Summary Product Characteristics

1. Name of the proprietary product: -

Name of the nonproprietary of Product: Artesunate for Injection 120 mg

Route of Administration: IM/IV

2. Qualitative and Quantitative composition:

Sr. No.	Ingredients	Specification	Label claim	Quantity / Vials (mg)	% Overages	Resion of inclusion
1.	Artesunate (Sterile)	In-House	120.00 mg	120.00	Nil	Antimalarial

3. Pharmaceutical Form: Powder for Solution for Injection

Artesunate : White to off white powder filled in 7.5 ml clear glass vial.

The color and nature of the product for Artesunate 120 mg, along with the accompanying components, are as follows:

- Artesunate 120 mg powder (7.5 ml vial): The color of the Artesunate powder is typically white to off- white. Its nature is crystalline and powdery.
- Sodium Bicarbonate (NaHCO3) 1ml ampoule: The color of the Sodium Bicarbonate solution is clear and colorless. Its nature is aqueous.
- Sodium Chloride (NaCl) 5ml ampoule: The color of the Sodium Chloride solution is also clear and colorless. Its nature is aqueous.

When combined, the final product will depend on the reconstitution process. If the Artesunate powder is dissolved in the Sodium Bicarbonate solution and further diluted with the Sodium Chloride solution, the resulting product is likely to be a clear or slightly opaque solution. The color of the solution will primarily be determined by the Artesunate powder, which is typically white to off-white. The nature of the final product will be aqueous.

4. Clinical Particulars:

4.1 Therapeutic Indications:
Artesunate 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: Artesunate Injection 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.
Artesunate Injection 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 Injection, and when able to tolerate oral medication, the patient should be switched to acomplete treatment course of an oral combination antimalarial regimen. Relevant treatment guidelines should be consulted when selecting an appropriate 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 responsibility. Throughout this WHOPAR the proprietary name is given a s an example only.
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 reconstitutedArtesunate solution should always be used immediately, and discarded if not used within onehour.
Following reconstitution the solution must be diluted according to the method of injection, as described below.
For intravenous (IV) injection
Using a syringe, add 10 ml of sodium chloride 0.9% for injection to the vial containing thereconstituted Artesunate solution. This will yield 6 ml of a solution containing

Artesunate10mg/ml. Shake to mix well, ensuring that the resulting solution is still clear. If the solutionappears cloudy or a precipitate is present, it should be discarded.

The volume required will be equal to: $\frac{\text{(desired dose in mg) ml}}{10}$

Withdraw the required volume of Artesunate solution from the vial with a syringe and theninject slowly intravenously, the speed of IV consistent with slow bolus:3-4 ml/min.

Artesunate Injection should NOT be administered as an intravenous drip.

For intramuscular (IM) injection

Using a syringe, add 2 ml of sodium chloride 0.9% for injection to the vial containing thereconstituted Artesunate solution. These will yield 3ml of a solution containing Artesunate20mg/ml. Shake to mix well, ensuring that the resulting solution is still clear. If the solutionappears cloudy or a precipitate is present, it should be discarded.

The volume required will be equal to: $\frac{\text{(desired dose in mg) ml}}{20}$

Withdraw the required volume of Artesunate solution from the vial with a syringe and theninject intramuscularly; the anterior thigh is usually the preferred site for injection. If the totalvolume of solution to be injected intramuscularly is large, it may be preferable to divide thevolume 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 ofthe resulting solution prior to injection.
Hepatic and renal impairment:
Dose adjustment is not necessary in patients with hepatic or renal impairment.

