# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT:

Brand Name: ARTEPIL

Generic Name: Artesunate for Injection Ph. Int. 60 mg

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

**Each vial contains:**

Artesunate (Sterile) Ph.Int 60 mg

In combipack with:

1ml ampoule of Sodium Bicarbonate Injection USP 5% w/v

5ml ampoule of Sodium Chloride Injection USP 0.9 %w/v

## 3. PHARMACEUTICAL FORM

White to almost white powder filled in 5ml clear USP type III glass vial with rubber bung aluminium seal having Taxim blue flip on top.

## 4. Clinical particulars

### 4.1.Therapeutic indications

Artesunate Injection is an Antimalarial drug. It is indicated for the treatment of severe malaria caused by Plasmodium falciparum, in adults and children.

### 4.2.Posology and Method of Administration

*Posology*

*Route of administration:*

Intravenous or Intramuscular Injection

Method of preparation

Using a syringe, withdraw 1 ml of the sodium bicarbonate solvent from the ampoule and inject into the vial containing the artesunate powder. Shake the vial for several minutes to form a solution. Following this reconstitution, the solution must be diluted according to the route 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

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

**Water for injection is not an appropriate diluents**

**Dose:**

Paediatrics less than 20 kg: 3 mg/kg

Patients above 20 kg: 2.4mg/kg

**NUMBER OF VIALS REQUIRED TO INITIATE A PARENTERAL DOSE**

| Weight | Less than 25kg | 26 to 50kg | 51 to 75kg | 76 to 100kg |
|---|---|---|---|---|
| 60mg vial of Artesunate for Injection | 1 vial | 2 vials | 3 vials | 4 vials |

**4.3 Contraindications**

Artesunate Injection is contraindicated in patients with hypersensitivity to Artesunate or other artemisinin.

**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 Fexona Artesunate Injection 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 Fexona Artesunate Injection.

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***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 posttreatment hemolytic 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 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 (halflife 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. 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 artemisinin (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 sulfadoxinepyrimethamine. 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.

**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, pruritus, oedema, and/or dyspnoea. More common minor side effects associated with IV administration have included dizziness, lightheadedness, 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
Frequency unknown: Post-treatment anaemia, 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: 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

**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, multi-organ failure and death. Treatment of overdose should consist of general supportive measures.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product, Healthcare professionals are asked to report any suspected adverse reactions to **TMDA.**

## 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. The mechanism of action of the artemisinin 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, artemisinin have also been reported to inhibit an essential parasite calcium adenosine triphosphatase. The artemisinin 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 artemisinin 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 artemisinin are essentially inactive against extra-erythrocytic forms, sporozoites, liver schizontes or merozoites.

### 5.2.Pharmacokinetic Properties Absorption:

***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 77µmol/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 esterase's, 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-glucuronides 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 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 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 embryo toxicity 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

Not Applicable

**For Reconstitution Diluent(s):**

Sodium Chloride Injection 0.9 % w/v**:** Sodium Chloride USP and Water for Injection USP

Sodium Bicarbonate Injection 5% w/v**:** Sodium Bicarbonate USP and Water for Injection USP

### 6.2.Incompatibilities

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

### 6.3.Shelf life

3 years

### 6.4.Special precautions for storage

Store below 30°C in a dry place away from light.

### 6.5.Nature and contents of container

5 ml clear USP Type-III glass vial packed in a Kit with 5ml ampoule of Sodium chloride Injection and 1ml ampoule of Sodium bicarbonate Injection. Such One kit of vials are packed in a Printed carton with Pack Insert.

### 6.6 Special precautions for disposal and other handling

Not Applicable

## 7. MARKETING AUTHORIZATION HOLDER

Psychotropics India Limited, Plot No. 12 & 12A, Industrial Park – II, Phase – I, Salempur, Mehdood – 2, Haridwar – 249403, India

Email: sid@pilindia.in

## 8. MARKETING AUTHORIZATION NUMBER(S)

TAN 22 HM 0494

## 9. DATE OF FIRST AUTHORIZATION /RENEWAL OF THE AUTHORIZATION

05th December, 2022

## 10. DATE OF REVISION OF THE TEXT