1.3.1 Summary of Product Characteristics (SmPC)

1. Name of Medicinal Product

MERONATE 60

Combi Pack Of Artesunate Injection ,Sodium Bicarbonate Injection BP And Sodium Chloride Injection BP

2. Qualitative and Quantitative Composition

Each Combi pack Contains

a) Artesunate Injection 60 mg

Each vial contains:

Artesunate 60 mg

b) Sodium Bicarbonate Injection BP 5.0% w/v

Each ml contains:

Sodium Bicarbonate BP 5%w/v

Water for Injection BP qs

Bicarbonate & Sodium Concentrate 595 millimoles/Litre

c) Sodium Chloride Injection BP 0.9% w/v

Each ml contains:

Sodium Chloride BP 0.9%w/v

Water for Injection q.s.

Excipients with Known effect:

Sodium Bicarbonate BP

Water for injection BP

Sodium chloride BP

3. Pharmaceutical Form

Solution for Injection

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: 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. 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

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) 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 either 5% glucose for injection or 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: (desired dose in mg) ml 10

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 either 5% glucose for injection or 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: (desired dose in mg) ml 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 is contraindicated in patients with hypersensitivity to artesunate or other artemisinins.

4.4 Special warnings and precautions for use

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

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.

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

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 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 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.It is not known whether amikacin is excreted in human milk. A decision should be made whether to discontinue breast-feeding or to discontinue therapy.

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.

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. 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. 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 (1/10000–1/1000), 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 haemolytic anaemia,*, mild and transient decrease in reticulocyte count.

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

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, openlabel, 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.

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. 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

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-βglucuronide 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

Efferth T, Kaina B. Toxicity of the antimalarial artemisinin and its derivatives Critical Reviews in Toxicol 2010;40:405-421. Centers for Disease Control and Prevention (CDC). Intravenous artesunate for severe malaria 2008: Investigator's Brochure, IND #64,769. 1-165.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sodium Bicarbonate BP

Water for injection BP

Sodium chloride BP

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C. Protect from light & moisture.

6.5 Nature and contents of container

A. 7.5 ml clear glass vial of Artesunate for Injection

B. 1 ampoule for sodium bicarbonate injection.

C. 5 ml Ampoule for sodium chloride injection

6.6 Special precautions for disposal and other handling

Keep out of reach of children.

7 APPLICANT/MANUFACTURER

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