## 1. NAME OF THE MEDICINAL PRODUCT

**FEST ARTESUNATE 60 INJECTION** (Artesunate for Injection 60 mg)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**Each combipack contains:**

| | |
|---|---|
| One vial of Artesunate (Sterile) | 60 mg |
| 1 ml Ampoule of Sodium Bicarbonate BP | 5%w/v |
| 5 ml Ampoule of Sodium Chloride injection BP | 0.9% w/v |

## 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 60 mg, along with the accompanying components, are as follows:

- Artesunate 60 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 ($NaHCO_3$) 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.

## 4.0 Clinical particular

### 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

Posology

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 then inject 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 antimalarial regimen.

*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 inpatients 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 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 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 monitoredforoneyear

## 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 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
veryrare (< 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 PROPERTIES

### 5.1 Pharmacodynamics 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 bio transformed 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 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 hydrolyzed by plasma esterase's, 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 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/orhepatic compromise of various degrees, no dose modifications are considered necessary inrenal 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 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

### 6.1 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 $30^0$C 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

No special requirements. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 6.7 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.

## 7 APPLICANT/MANUFACTURER

**APPLICANT :**

**Fest Pharmacy Nigeria limited, Nigeria**

**MANUFACTURER:**

**Pharmax India Pvt. Ltd**
**Kurla Industrial Estate, Netaji Palkar Road,**
**Narayan Nagar, Ghatkopar West, Mumbai – 400086**

# National Agency for Food & Drug Administration & Control (NAFDAC)

## Registration & Regulatory Affairs (R & R) Directorate

**PATIENT INFORMATION LEAFLET: INFORMATION FOR THE USER**
**FEST ARTESUNATE 60 INJECTION**
**Artesunate 60 mg for injection and sodium bicarbonate injection 50 mg/ml (1ml) and sodium chloride injection 9 mg/ml (5ml)**
**for preparation of solution for intravenous or intramuscular injection**

**Read all of this leaflet carefully before you start taking this medicine.**

- Keep this leaflet. You may need to read it again before, during or after use of this medicine.
- If you have any further questions, ask your health care provider.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please inform your health care provider.

**In this leaflet:**

## 1. WHAT FEST ARTESUNATE 60 INJECTION IS AND WHAT IT IS USED FOR

**FEST ARTESUNATE 60 INJECTION** contains Artesunate and is for preparation of a solution for intravenous or intramuscular injection.

**FEST ARTESUNATE 60 INJECTION** is used for the treatment of severe *falciparum* malaria caused by the parasite.

## 2. WHAT YOU NEED TO KNOW BEFORE USE OF FEST ARTESUNATE 60 INJECTION

### FEST ARTESUNATE 60 INJECTION should not be used

If the patient is allergic to the active substance or any of the other ingredients of this product (see section 6).

### Warnings and Precautions

After intravenous or intramuscular treatment of the critical phase of the *falciparum* malaria infection, the patient will need to take oral medication to complete the treatment and avoid relapse.

Delayed haemolytic anaemia (a reduction of red blood cells) within the first month after treatment with Artesunate has been reported, particularly in small children and travelers. The health care provider may therefore monitor the patient's blood count within 28 days after malaria therapy. If you feel excessively tired, weak or short of breath up to 4 weeks after treatment, inform your health care provider.

### Taking other medicines

Please inform the health care provider if the patient is taking or has recently taken any other medicines, including medicines bought without prescription

### Pregnancy and breastfeeding

Pregnancy

Severe malaria is especially hazardous during pregnancy, therefore full dose parenteral artesunate treatment should be administered at any stage of pregnancy without delay.

Breastfeeding

A small amount of the medicine enters human breast milk, but it will not protect the child from malaria. The health care provider will advise the patient on breast-feeding.

## 3. HOW TO TAKE FEST ARTESUNAYTE 60 INJECTION.

Artesunate may be injected intravenously (into a vein) or intramuscularly (into a muscle).



The duration of treatment is at least one day, and will be determined by the health care provider.

For each dose a new syringe and injection needle must be used. Further information on the method of administration for health care professionals is attached to this leaflet.

If you have any further questions on the use of this product, ask your health care provider.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, **FEST ARTESUNATE 60 INJECTION** can cause side effects, but not everybody gets them. Some of these may be difficult to detect, and may be similar to effects of the disease itself.

