SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product

Azunate (Artesunate Powder for Injection Ph .Int 60 mg)

2. Qualitative and Quantitative Composition

Each vial contains:

Sterile Artesunate Int. Ph . 60mg

Each ampoule of solvent contains:

Sodium Bicarbonate USP 50mg/ml,

1ml Each ampoule of diluent contains: Sodium Chloride 9 mg/ml, 5ml

For Excipients see point 6.1

3. Pharmaceutical Form

Aretsunate for Injection:

White powder

Solvent (sodium bicarbonate):

Clear colourless solution Diluent (sodium chloride): Clear colourless solution

4. Clinical Particulars

4.1 Therapeutic indications

Artesunate 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

Dose:

Adults and children weighing more 20 kg or more: Artesunate 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: Artesunate 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.

Artesunate 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, 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

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 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.

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. 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 required will be equal to:

$$\frac{\text{(desired dose in mg)}}{10}\ \text{ml}$$

Withdraw the required volume of artesunate solution from the vial with a syringe and then inject slowly intravenously, over 1-2 minutes.

Artesunate 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 the reconstituted artesunate solution. This will yield 3 ml of a solution containing artesunate 20 mg/ml. 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 required will be equal to: $\frac{\text{(desired dose in mg)}}{20}$ ml

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.

Hepatic and renal impairment:

Dose adjustment is not necessary in patients with hepatic or renal impairment.

4.3 Contraindications

The drug is contraindicated in patients with prior hypersensitivity to artesunate or artemisinin derivatives.

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 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. Relevant treatment guidelines should be consulted (e.g. those of the WHO).

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.

Post-treatment haemolytic anaemia: Delayed haemolytic anaemia following treatment with injectable artesunate has been observed in children in malaria endemic areas and in non-immune travellers presenting with severe falciparum malaria. The risk was most pronounced in patients with hyperparasitaemia and in younger children. Some cases have been severe and required blood transfusion. Vigilance for delayed onset anaemia is therefore advised, particularly in hyperparasitaemic patients and younger children, and prolonged follow-up should be considered (e.g. 14-28 days). As the overall benefit-risk ratio remains highly favourable for injectable artesunate in the treatment of severe malaria, WHO strongly recommends its continued use.

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 Pregnancy and Lactation

Pregnancy:

Severe malaria is especially hazardous during pregnancy, therefore full dose parenteral antimalarial treatment should be administered without delay.

In animal studies, artesunate has been associated with foetal toxicity during the first trimester of pregnancy. Limited clinical experience with the use of artesunate

in the first trimester of pregnancy as well as clinical data from more than 4,000 pregnant women, treated with artemisinin derivatives in the second and third trimester, do not indicate adverse effects of artesunate on pregnancy or on the health of the fetus/newborn child.

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.

Fertility:

No specific studies with artesunate in humans have been conducted to evaluate effects on fertility. In a reproduction toxicity study in rats, testicular and epididymal lesions were seen, but there were no effects on fertility. The relevance of this finding for humans is unknown.

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, 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.

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 Post-treatment anaemia:

Cases of delayed haemolytic anaemia have been identified in non-immune travellers following treatment of severe malaria with injectable artesunate. Some were severe and required blood transfusions. In a study in African children aged 6 months to 10 years of age in malaria endemic areas, 5 out of 72 children (7%) experienced delayed haemolytic anaemia following treatment with injectable artesunate, and one child required transfusion. Risk was increased with hyperparasitaemia in all age groups and with younger age in children. Onset of haemolysis and anaemia was evident by 14-28 days after artesunate treatment. Vigilance for this adverse event is advised.

Paediatric *population:*

The safety profile of injectable artesunate is similar in children and adults.

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.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

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 schizontes 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 (t½) 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 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 (t_{max}) and t½ 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 t1/2 values were estimated to be 48 minutes in children and 41 minutes in adults, and C_{max} values were 1.7 and 2.3µmol/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. A study of artesunate administered to male rats daily for 6 weeks noted testicular and epididymal lesions, although these lesions did not affect fertility. The lesions were

reversible after cessation of treatment.

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

Artesunate powder for injection: no
excipients Solvent: sodium bicarbonate and
disodium edetate Diluent: sodium chloride
and water for injection

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

Do not store above 30°C in dry place protected from light. Do not refrigerate or freeze and for single use only. Discard unused portion.
The reconstituted and diluted solutions should be store below 30°C and to be use with 1 hour.

6.5 Nature and contents of container

Azunate: Sterile white powder, 60 mg Solvent (sodium

bicarbonate): Sterile clear colourless solution, 50 mg/ml, 1 ml. Diluent (sodium chloride): Sterile clear colourless solution, 9 mg/ml, 5 ml. A plastic tray containing one vial of artesunate for injection, one ampoule of sodium bicarbonate injection (solvent) and one ampoule of the sodium chloride injection (diluent) in a carton.

6.6 Special Precaution for disposal

None.

7. Marketing authorization holder and manufacturing site addresses

Macleods Pharmaceuticals Ltd.
304, Atlanta Arcade, Marol Church
Road, Andheri (East), Mumbai- 400
059, India

8. Marketing authorization number

H2021/CTD8313/16637

9. Date of first Prequalification/ last renewal

September 2021

10. Date of Revision of the Text: