| GENERIC NAME: | ARTESUNATE FOR INJECTION 120 MG |
|---|---|

**MODULE-1 ADMINISTRATIVE INFORMATION**

**1.3.1 Summary of Product Characteristics (SmPC)**

**1. Name of drug product**

ARTESUNATE FOR INJECTION 120 MG

**1.1 (Trade) name of product**

ARTESUNATE FOR INJECTION 120 MG

**1.2 Strength**

Composition:

Each Vial Contains:

Artesunate (Sterile)…….120 mg

**1.3 Pharmaceutical Dosage Form**

Small Volume Parental

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**MODULE-1 ADMINISTRATIVE INFORMATION**

**2. Qualitative & Quantitative Composition**

**2.1 Qualitative Declaration**

Composition:

Each Vial Contains:

Artesunate (Sterile)…….120 mg

**2.2 Quantitative Declaration**

**Batch Formula:**

**Batch Size:** 1,00,000 Vial

| Sr. No. | Material Name | Grade | Rationale | Label Claim | Quantity /unit (mg) | Quantity /batch (Kg) |
|---|---|---|---|---|---|---|
| 1 | Artesunate | IH | Active | 120 mg | 120.00 | 120.00 |

## MODULE-1 ADMINISTRATIVE INFORMATION

### 3. Pharmaceutical Dosage Form

For Intravenous Administration

### 4. Clinical particulars

### 4.1 Therapeutic indications

ARTESUNATE FOR INJECTION 120 MG, 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

Posology

**Dose:**

Adults and children: ARTESUNATE FOR INJECTION 120 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 treatment can be substituted.

ARTESUNATE FOR INJECTION 120 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 least 24 hours of ARTESUNATE FOR INJECTION 120 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

**MODULE-1 ADMINISTRATIVE INFORMATION**

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 required will be equal to: (desired dose in mg)/ 10 ml withdraw the required volume of artesunate solution from the vial with a syringe and then inject slowly intravenously, the speed of IV consistent with slow bolus: 3-4 ml/min. ARTESUNATE FOR INJECTION 120 MG 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 the reconstituted artesunate solution. This will yield 3 ml of a solution containing artesunate 20 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 required will be equal to: (desired dose in mg) /20 ml 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, 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

**MODULE-1 ADMINISTRATIVE INFORMATION**

**4.3 Contraindications**

ARTESUNATE FOR INJECTION 120 MG 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 ARTESUNATE FOR INJECTION 120 MG should always be followed by a complete treatment course of an appropriate oral combination antimalarial regimen (see Section 4.2)

**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 ARTESUNATE FOR INJECTION 120 MG. Relevant treatment guidelines should be consulted.

**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 (see Section 4.8).

**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 (see Section 5.2), dosage adjustment is not considered necessary in patients with hepatic or renal impairment.

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**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 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 Fertility, 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.

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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 aplasiall 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: Hepatitistis

**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. 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**

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.

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## MODULE-1 ADMINISTRATIVE INFORMATION

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**

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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.

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### 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. 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

**MODULE-1 ADMINISTRATIVE INFORMATION**

**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).

**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.

**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

### 6.1 List of excipients

None

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

24 month

### 6.4 Special precautions for storage

Store below 30°C. Protect from light.

The reconstituted solution should be stored below 30°C and should be used within 1 hour.

**MODULE-1 ADMINISTRATIVE INFORMATION**

**6.5 Nature and contents of container**

1 vial of artesunate powder, 2 ampoules of diluents are placed in a plastic tray. Such a tray packed in monocarton along with package insert.

**7. Marketing authorisation holder**

**VITBORAH PHARMACEUTICAL COMPANY LTD.**

2 olori elegushi street Awoyaya ibeju lekki

**8. Marketing authorisation number(s)**

**9. Date of first authorisation/renewal of the authorisation**

**10. Date of revision of the text**