**Very common side effects (≥ 1/10):**

Post-treatment hemolytic anemia (low red blood cells) in travelers and children, sometimes serious. Mild and transient decrease in reticulocyte count (blood elements important for clotting).

**Common side effects (1/100-1/10):**

Dizziness, vomiting, light-headedness, headache, altered taste, abdominal pain or cramps, diarrhea, rash, pain at injection site, insomnia, tinnitus (ringing in ears, with or without decrease in hearing), cough and / or nasal symptoms, nausea, hair loss, joint pain, bone and muscle disorders, fatigue, malaise, and fever.

**Uncommon side effects (1/1000-1/100):**

Low red and white blood cell counts, clotting factor decreases, rises in liver enzymes, allergic reactions, heart rhythm and rate problems.

**Rare side effects (1/10,000-1/1000):**

Inflammation of the liver or pancreas. Bile stones. Artery narrowing, high blood pressure affecting the eyes.

**Very rare side effects (< 1/10,000):**

Severe reduction in red blood cells, tingling sensation and nerve pain.

## 5. HOW TO STORE FEST ARTESUNATE 60 INJECTION

**FEST ARTESUNATE 60 INJECTION** should be kept out of the sight and reach of children.

**FEST ARTESUNATE 60 INJECTION** stored in the original packing, below 30° C, until it is ready to be used to create a solution. The reconstituted and diluted solutions should be stored below 30°C and the total in-use period should not exceed one hour.



Protect against direct sunlight. Do not store in a refrigerator or freezer.

The product must be destroyed if crystals or cloudiness are visible in the solution.

Do not use **FEST ARTESUNATE 60 INJECTION** after the date indicated by "EXP" on the immediate and the outer labelling.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. What {product name, CONTENTS OF THE PACK AND OTHER INFORMATION

**What FEST ARTESUNATE 60 INJECTION contains**
Artesunate powder for injection (no other excipients)
Solvent: sodium bicarbonate and water for injection
Diluent: sodium chloride and water for injection

**What FEST ARTESUNATE 60 INJECTION looks like and contents of the pack**
Artesunate for injection is a sterile white crystalline powder, 60 mg.

Sodium bicarbonate injection is a sterile clear colourless liquid, 50 mg/ml, 1 ml.

Diluent: Sodium chloride injection is a sterile clear colourless liquid, 9 mg/ml, 5 ml.

**FEST ARTESUNATE 60 INJECTION** is supplied in a carton box.

**Manufacturer**
**Pharmax India Pvt. Ltd**
**9 Kurla Industrial Estate, Netaji Palkar Road,**
**Narayan Nagar, Ghatkopar West, Mumbai – 400086**

This information is intended for healthcare professionals only:

INFORMATION FOR HEALTHCARE PROFESSIONALS

FEST ARTESUNATE 60 INJECTION

Artesunate for injection

Please refer to the Summary of Product Characteristics for full prescribing information.

**Posology and method of administration**

Dose:

*Adults and children weighing at least 20 kg:* **FEST ARTESUNATE 60 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.

*Children weighing less than 20 kg***: FEST ARTESUNATE 60 INJECTION** 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.

**FEST ARTESUNATE 60 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 **FEST ARTESUNATE 60 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 (e.g. those of the WHO:

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 or dose in mg = patient's weight in kg x 3 for children weighing less than 20 kg, respectively) and the number of vials of artesunate needed should be determined prior to reconstituting the artesunate powder.*

Reconstitution of the Artesunate solution

1. Using a syringe, withdraw 1 ml of the supplied sodium bicarbonate solvent from the ampoule
2. Inject the sodium bicarbonate into the vial containing the artesunate powder.
3. 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.
4. 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.*

Dilution for intravenous (IV) injection (10 mg/ml)

1. 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.
2. 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 of the solution required (ml) will be:
   Volume (ml) = [dose (mg)] ÷ 10
3. Withdraw the required volume of artesunate solution from the vial with a syringe
4. Then inject slowly intravenously, over 1-2 minutes.

**FEST ARTESUNATE 60 INJECTION** should NOT be administered as an intravenous drip.

Dilution for intramuscular (IM) injection (20 mg/ml)

1. 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.
2. 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 of the solution required (ml) will be:
   Volume (ml) = [dose (mg)] ÷ 20
3. 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.***