1. NAME OF THE MEDICINAL PRODUCT

AKENART 120MG: Artesunate for Injection & Sodium Bicarbonate Injection BP & Sodium Chloride Injection BP (Combipack)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sr. No.	Ingredient	Specification	Label Claim	Qty./Batch in kg	Reason on Inclusion
1.	Artesunate	IH	120 mg	1 kg*	Active

IH: In-House Method

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. Consideration should be given to official treatment guidelines for malaria.

4.2 Posology and method of administration

Dose:

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

Children weighing less than 20 kg: **Artesunate for Injection 120 mg** 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.

Method of administration

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. Relevant treatment guidelines should be consulted when selecting an appropriate regimen.

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 2 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 (10 mg/ml)

Using a syringe, add 10 ml of sodium chloride 0.9% for injection to the vial containing the reconstituted artesunate solution. This will yield 12 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 of the solution required (ml) will be:

$$\text{Volume (ml)} = [\text{dose (mg)}] \div 10$$

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

Artesunate for Injection 120 mg should NOT be administered as an intravenous drip.

For intramuscular (IM) injection (20 mg/ml)

Using a syringe, add 4 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 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 of the solution required (ml) will be:

$$\text{Volume (ml)} = [\text{dose (mg)}] \div 20$$

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

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 malaria or Plasmodium ovale.

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**. Relevant treatment guidelines should be consulted such as those of the WHO and public health authorities.

Post-treatment haemolyticanaemia

Delayed haemolytic anaemia following treatment with injectable artesunate has been observed in

children in malaria endemic areas and in non-immune travelers 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. Given the persistent uncertainties regarding the risk of delayed hemolysis, a minimum follow-up should be strictly observed until day 28.

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 artesunate treatment should be administered at any stage of pregnancy without delay.

In animal studies, artesunate has been associated with fetal 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 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. In addition, an

observational study conducted in 1179 pregnant women with first-trimester falciparum malaria (of which 183 were treated with first line artemisinin derivatives) showed no differences in the risk of miscarriage or major congenital malformation in artemisinins derivatives versus quinine treatment.

Breast-feeding

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 (estimated risk approximately 1 in 3000 patients), which has involved urticarial rash as well as other symptoms, including hypotension, pruritus, oedema, and/or dyspnoea. A potentially serious delayed hemolysis (Post-Artesunate Delayed Hemolysis, PADH) has been reported frequently in travellers and in children. See below.

More common minor side effects associated with IV administration have included dizziness, light-headedness, rash, and taste alteration (metallic/ bitter taste). Transient elevation in liver transaminases, nausea, vomiting, anorexia and diarrhea have also been commonly reported, however it is uncertain whether such events may 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

Very common: Post-treatment haemolytic anaemia in travellers, mild and transient decrease in reticulocyte count.

Common to very common: Post-treatment haemolytic anaemia in endemic areas

Uncommon: Neutropenia and anaemia (both occasionally severe), thrombocytopenia, agranulocytosis, reticulocytopenia, erythroblastopenia

Very rare: Pure red cell aplasia

Nervous system disorders

Common: Dizziness, light-headedness, headache, insomnia, tinnitus (with or without decrease in auditory function) Very rare: Peripheral neuropathy (or paraesthesia)

Cardiovascular disorders

Uncommon: Rhythm and conduction disorders. Some cases of cardiac adverse events and particularly rhythm (bradycardia, sinus arrhythmia) and conduction disorders (QTc lengthening, abnormal sinoatrial conduction) have been recently described. One case of cardiac arrest has been reported in a context of severe malaria with multi-organ failure but the causality by Artesunate has not been established. Whether or not cardio-vascular events should be attributed to artesunate or to severe malaria is not known, but considering that other artemisinin derivatives (arthemeter, arteether) have been associated with QT prolongation in pre-clinical data, EKG should be monitored before and during treatment, especially in patients with a history of cardiovascular impairment or having risk factors.

Rare: Arterial ischemia, hypertensive retinopathy

Respiratory disorders Common: Cough and/or nasal symptoms.

Gastrointestinal disorders Common: Altered taste, nausea, vomiting, abdominal pain or cramps, diarrhea.

Rare: Raised serum amylase, pancreatitis.

Hepatobiliary disorders

Uncommon: Transient rises in liver transaminases (AST, ALT).

Rare: Hepatitis, calculous cholecystitis.

Respiratory disorders.

Common: Cough and/or nasal symptoms.

Gastrointestinal disorders

Common: Altered taste, nausea, vomiting, abdominal pain or cramps, diarrhea.

Rare: Raised serum amylase, pancreatitis.

Hepatobiliary disorders.

Uncommon: Transient rises in liver transaminases (AST, ALT).

Rare: Hepatitis, calculous cholecystitis.