4.3 Contraindications
Artesunate Injection 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 Plasmodiumvivax, Plasmodium malariae or Plasmodium ovale.
Switching to oral treatment regimen
Acute treatment of severe falciparum malaria with Artesunate Injection 60mg should always be followed by a complete treatment course of an appropriate oral combination antimalarialregimen
Resistance to Antimalarials
Local information on the prevalence of resistance to antimalarials should be considered inchoosing the appropriate combination antimalarial regimen for use with Artesunate Injection.
Relevant treatment guidelines should be consulted.
Post-treatment anaemia
Despite transient decreases in reticulocyte counts, clinically significant anaemia associatedwith IV Artesunate has not been common in clinical trials. However, occasional cases of post
-treatment haemolyticanaemia 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.
Pediatric population
In clinical trials, the efficacy and safety of intravenous and intramuscular Artesunate havebeen 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 activemetabolite, 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 oncytochrome P450 isoenzymes. Few clinical drug-drug interaction studies have beenperformed, 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. 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 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. In a study of 461 pregnant Thai women (44 in their first trimester) who were treated with artemisinins (predominantly artesunate), there was no obvious evidence of adverse effects amongst the 414 women for whom pregnancy outcomes were known. The observed rates of abortion, stillbirth, congenital anomalies and low birth weight were comparable to community rates. In clinical trials from 1999 to 2006, 2,045 pregnant women in Thailand, the Gambia, and Sudan were treated with artesunate, either alone or in combination with other antimalarials, including quinine, mefloquine, atovaquone-proguanil and sulfadoxine-pyrimethamine. In these patients, most of whom were in their second or third trimesters of pregnancy, there were no significant differences compared to the general community in birth weights, duration of gestations, placental weights, or rates of congenital abnormalities, or in growth and developmental parameters of infants monitored for one year

4.7 Effects on the 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 wellas other symptoms, including hypotension, prutitus, 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 bodysystem, 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

ll aplasia

Frequency unknown: Post-treatment anaemia (see below), mild and transient decrease inreticulocyte count

Nervous system disorders

Common: Dizziness, light-headedness, headache, insomnia, tinnitus (with or withoutdecrease 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 anaemiaattributed 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 forsevere malaria acquired in an endemic area, 6 patients developed significant post-treatmenthaemolyticanaemia, presenting as late as 3weeks after treatment, and 5 of them requiredtransfusion. The aetiology of the haemolysis remains unknown

4.9 Overdose
Experience of acute overdose with Artesunate is limited. A case of overdose has beendocumented 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 thehighest 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 Particulars:

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 through reaction with haeme within the infected erythrocyte, therebygenerating free radicals which alkylate vital parasite proteins. However, artemisinins havealso been reported to inhibit an essential parasite calcium adenosine triphosphatase.

The artemisinins are distinguished from other antimalarials by their ability to kill allerythrocytic 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 lessthan 5minutes. Following a single IV dose of 2.4 mg/kg, maximum Artesunate plasmaconcentrations (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 withuncomplicated 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 tomaximum concentration (tmax) and t½ for DHA were 0.5-15 minutes and 21-64 minutes,respectively, while DHA Cmax values ranged from 5.3-10.6 μmol/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 Tmax values of 8 and 12 minutes, respectively. The corresponding Artesunate t1/2 values wereestimated 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.

After IM injection Artesunate Cmax values were therefore lower by roughly 45-fold inchildren 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, followingIM injection, compared to IV administration.

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 thein vivo antimalarial activity of oral Artesunate, however, following IV administration. Artesunate may contribute more significantly. DHA is further metabolized in the liver viaglucuronidation and is excreted in the urine; α-dihydroartemisinin-β-glucuronide has beenidentified 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/orhepatic compromise of various degrees, no dose modifications are considered necessary inrenal or hepatic impairment.

5.3 Pre-clinical Safety:
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 hematopoietic 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 Oral artesunate caused dose-dependent foetal toxicity in rats, rabbits and monkeys, resulting in foetalresorption and abortion, as well as a low incidence of cardiac and skeletal defects. The no-observedadverse-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. 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.

6. Pharmaceutical Particulars:

List of Excipients:
No excipients added.

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 in a dry place, protected from light.
The reconstituted solution should be stored below 30^0C and should be used within 1hour.

6.5 Nature and contents of container:
White to off white powder filled in a 7.5 ml Clear glass vial, plugged with grey butyl rubber plug with dark red flip-off seal, packed in a carton along with a plastic tray containing 1 ml ampoule of Sodium Bicarbonate Injection BP (5 % w/v) , 5 ml ampoule of Sodium Chloride Injection BP (0.9%w/v) and Pack insert.

6.6 Special precautions for disposal and other handling:
No special requirements. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Applicant:

ZMC INT'L LIMITED, NO 6 DAMATTA WAY AIR-PORT ROAD KANO, KANO.

Manufacturer:

M/S KAMLA LIFE SCIENCES PVT.LTD, Plot No. G-84/1, Tarapur, M.I.D.C, Boisar-401506, Tal. & Dist. Palghar, Maharashtra, India.