

1. Name of the medicinal product

Artesunate for Injection 120 mg

2. Qualitative and quantitative composition

Composition:

Each pack contains:

Each vial contains:

Artesunate (sterile) 120 mg

Each ampoule contains:

Sodium Bicarbonate BP 5%w/v

Water for Injection BP q.s.

Each ampoule contains:

Sodium Chloride BP 0.9%w/v

Water for Injection BP q.s.

3. Pharmaceutical form

Dry Powder Injection

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

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.

Method of Administration:

For I.M/I.V Administration

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.

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.

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 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 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

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, 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.

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.

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. 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 schizonts or merozoites.

5.2 Pharmacokinetic properties

Intravenous After intravenous injection artesunate is very rapidly biotransformed 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 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 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 μmol/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; 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

Not Applicable

6.2 Incompatibilities

None

6.3 Shelf life

36 Months.

6.4 Special precautions for storage

Store in a dry place, away from light and humidity below 25° C.

6.5 Nature and contents of container

1 glass vial in a plastic tray with 1 ampoule of sodium chloride and 1 ampoule of sodium bicarbonate along with literature in one unit carton. And 10 such unit carton in one shrink.

6.6 Special precautions for disposal and other handling

None

7. Registrant/Applicant

EMBASSY PHARMACEUTICAL & CHEMICAL LTD.

41, Ademola Street, South West Ikoyi,

Lagos, Nigeria. Tel.: 01-2900791

Manufacture

Laborate Pharmaceutical (India)

E-11, Industrial Area,

Panipat – 132103, Haryana (India)

Telephone: +91-180-2650072, 2651248, 26520385, 2655741

Telefax: +91-180-2651072

E-Mail: laborate@laborate.com

8. Marketing authorisation number(s)

None

9. Date of first authorisation/renewal of the authorisation

None

10. Date of revision of the text

None