys induces a dose-dependent increase in embryolethality and fetal malformations (including cardiovascular, brain, and/or skeletal) at 0.3 to 1.6-times the clinical dose based on body surface area (BSA) comparisons. Although animal reproduction studies in several species have demonstrated fetal harm from oral and IV administered artesunate and other artemisinin class drugs, the clinical relevance of the animal data is uncertain. Studies in the literature indicate that artesunate oral administration in the male rat can cause a dose and duration dependent effect on the epididymis and testes with reversible decreases in the production of viable sperm at near clinical doses. No such effects were noted in rats or dogs in 28-day Good Laboratory Practice (GLP) studies conducted using IV dosing.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

2ml Sodium Bicarbonate Injection USP 5% w/v.
10ml Sodium Chloride Injection USP 0.9% w/v.

6.2 Incompatibilities

None.

6.3 Shelf life

36 months (3 Years)

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 5Y%w/v and another containing 10ml

ampoule containing Sodium Chloride Injection 0.9%w/v.

6.6 Special precautions for disposal and other handling

None.

7. MARKETING AUTHORISATION HOLDER

Shalina Healthcare DMCC
30% Floor, Almas Towers,
Jumeirah Lakes Towers Dubai-UAE.

Telephone: +971 4 4309111

Telefax: +971 4 4309112

Website: www.shalina.com

SHALINA HEALTHCARE NIGERIA LIMITED,
19 FATAI ATERE WAY, MATORI,
MUSHIN, LAGOS STATE, NIGERIA

8. MANUFACTURER

Samrudh Pharmaceuticals Pvt. Ltd,
J-174, J-168 & J-168/1, M.LD.C,
Tarapur, Boisar, Thane — 401 506,

Maharashtra, India.

DATE OF REVISION OF TEXT
Every two years.

10. LEGAL CATERGORY
POM (Prescription Only Medicines)