

# PHARMAX (INDIA) PVT.LTD.

|                      |                                 |
|----------------------|---------------------------------|
| <b>BRAND NAME:</b>   | <b>FEST ARTESUNATE 120</b>      |
| <b>GENERIC NAME:</b> | ARTESUNATE FOR INJECTION 120 MG |

## MODULE 1 APPLICATION INFORMATION

### SUMMARY OF PRODUCT CHARACTERISTIC

#### 1. Name of the proprietary product ARTESUNATE INJECTION

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

**Route of Administration:** Intramuscular, Intravenous injections

#### 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        |

Potency /Assay = 100.00%

Strength = 120 mg

Therefore Qty per/ vial =  $\frac{120 \times 100}{100.00}$

= 120.00 mg

For Sodium Bicarbonate Injection BP 5.0% w/v

Each ampoule contains:  
Sodium Bicarbonate BP 5% W/v  
Water for injection BP q.s

| Sr. No | Ingredients           | Specification | Satndard quantity/(%w/v) | Resion of inclusion |
|--------|-----------------------|---------------|--------------------------|---------------------|
| 1.     | Sodium Bicarbonate BP | BP            | 5.00                     | Alkalizing agent    |
| 02     | Water for injection   | BP            | Q.s                      | Vehicle             |

For Sodium chloride Injection BP 0.9% w/v

| Sr. | Ingredients | Specification | Satndard quantit | Resion of inclusion |
|-----|-------------|---------------|------------------|---------------------|
|-----|-------------|---------------|------------------|---------------------|

| No |  |  | y/(%w/v) |  |
|----|--|--|----------|--|
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|    |                     |    |     |                |
|----|---------------------|----|-----|----------------|
| 1. | Sodium Chloride     | BP | 0.9 | Tonicity agent |
| 02 | Water for injection | BP | Q.s | Vehicle        |

### 3. Pharmaceutical Form:

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

- Artesunate 120mg powder (15ml vial): The color of the Artesunate powder is typically white to off- white. Its nature is crystalline and powdery.
- Sodium Bicarbonate ( $\text{NaHCO}_3$ ) 2ml ampoule: The color of the Sodium Bicarbonate solution is clear and colorless. Its nature is aqueous.
- Sodium Chloride ( $\text{NaCl}$ ) 10ml 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 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 responsibility). Throughout this WHOPAR the proprietary name is given as 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 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

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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 Artesunate 10mg/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:  $\frac{(\text{desired dose in mg}) \text{ ml}}{10}$

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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 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 Artesunate 20mg/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:  $\frac{(\text{desired dose in mg}) \text{ ml}}{20}$

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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.

### 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 *Plasmodium vivax*, *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 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 Artesunate Injection.

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.

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 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.

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### 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 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 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 ( $\geq 1/10$ ), 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

II 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

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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 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 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, 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

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enhance splenic clearance of infected erythrocytes by reducing cytoadherence.

### 5.2 Pharmacokinetic properties

#### Intravenous

After intravenous injection Artesunate is very rapidly bio-transformed 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 ( $C_{max}$ ) were estimated to be 77  $\mu\text{mol/L}$  in a study in Gabonese children with severe malaria, and 42 and 36  $\mu\text{mol/L}$  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 ( $t_{max}$ ) and  $t_{1/2}$  for DHA were 0.5-15 minutes and 21-64 minutes, respectively, while DHA  $C_{max}$  values ranged from 5.3-10.6  $\mu\text{mol/L}$ .

#### 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  $T_{max}$  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  $C_{max}$  values were 1.7 and 2.3  $\mu\text{mol/L}$ , for children and adults, respectively.

After IM injection Artesunate  $C_{max}$  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;  $\alpha$ -dihydroartemisinin- $\beta$ -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 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



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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:

#### 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: 24 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°C and should be used within 1 hour.

#### 6.5 Nature and contents of container:

White to off white powder filled in a 15ml Clear glass vial, plugged with grey butyl rubber plug with Dark green flip-off seal, packed in a carton along with a plastic tray containing 2 ml ampoule of Sodium Bicarbonate Injection BP (5 % w/v) , 10 ml ampoule of Sodium Chloride Injection BP (0.9%w/v) and Pack insert.

Packing size : 1×1 vial + 2ml ampoule of sodium bicarbonate BP 5%(W/V) + 10ml of sodium chloride BP 0.9% (W/V)

#### 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. Marketing Authorization Holder:

**FEST PHARMACY NIGERIA LTD**  
**NIGERIA**

#### MANUFACTURED BY:

**PHARMAX (INDIA) PVT.LTD.**

9, Kurla Industrial Estate, Ghatkopar (W),  
Mumbai - 400 086.

### 8. Marketing Authorization Number: ---

### 9. Date of first Authorization /renewal of the authorization: ---

### 10. Date of revision of text: