1.5. Product Information

1.5.1 Prescribing information

Summary of Product Characteristics

1. Name of the medicinal product: INDART- 60

1.1 (Invented) name of the medicinal product: Artesunate 60 mg injection

1.2 Strength: 60 mg

2. Qualitative and quantitative composition:

Each Combipack contains:

One vial of Artesunate Injection

Each vial contains

Artesunate 60 mg

One 6 ml ampoule of Sodium phosphate injection USP.

Each ampoule contains:

Anhydrous Disodium Hydrogen Phosphate BP 4.0 % w/v

Anhydrous Sodium Dihydrogen Phosphate BP 0.2 % w/v

3. Pharmaceutical form: White crystalline powder for injection

4. Clinical Particulars

4.1 Therapeutic indications:

INDART- 60, administered intravenously or intramuscularly, is indicate for the treatment of sever malaria caused by *Plasmodium falciparum,* in adults and children.

4.2 Posology and method of administration:

Dosage: Adults and Children:

INDART- 60 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.

INDART- 60 should be administered for a minimum of 24 hours (3doses), regardless of the patient's ability to tolerate oral medication earlier.

INDART- 60 Injection Reconstitution & Administration:

Add 6 ml Ampoule of Sodium phosphates Injection USP to Artesunate for injection 60 mg vial, mix and shake well until the solution becomes clear.

4.3 Contraindications:

INDART- 60 is contraindicated in patients hypersensitive to Artesunate, other Artemisinin or any other ingredient of the product.

4.4 Special warnings and precautions for use:

Artesunate has not been evaluated in the treatment of severe malaria due to Plasmodium vivax, Plasmodium malariae or Plasmodium ovale.

Prevalence of resistance to antimalarials should be considered in choosing the appropriate combination antimalarial regimen for use with INDART - 60 ®.

Caution should be taken while administering Artesunate injection to patients with hepatic or renal impairment.

4.5 Interaction with other medicinal products and other forms of interactions:

The elimination of Artesunate metabolites is rapid hence the potential for drug-drug interactions is limited. In vitro drug interaction studies have demonstrated minimal effects of Artesunate on cytochrome P450 isoenzymes.

4.6 Pregnancy and lactation:

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 and lactation. In general cases parenteral Artesunate may be used in pregnancy and lactation under medical supervision only if benefits to the mother outweigh the risk to fetus or the child.

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:

Certain common side effects observed with the use or Artesunate injection are dizziness, light headedness, headache, insomnia, tinnitus, cough, nasal symptoms, altered taste, nausea, vomiting, abdominal pain or cramps, diarrhoea, rash, alopecia, arthralgia, muscle disorders, fatigue, malaise, fever and pain at the injections site. Other uncommon and rare side effects are neutropenia, anaemia, aplasia, neuropathy, pancreatitis and hepatitis.

4.9 Overdose:

In case of accidental overdose supportive measures should be initiated.

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 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.

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.

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 6 mlinutes, 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.

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; a-Dihydroartemisinin-ß-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.

Geno toxicity

Artesunate did not show any mutagenic or clastogenic potential in in vitro and in vivo tests (Ames, mouse micronucleus).Carcinogenesis

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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 6 mlg/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 included any excipients in formulation of sterile powder.

Solvent for reconstitution: Sodium Phosphates 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: 24 months

6.4 Special precautions for storage

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

The reconstituted solution should be used immediately.

6.5 Nature and contents of container

One vial of Artesunate Powder for injection 600 mg + 6 ml Ampoule of Sodium phosphates Injection USP in a monocarton along with leaflet.

6.6 Special precautions for disposal and handling

No special requirements

7. Marketing authorization holder and Manufacturing addresses:

Name of Applicant and manufacturer	INDASI LIFESCIENCE PVT. LTD (Formerly known as Bliss Indasi Lifescience Pvt. Ltd.)
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