1. NAME OF THE MEDICINAL PRODUCT

AVINATE 120 (Artesunate Injection 120 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

The Pack contains:

One Vial of Artesunate..... 120 mg

2 ml Ampoule of Sodium Bicarbonate Injection USP 5% w/v

10 ml Ampoule of Sodium Chloride Injection USP 0.9 % w/v

Sr. No.	Ingredient	Specification	Label Claim/ Vial	Qty.kg	Use
1.	Artesunate	IH/IP	120 mg	2000 gms	Antimalarial
2.	Nitrogen		q.s.	q.s.	--

3. PHARMACEUTICAL FORM:

Dry Powder Injection

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications:

AVINATE 120 is 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

Dosage Form : Dry Powder Injection

Child under 20 kg: 3 mg/kg/dose

– Child 20 kg and over and adult: 2.4 mg/kg/dose

Artesunate Injection 30 mg 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 treatnent can be substituted. Artesunate Injection 30 mg should be

administered for a minimum of 24 hours (3 doses),regardless of the patient's ability to tolerate oral medication earlier. After at least24 hours of Artesunate Injection 30 mg 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.

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.

4.3 Contraindications

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

4.4 Special Warning and Precautions for use.

The results of animal experiment has shown some embryo toxic effect. Therefore it should be used with extreme caution in pregnancy within first three months. 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 AVINATE 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 AVINATE 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 Interactions with other FPPs and other forms of interactions

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.

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 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. 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. 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, 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 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 ll 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

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

Artemisinin compounds are concentrated in parasitized erythrocytes.Endoperoxide bridge is essential for antimalarial activity. They are thought to cause free-radial damage to parasite membrane system, although precise mechanism is unclear. Artemisinin compounds act rapidly stopping parasite development and preventing subsequent cytoadherence. Clinical effectiveness of artemisinin compounds have been confirmed in P.vivax and P. falciparum malaria (both in chloroquine sensitive and resistant strains). Artemisinin compounds are rapidly acting blood schizonticides for these species. They act early in the asexual parasite developmental cycle by destroying early ring forms. They have no activity on persistent hepaticfonns (hypnozoites) and nogametocytes. Their effectiveness in other species of malariai i.e.P.ovale and P. malariae is yet not fully evaluated.

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 parisitemia >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.

Paediatrics:

The AQUAMAT (African Quinine Artesunate Malaria Trial) was an international, randomized open-label multicenter trial which sought to extend the results of the SEAQUAMAT 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 SEAQUAMAT, 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 SEAQUAMAT, post-treatment hypoglycaemia was more common in the quinine-treated group.

Pharmacokinetic properties:

Plasma drug concentration decreases rapidly after intravenous administration of artesunate. The plasma half-life is about 30 minutes. It distributes widely throughout the body and with high concentration in intestines, liver and kidneys.Only small quantity excretes in urine and in stools. It is mainly eliminated by metabolic biotransformation.

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. In the above studies (adult and paediatric), the ranges of values for the estimated time to maximum 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 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.

After IM injection artesunate Cmax 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.

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).

5.4. ATC Code:

Artesunate Injection - P01BE03

6. PHARMACEUTICAL PARTICULARS:

6.1 No Excipient are used in the formulation of **AVINATE 120** (Artesunate Injection 120 mg).

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products .

6.3 Shelf life

30 Months from the date of manufacture.

6.4 Special precautions for storage

Store below 25°C, protected from light & Moisture.

6.5 Nature and contents of container:

AVINATE 120 (Artesunate Injection 120mg) is filled in 15 ml USP Type III clear glass vial, Bromo Butyl Rubber Plug RFS with 20 mm Blue Flip off seal is labelled and placed in PVC Tray, this tray is placed in monocarton along with 2 ml Ampoule of Sodium Bicarbonate Injection USP 5% w/v and 10 ml Ampoule of Sodium Chloride Injection USP 0.9 % w/v along with leaflet.

6.6 Instructions for use and handling

Keep out of reach of children.

7. MARKETING AUTHORISATION HOLDER

Manufactured By:

SYSTACARE REMEDIES:

Village & Post Office Balkalan, Majitha Road, Amritsar - 143601, INDIA

Marketed by:

TYONEX NIGERIA LTD.

KM 10, LASU-Ojo Road, Egan, Igando-lkotun LGA, Lagos, NIGERIA.

Exported By :

KILITCH DRUGS (INDIA) LTD.

39, Ujagar Industrial Estate, W. T. Patil Marg, Deonar, Mumbai - 400088 INDIA.

8. MARKETING AUTHORISATION NUMBER(S) :

Not Applicable

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

Not Applicable

10. DATE OF REVISION OF THE TEXT:

Not Applicable

The Summary of Product Characteristics (SPC) is satisfactory.

11. DOSIMETRY (IF APPLICABLE):

Not Applicable

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE):

Not Applicable