PROFESSIONAL INFORMATION FOR HUMAN USE

ARTESUNATE 60 MG

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Artesunate 60 mg Cospharm (powder for solution for injection).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains: Artesunate Powder 60 mg powder for solution.

Each ampoule of solvent contains: Sodium Bicarbonate 5 % w/v (50 mg/mL), 2 mL.

Each ampoule of diluent contains: Sodium Chloride 0,9 % (9 mg/mL), 5 mL.

For a full list of excipients, see section 6.1.

Sugar free.

3 PHARMACEUTICAL FORM

A fine, white crystalline powder.

Artesunate 60 mg Cospharm: Vial 5 mL Clear, Colourless (USP Type I) with rubber stopper 20 mm grey bromobutyl and flip off seal.

Sodium Bicarbonate 5 % w/v solvent for Artesunate 60 mg: Ampoule 2 mL. Clear with white ring (USP Type I).

Sodium chloride 0,9 % w/v diluent for Artesunate 60 mg: Ampoule 5 mL. Clear with white ring (USP Type I).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of severe malaria caused by *Plasmodium falciparum* in adults and children.

4.2 Posology and method of administration

Dose:

Severe malaria is a medical emergency and treatment should be started without <u>any</u> delay.

Adults and children

Artesunate 60 mg Cospharm is administered at a dose of 2,4 mg of artesunate/kg body weight, by intravenous (IV) injection, at 0,12 and 24 hours, then once daily until oral treatment can be substituted. Artesunate 60 mg Cospharm 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 60 mg Cospharm and when able to tolerate oral medication, the patient should be put on a complete treatment course with a combination of appropriate antimalarial medicines (see section 4.4).

Method of administration

For intravenous or intramuscular injection use only.

4.3 Contraindications

Known hypersensitivity to artesunate or other artemisinins or to any other of the excipients of Artesunate 60 mg Cospharm listed in section 6.1.

4.4 Special warnings and precautions for use

Severe malaria is a medical emergency and treatment must be started without any delay.

Non-falciparum Malaria

Artesunate 60 mg Cospharm has not been evaluated in the treatment of severe malaria due to *Plasmodium vivax, Plasmodium malariae, Plasmodium ovale.*

Switching to oral treatment regimen

Acute treatment of severe falciparum malaria with Artesunate 60 mg Cospharm should always be followed by a complete treatment course of an appropriated oral combination antimalarial regimen (see section 4.2).

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 60 mg Cospharm. Relevant treatment guidelines should be consulted.

There is a risk of neurological sequelae, e.g. convulsions associated with treatment with Artesunate 60 mg Cospharm. Severe malaria may cause hypoglycaemia and frequent monitoring of blood glucose is necessary.

Post-treatment anaemia

Post-artesunate delayed haemolysis is characterized by decreased haemoglobin with laboratory evidence of haemolysis (such as decreased haptoglobin and increased lactate dehydrogenase) occurring at least 7 days after initiating artesunate treatment.

Transient decreases in reticulocyte counts and cases of post-treatment haemolytic anaemia severe enough to require transfusion have been reported up to 3 months after the use of Artesunate 60 mg Cospharm (see section 4.8).

Monitor patients for 4 weeks after treatment with Artesunate 60 mg Cospharm for evidence of haemolytic anaemia.

Since a subset of patients with delayed haemolysis after artesunate therapy have evidence of immune-mediated haemolysis, consider performing a direct antiglobulin test to determine if therapy, e.g. corticosteroids, are necessary.

The etiology of haemolysis remains unknown.

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 (see section 5.2), dosage adjustment is not considered necessary in patients with hepatic or renal impairment.

The vital signs of patients including level of consciousness, temperature, blood glucose, haemoglobin, acid-base status, blood coagulation status, renal and hepatic function should be regularly monitored.

Paediatric population

In clinical trials, the efficacy and safety of intravenous and intramuscular artesunate have been similar in adult and paediatric populations.

Hypersensitivity

Hypersensitivity to artesunate including cases of anaphylaxis have been reported during the use of parenteral artesunate.

If hypotension, dyspnoea, urticaria, or generalized rash occurs during administration of this product, consider discontinuing Artesunate 60 mg Cospharm administration and continuing therapy with another antimalarial drug.

Excipients

This medicinal product contains sodium.

