1. Name of the Medicinal Product

Berlin Artesunate Injection 120 Mg

2. Qualitative and Quantitative Composition Each vial contains: Sterile Artesunate 120 mg The Pack contains:

2 ml ampoule of Sodium Bicarbonate Injection BP 5 % w/v

10 ml ampoule of Sodium Chloride Injection BP 0.9 % w/v

3. Pharmaceutical Form

Dry Injection

4. Clinical Particulars

4.1 Therapeutic indications

For killing the erythrocytic stage

of plasmodium asexual form. It is effective to malaria caused by chloroquine resistant stain of plasmodium falciparum. It can quickly and reliably control the acute attack of malaria. It is suitable to salvage the patients with pernicious malaria and treat P. falciparum malaria and P. vivax malaria. Artesunate Injection is indicated for the treatment of serious malaria infections and the patients with cerebral malaria.

4.2 Posology and method of administration

Dosage and Administration

Artesunate for Injection (120 mg/vial)

It should be administered in a dose of 120 mg via intra-muscular or intravenous infusion, once daily for 5-7 days for a course. Double the first dose! Total doses are 360-480 mg for adults. The vial of Artesunate powder should be mixed with 1 ml of 5% sodium biocarbonate solution (provided) and shaken 2-3 minutes for better dissolution.

Add 5 ml of 5% glucose or normal saline to make the concentration of Artesunate in 10 mg/ml for slow intravenous infusion.

Add 2 ml of 5% glucose or normal saline to make the concentration of Artesunate in 20 mg/ml for intra-muscular injection!

Doses for Children: 1.2mg/kg for children.

Falciparum malaria

Adult: 2.4 mg/kg via IM or IV admin. Repeat 12 hr and 24 hr later, then once daily thereafter.

Child: 2.4 mg/kg via IM or IV admin. Repeat 12 hr and 24 hr later, then once daily thereafter.

4.3 Contraindications

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

4.4 Special warning and special precaution for use

Avoid in pregnant woman, especially in the first trimester.

Paediatrics: May be used if chloroquine resistant.

4.5 Interaction with other medicinal products and form 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 life-saving 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.

In a study of 461 pregnant Thai women (44 in their first trimester) who were treated with artemisinins (predominantly artesunate), there was no obvious evidence of adverse effects amongst the 414 women for whom pregnancy outcomes were known. The observed rates of

abortion, stillbirth, congenital anomalies and low birth weight were comparable to community rates.

In clinical trials from 1999 to 2006, 2,045 pregnant women in Thailand, the Gambia, and Sudan were treated with artesunate, either alone or in combination with other antimalarials, including quinine, mefloquine, atovaquone-proguanil and sulfadoxinepyrimethamine. In these patients, most of whom were in their second or third trimesters of pregnancy, there were no significant differences compared to the general community in birth weights, duration of gestations, placental weights, or rates of congenital abnormalities, or in growth and developmental parameters of infants monitored for one year.

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

Transient and reversible reticulocytopaenia, drug fever, rash, bradycardia, transient 1st-degree heart block and reversible elevation of serum transaminases.

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 7fold 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

Artesunate has an excellent anti-malarial activity on the asexual forms of malaria parasites with high, quick efficiency to bring about rapid control of an acute attack. It has advantages of no cross resistance to Chloroquine.

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 2.3 µmol/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.

6.0 PHARMACEUTICAL EXCIPIENTS

6.1 List of excipients

Not applicable

6.2 Incompatibilities None known

6.3 Shelf life

2 years

6.4 Special precaution for storage Store in a cool place.

Protect from light.

6.5 Nature contents of container 20 ml glass vial

2 ml glass ampoule

10 ml glass ampoule

6.6 Instruction for use handling and disposal

Keep out of reach of children.

7. Applicant:

Berlin Pharma & Healthcare Ltd, Comfort Oboh, Kirikiri Estate, Amuwo Odofin, Amuwo, Lagos.

Manufacturer:

ALPHA LABORATORIES LTD, 32/2,A.B ROAD, PIGDAMBER -453 446 INDORE, INDIA.