**Summary of product characteristics for pharmaceutical products**

## 1.Name of the medicinal product

Indart-60 Plus

## 2.Qualitative and quantitative composition

Each Combipack contains:
One vial of Artesunate Injection
Each vial contains:

| | |
|---|---|
| Artesunate | 60 mg |

One 1 ml ampoule of Sodium Bicarbonate Injection BP
Each ml contains:

| | |
|---|---|
| Sodium Bicarbonate B.P | 5.0% w/v |
| Water for Injection BP | q.s. |

One 5 ml ampoule of Sodium Chloride Injection B.P.
Each ml contains:

| | |
|---|---|
| Sodium Chloride B.P. | 0.9% w/v |
| Water for Injection BP | q.s. |

## 3.Pharmaceutical form

A white crystalline powder distributed in sealed container

## 4.Clinical particulars

### 4.1 Therapeutic indications

INDART - 60 Plus 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:*

INDART - 60 Plus 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 Plus should be administered for a minimum of 24 hours (3doses).

*Reconstitution of INDART - 60 Plus Injection:*

Add 1 ml of the Sodium bicarbonate injection 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. The reconstituted Artesunate solution should always be used when clear, 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:

**Method of administration**

## 4.3 Contraindications

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, anemia, aplasia, neuropathy, pancreatitis and hepatitis.

## 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 Plus.

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 interaction

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 Fertility, pregnancy and lactation

Should be administered during pregnancy and lactation only if benefits outweigh the risk. Severe malaria during pregnancy is very hazardous; hence INDART - 60 Plus

## 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, anemia, aplasia, neuropathy, pancreatitis and hepatitis.

## 4.9 Overdose

In case of accidental overdose supportive measures should be initiated

# 5.Pharmacological properties

## 5.1 Pharmacodynamic properties

- Pharmacotherapeutic group: Antimalarial
- ATC Code: P01BE03

### Mechanism of action

Artesunate is a hemisuccinate derivative of Dihydroartemisnin, 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, Dihydroartemisnin (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 schizontes or merozoites.

Clinical efficacy and safety

In the SEAQUAMAT (South East Asian Quinine Artesunate Malaria Trial), an international randomised, open-label, multicentre 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,

Dihydroartemisnin (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 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.

<u>Distribution</u>

DHA has been shown to substantially accumulate in P. falciparum-infected erythrocytes. Plasma protein binding of Dihydroartemisnin 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, Dihydroartemisnin, 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-Dihydroartemisnin-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.

*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 included any excipients in formulation.
Solvent for reconstitution: Sodium bicarbonate & Sodium Chloride

## 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 in a cool and dry place, store below 30°C. Protect from light. Do not refrigerate or freeze.
Keep out of reach of children.
The reconstituted solution should be used immediately

## 6.5 Nature and contents of container

One vial of Artesunate Powder for injection 60 mg + 1 ml Ampoule of 5.0% w/v Sterile Injection of Sodium Bicarbonate and 5 ml Ampoule of 0.9% w/v Sterile Injection of Sodium Chloride in a carton along with leaflet.

## 6.6 Special precautions for disposal and other handling

Food, drug, devices and cosmetics act prohibits dispensing without prescription.

## 7.Marketing Authorization Holder

Indasi Lifescience Pvt. Ltd
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## 8. Marketing Authorization Number

CTD9422

## 9.Date of first authorization/Renewal of the authorization

29/06/2023

## 10.Date of revision of the text

16/05/2023