1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. NAME OF THE MEDICINAL PRODUCT:

Artesunate for Injection 120 mg

(JAWA ARTESUNATE)

1.1 STRENGTH

120 mg/vial

1.3 PHARMACEUTICAL FORM

Powder for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 QUALITATIVE DECLARATION

Artesunate

2.2 QUANTITATIVE DECLARATION

Each vial contains:

Artesunate.....120 mg

3. PHARMACEUTICAL FORM

Powder for Injection

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Artesunate Injection is 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

Artesunate injections are for intravenous or intramuscular use. The usual dose of artesunate is 60 mg daily. The first dose is doubled. The usual duration of the treatment is for 5 to 7 days. The total dose is 360 mg -480 mg for adult. for children the recommended dose is 1.2 mg/kg.

If patient is infected with high parasitaemia (RBC infection> 10%) an additional dose of 60mg should be given after 4-6 hours of first dose of 120 mg.

The usual duration of treatment is 5 days. The recrudescence rate is < 10% in chloroquin resistant areas. The duration of treatment is 7 days in very serious and nonimmune patients. Before administration artesunate powder is mixed with 1 ml of 5% sodium bicarbonate and shaken for 2-3 minutes. After it dissolves completely and solution becomes clear, air is eliminated from the vial with syringe and needle. For i.v. use add 5 ml (and for i,m. use add 2 ml) of 0.9% sodium chloride injection to make final concentration of 10 mg / ml of artesunate (i.m. 20mg/ml). For iv. use the required amount of drug is administered slowly at a rate of 3-4 mI / minute.

It should be injected immediately after the powder of artesunste disolves. If the solution appears cloudy or sediment occurs it should not be used. It should not be used as intravenous infusion.

4.3 CONTRAINDICATIONS

Artesunate Injection 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 malariae or Plasmodium ovale.

Switching to oral treatment regimen

Acute treatment of severe falciparum malaria with Artesunate Injection 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 Injection.

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.

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.

There has been limited clinical experience with the use of artesunate in pregnancy. In animal studies, artesunate has been associated with foetal toxicity during the first trimester of pregnancy. To date, clinical data regarding safety in the first trimester have not indicated an increased risk of foetal harm.

Treatment with artesunate should not be withheld during the first trimester if it is potentially lifesaving for the mother. As in other populations, the evidence that artesunate reduces the risk of death from severe malaria compared to other treatments should be borne in mind.

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.

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, prutitus, edema, and/or dyspnoea.

More common minor side effects associated with IV administration have included dizziness, lightheadedness, 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

(1/1001/10), uncommon (1/10001/100), rare (1/10 0001/1000), 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 (see below), 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

4.9 OVERDOSAGE AND TREATMENT

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, multiorgan failure and death.Treatment of overdose should consist of general supportive measures.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antimalarials,

ATC code: P01BE03

Mode 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.

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-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.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

None

6.2 INCOMPATIBILITIES

None stated.

6.3 SHELF LIFE

36 Months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Protect from light.

KEEP OUT OF THE REACH OF CHILDREN

6.5 NATURE AND CONTENTS OF CONTAINER

10 ml plain glass vial of Artesunate Injection 120 mg, With 2 ml Sodium Bicarbonate injection BP 5% w/v & 10 ml Sodium Chloride Injection BP 0.9% w/v packed in a carton along with an insert.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Not Applicable

7.0 APPLICANT/MANUFACTURER

MARKETED BY:

JAWA INTERNATIONAL LTD.

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