For Intravenous (IV) Injection (10 mg/mL)

This medicinal product contains 31,40 mg (1,365 mmol) sodium per one injection (prepared by dissolving 60 mg artesunate in 1 mL sodium bicarbonate (50 mg/mL) injection and diluting this with 5 mL (9 mg/mL) sodium chloride), is equivalent to 1,6 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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

This medicinal product contains 20,77 mg (0,903 mmol) sodium per one injection (prepared by dissolving 60 mg artesunate in 1 mL sodium bicarbonate (50 mg/mL) injection and diluting this with 2 mL (9 mg/mL) sodium chloride), is equivalent to 1,06 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

Data on interactions between Artesunate 60 mg Cospharm and other medicines are limited.

There are limited data on the treatment of malaria in HIV-infected patients.

Few clinical drug-drug interaction studies have been performed, however no clinically significant interactions have been identified. An increase in plasma concentrations of artesunate was observed with nevirapine and a reduced plasma concentration of dihydroartemisinin was observed when artesunate is given with ritanovir.

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 minutes) and the potential for drug-drug interactions appears limited. *In vitro* drug-interaction studies have demonstrated minimal effects of artesunate on cytochrome P450 isoenzymes.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety and efficacy of Artesunate 60 mg Cospharm in pregnancy have not been established.

There are serious risks to the mother and foetus associated with untreated severe malaria during pregnancy; delaying treatment of severe malaria in pregnancy may result in serious morbidity and mortality to the mother and foetus, therefore full dose parenteral artesunate treatment should be administered at any stage of pregnancy without delay.

Embryotoxicity (foetal resorption) and deformities were observed in animal studies. In animal studies, artesunate has been associated with foetal toxicity during the first trimester of pregnancy.

Animal reproduction studies show that a single intravenous administration of artesunate to rats early in gestation results in embryolethality.

Treatment of severe life-threatening malaria in pregnancy are only indicated when other safer anti-malarial medicines are not available or inappropriate.

Lactation

The active metabolite of Artesunate 60 mg Cospharm namely dihydroartemisinin, is present in low levels in breast milk.

Mothers on treatment with Artesunate 60 mg Cospharm should not breastfeed their infants.

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

No studies on the effects on the ability to drive and use machines have been performed. The patient's clinical status should be considered when assessing ability to drive and operate machines.

4.8 Undesirable effects

Severe allergic reactions with an urticarial rash, hypotension, pruritus oedema, and/or dyspnoea have been reported less frequently.

Frequent side effects associated with IV administration~~s~~ have included dizziness, light-headedness, rash, and taste alteration (metallic/ bitter taste).

Nausea, vomiting, anorexia and diarrhoea have also been reported, however it is uncertain whether such events have been symptoms of severe malaria.

Side effects considered at least possibly related to artesunate are listed below by body system, organ class.

Blood and lymphatic system disorders:

Less frequent: neutropenia and anaemia (both occasionally severe), thrombocytopenia, pure red cell aplasia.

Frequency unknown**:** post-treatment haemolytic anaemia (see below), mild and transient decrease in reticulocyte count.

Immune system disorder:

Less frequent: hypersensitivity, Stevens-Johnson syndrome, anaphylaxis.

Nervous system disorders:

Frequent: dizziness, light-headedness, headache, insomnia, tinnitus (with or without decrease in auditory function), convulsions, dysgeusia.

Frequency unknown: peripheral neuropathy (or paraesthesia).

Respiratory, thoracic, and mediastinal disorders:

Frequent: cough, nasal symptoms.

Gastrointestinal disorders:

Frequent: altered taste, nausea, vomiting, abdominal pain or cramps, diarrhoea.

Less frequent: raised serum amylase, pancreatitis.

Hepato-biliary disorders:

Less frequent: transient rises in liver transaminases (AST/ALT)**,** hepatitis.

Skin and subcutaneous tissue disorders:

Frequent: rash, alopecia, urticaria.

Musculoskeletal and connective tissue disorder:

Frequent: arthralgia, muscle disorders.

General disorders and administration site conditions:

Frequent: fatigue, malaise, fever, pain at injection site.

****Post-treatment anaemia***

Cases of delayed haemolytic anaemia have been reported in non-immune travelers 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

Healthcare providers should also report adverse reactions to the Holder of Certificate of Registration, Cospharm Investments (Pty) Ltd.