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-Artesunate Delayed Hemolysis (PADH)**

A delayed hemolysis was detected in prospective studies with a frequency ranging from 7 to 27% of patients treated with artesunate. This adverse event has been observed both in travelers (15%) and among young African children (7-22%) in cases of severe malaria. The best-known cases of delayed haemolysis have been reported in travelers (including non-immune tourists and "visiting friends and relatives" persons). The pathophysiology of this phenomenon has not been fully elucidated but may include various combinations of delayed destruction of different subpopulations of erythrocytes and an immune-mediated etiology. All patients treated with parenteral artesunate should be followed for at least 4 weeks to detect signs of hemolysis anJd enable appropriate treatment.

Background

Definition: The current definition of PADH is the association of a drop-in hemoglobin levels of more than 10% and a rise in lactate dehydrogenase levels greater than 10 %, both occurring more than 8 days after starting treatment with artesunate.

Incidence: Reported incidence ranges between 0% and 63 %. A recent systematic analysis (Roussel et al, 2017) found 15.3% (74/485) of patients to be affected by delayed hemolysis. Exactly half of PADH patients with available data were transfused (27/54 patients). Assessment in the single prospective study available so far (Jaureguiberry et al, 2015) reported that 27% (21/78) of patients with follow-up data beyond Day 8 had PADH per the current definition. The nadir (lowest value) in hemoglobin during follow-up was lower than 7 g /dL in 15% of patients with PADH. One

of those patients required a transfusion. No sequelae or death have been reported in patients with PADH so far, but in one report in an endemic area (Plewes et al, 2015) a patient had acute renal insufficiency probably related to the acute hemolytic event with hemoglobinuria , and one African child had coma probably related to PADH (Rolling et al, 2014). Delayed hemolytic episodes have not been reported in Phase 3 clinical trials in endemic areas possibly due to the lack of precise follow-up between Day 3-7 and Day 28 in these trials. An incidence of PADH of 7% was observed in a prospective study of 72 African children treated with artesunate for severe malaria. Parameters associated with PADH were younger age and higher initial parasitemia. PADH affected 11.4% of patients (children and adults) in the Democratic Republic of Congo. All episodes resolved rapidly. The impact of the declining incidence of malaria and waning antimalarial immunity in endemic countries on the incidence and impact of PADH is not known, although these parameters have an influence on the mechanism of parasite clearance, related itself to the mechanism of PADH.

Impact: PADH and other post-artesunate hemolytic episodes almost invariably resolve in less than a few weeks, often in a few days. Transfusion indication is per current standard of care. Whether long term sequelae occur in a small proportion of patients is not known. The overall risk/benefit remains highly favourable for injectable artesunate, with a large mortality advantage over quinine. WHO strongly recommends continued use of artesunate for severe malaria.

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 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 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.

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 parasitaemia >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. Post-treatment hypoglycaemia was more common in the quinine-treated group.

Paediatrics

The AQUAMAT (African Quinine Artesunate Malaria Trial) was an international, randomized open-label multicenter trial which sought to extend the results of the SEAQUAMAT study by comparing parenteral artesunate versus IV quinine for severe malaria in 5425 African children (< 15 years) in 9 African countries (Mozambique, The Gambia, Ghana, Kenya, Tanzania, Nigeria, Uganda, Rwanda, and Democratic Republic of the Congo). Dosing was similar to SEAQUAMAT, except that both artesunate and quinine could be administered either intravenously or intramuscularly, using the same doses for IM and IV administration for each drug. Roughly one third of patients received study drug by intramuscular injection. Mortality in the artesunate group was 8.5% compared to 10.9% in the quinine group, resulting in a relative risk reduction for death of 22.5% (p=0.0022); the risk reduction was similar for IV and IM administration. In addition, although the risk of neurological sequelae in survivors in both groups did not differ significantly by 28 days following treatment, in-hospital coma, convulsions, and deterioration of coma were all less frequent in the artesunate-treated patients. As in the SEAQUAMAT, post-treatment hypoglycaemia was more common in the quinine-treated group.

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 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 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 -lucuronide 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, rare occurrences of moderate hepatotoxicity (4%)

were reported, with regression in 100% of cases without sequelae. Hematopoietic toxicity on the red and white line is responsible for reticulocytopenia and leucopenia of central origin. The toxicity appears to be on the progenitors of the erythroid lineage. There is also a negative effect on the phagocytosis capacities of neutrophils and inhibition of lymphocyte proliferation (in vitro).

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.

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

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 below 30°C in a dry place. Protect from light and moisture.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

15 ml Clear vial with 20 mm Gray Butyl Rubber Stopper and 20 mm Flip of Aluminium Seal Cap. 1 Sticker labelled Vial packed in PVC Tray with 2 ml Sodium Bicarbonate, 10 ml Sodium Chloride. 1 PVC Tray Packed in 1 Mono Carton with leaflet

6.6 Special precautions for disposal and other handling

No special requirements.

7. MANUFACTURER

MONTAGE LABORATORIES PVT. LTD.

AT: Dhandha, Idar Road, Himatnagar-383001

Sabarkantha, Gujarat, India.