Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:
Sunat 60 Injection

2. Qualitative and quantitative composition
Each vial contains Artesunate 60.0 mg
Excipients with known effects

For a full list of excipients, see section 6.1

3. Pharmaceutical form
White crystalline powder

4. Clinical particulars

4.1 Therapeutic indications
Sunat 60 injection, 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

Dose
Adults and children weighing 20 kg or more: Sunat 60 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
Children weighing less than 20 kg: Sunat 60 is administered at a dose of 3 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 (see section 5.1).
Sunat 60 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 Artesunate 180mg and when able to tolerate oral medication, the patient should be switched to a complete treatment course of an oral antimalarial regimen.

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 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 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 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.

4.3 Contraindications

Sunat 60 is contraindicated in patients with hypersensitivity to artesunate or other artemisinin derivatives.

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 60 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 60. 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

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 minutes) 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. An increase in plasma concentrations of artesunate was observed with nevirapine and a reduced plasma concentration of dihydroartemisinin was observed when artesunate is given with ritanovir.

4.6 Pregnancy and Lactation

Pregnancy

Severe malaria is especially hazardous during pregnancy, therefore full dose parenteral artesunatetreatment 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 andthird 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. 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 frommalaria.

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

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org The most important reported side effect of artesunate is a rare severe allergic reaction (estimated risk approximately 1 in 3000 patients), which can present as an urticarial rash or more severe allergic symptoms, including hypotension, pruritus, oedema, and/or dyspnoea. More common minor side effects described in association with parenteral administration of artesunate include dizziness, light-headedness, rash, and taste alteration (metallic/ bitter taste). Nausea, vomiting, anorexia and diarrhea have also been reported, however it is uncertain whether these are attributable to the drug or to the disease 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),
• 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 haemolytic anaemia*, 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 Cases of delayed haemolytic anaemia have been identified in non-immune travellers 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 recognizing this adverse event is advised (see section 4.4).

4.9 Overdose

Experience of acute overdose with artesunate is limited.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimalarial, 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 in the molecule through reaction with heme within the infected erythrocyte, thereby generating free radicals which alkylate vital parasite proteins. However, other studies have described specific target proteins in the parasite as mechanism of action. The artemisinins are distinguished from other antimalarials by their ability to kill all erythrocytic stages of the malaria parasite, including the ring stage and schizonts, as well as the early stage gametocytes, the sexual stage of the parasite responsible for malaria transmission. Artesunate and the artemisinins are currently the most rapidly acting of the antimalarials.

In vitro, dihydroartemisinin (DHA), the active metabolite of artesunate, exhibits similar potency against chloroquine-resistant and chloroquinesensitive strains of P. falciparum.

Artesunate and the other artemisinins are not active against preerythrocytic parasite stages including sporozoites and liver schizontes, or against mature stage gametocytes.

5.2 Pharmacokinetic properties

Intravenous: After intravenous injection artesunate is very rapidly biotransformed to its active metabolite, dihydroartemisinin (DHA). Consequently, artesunate half-life (t1⁄2) 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 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 safety data

6. Pharmaceutical Particulars

6.1 List of Excipients

Solvent- Sodium bicarbonate
Diluent – Sodium chloride
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 (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 Content of container

Each combipack contains: One glass vial containing Artesunate Injection 60mg along with 2 glass ampoules, one 1ml ampoule containing Sodium Bicarbonate Injection 5%w/v and another containing 5ml ampoule containing Sodium Chloride Injection 0.09%w/v.

6.6 Special precautions for disposal and other handling

None.

7. Marketing Authorization Holder

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8. Marketing Authorization Number

CTD8712

9. Date of first authorization/renewal of the authorization

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10. Date of revision of the text

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