The contact details for our national reporting system are:

Email: rp@cospharm.org

4.9 Overdose

Experience of acute overdose with artesunate is limited.

Treatment of overdose should be symptomatic and should consist of general supportive measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.2.6 Medicines against protozoa.

Pharmacotherapeutic group: Antimalaria, ATC code: P01BE03

Artesunate is a hemisuccinate derivative of dihydroartemisinin, which is extracted from ging hao (sweet wormwood, artemisia annua L plant) and used to treat malaria caused by *Plasmodium falciparum.*

The mechanism of action of artesunate involves cleavage of the internal endoperoxide bridge through reaction with haeme within the *Plasmodium falciparum*-infected erythrocyte, thereby generating free radicals which alkylate vital parasite proteins. However, artesunate has also been reported to inhibit an essential parasite calcium adenosine triphosphate.

Artesunate kills all erythrocytic stages of the *Plasmodium falciparum* malaria parasite, including the relatively inactive ring stage and late schizonts, as well as the gametocytes responsible for malaria transmission. Artesunate is a rapidly acting antimalarial that has also been shown to enhance splenic clearance of infected *Plasmodium falciparum* 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 is inactive against extra-erythrocytic forms sporozites, liver schizontes or merozoites.

5.2 Pharmacokinetic properties

Intravenous

After intravenous injection artesunate is rapidly biotransformed to its active metabolite, DHA. Consequently, artesunate half-life ($t_{1/2}$) is estimated to be less than 15 minutes after a single IV dose of 2,4 mg/kg. Peak concentrations (C_{max}) of DHA are observed within 25 minutes (T_{max}) of artesunate IV administration with a half-life ranging from 30-60 minutes.

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, DHA, accounts for most of the *in vivo* antimalarial activity of oral artesunate, however, following IV administration, artesunate may contribute more significantly. DHA is further metabolised in the liver via glucuronidation and is excreted in the urine, a- dihydroartemisinin-β-glucuronide has been identified as the major urinary product in patients with *falciparum malaria.*

Special Populations

No pharmacokinetic data are available for patients with impaired renal or hepatic function.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Artesunate powder for injection: No excipients.

Solvent: Sodium bicarbonate and water for injection.

Diluent: Sodium chloride and water for injection.

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

36 months.

After reconstitution: the total in-use period should not exceed 1 hour.

6.4 Special precautions for storage

Store at or below 30 °C. Protect from light.

Do not refrigerate or freeze.

The reconstituted solution should be stored at or below 30 °C and should be used within 1 hour of preparation.

6.5 Nature and contents of container

Product: Artesunate 60 mg Cospharm is packed in 5 mL clear vials fitted with rubber stopper.

The stopper used for Artesunate 60 mg Cospharm is 20 mm Grey Bromobutyl RFU Sterile Rubber stopper.

Diluent: Sodium Chloride 0.9 % w/v for Artesunate 60 mg is packed in 5 mL clear ampoules.

Solvent: Sodium Bicarbonate 5 % w/v is packed in 2 mL clear ampoules.

Pack size: A box containing one vial of Artesunate powder for injection, one ampoule of Sodium Bicarbonate injection and one ampoule of Sodium Chloride injection.

6.6 Special precautions for disposal and other handling

Parenteral medicines should be inspected visually for particulate matter and discoloration prior to administration.

Preparation

Because of the instability of the medicine 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 60 mg Cospharm needed should be determined prior to reconstituting the powder.

Reconstitution of the artesunate solution

Using a syringe, withdraw the supplied sodium bicarbonate solvent from the ampoule and inject into the vial containing the artesunate powder. Shake the vial for several minutes to mid 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 the either the supplied sodium chloride 0,9 % for injection solvent or the same volume of 5 % glucose for injection to the vial containing the reconstituted artesunate solution. This will yield 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)/10 mL. Withdraw the required volume of artesunate solution from the vial with a syringe and then inject slowly intravenously, over 1-2 minutes.

Artesunate 60 mg Cospharm **should not be administered as an intravenous infusion.**

Do not use water for injection for reconstitution of the artesunate powder or for dilution of the resulting solution prior to injection.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Cospharm Investments (Pty) Ltd

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Johannesburg, Gauteng, 2191

8 REGISTRATION NUMBER(S)

55/20.2.6/0742

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 December 2023

10 DATE OF REVISION OF THE TEXT

21 March 2025