PACKAGE INSERT FOR GARSUN

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

GARSUN (powder and solvent for solution for injection)

COMPOSITION

Each vial contains 60 mg artesunate.

Excipients

No excipients are included in the powder formulation.

Solvent: 5 % Sodium Bicarbonate Solution for Injection (50 mg/ml)

Diluent: 0,9 % Sodium Chloride Solution for Injection (9 mg/ml)

PHARMACOLOGICAL CLASSIFICATION

A 20.2.6 Medicines against protozoa

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Artesunate is a hemisuccinate derivative of dihydroartemisinin, which is extracted from qing 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 triphosphatase.

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 cyto-adherence.

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, sporozoites, liver schizontes or merozoites.

Pharmacokinetic properties

Intravenous

After intravenous injection artesunate is rapidly biotransformed to its active metabolite, DHA. Consequently, artesunate half-life (t½) 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; 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.

INDICATIONS

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

CONTRAINDICATIONS

Known hypersensitivity to artesunate or to any of the excipients of **GARSUN**.

WARNINGS AND SPECIAL PRECAUTIONS

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

Non-falciparum malaria

GARSUN 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 GARSUN should always be followed by a complete treatment course of an appropriate oral combination antimalarial regimen (see DOSAGE AND DIRECTIONS FOR USE).

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 **GARSUN**. Relevant treatment guidelines should be consulted.

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

Post-treatment anaemia

Transient decreases in reticulocyte counts and, post-treatment haemolytic anaemia severe enough to require transfusion have been reported up to 3 months after the use of **GARSUN** (see SIDE EFFECTS).

The etiology of haemolysis remains unknown.

Hepatic / renal impairment

Data regarding artesunate pharmacokinetics in patients with hepatic and/or renal impairment are insufficient to make a dosing recommendation in these patients.

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.

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 or operate machinery.

INTERACTIONS

No formal interaction studies have been performed and data on interactions between **GARSUN** and other medicines are limited. There are limited data on the treatment of malaria in HIV-infected patients.

PREGNANCY AND LACTATION

Pregnancy

Safety and efficacy of **GARSUN** in pregnancy have not been established.

Embryotoxity (foetal resorption) and deformities were observed in animal studies.

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 **GARSUN**, namely dihydroartemisinin, is excreted in breast milk.

Mothers on treatment with **GARSUN** should not breastfeed their infants.

DOSAGE AND DIRECTIONS FOR USE

Dose:

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

Adults and children:

GARSUN 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.

GARSUN 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 **GARSUN**, 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 WARNINGS AND SPECIAL PRECAUTIONS).

Country-specific guidelines should be consulted when selecting an appropriate regimen.

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 **GARSUN** 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 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 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.

GARSUN 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.

SIDE EFFECTS

Allergic reactions with an urticarial rash, hypotension, pruritus, oedema, and/or dyspnoea have been reported.

Common side effects associated with IV administration have included dizziness, light-headedness, rash, and taste alteration (metallic/bitter taste). Nausea, vomiting, anorexia and diarrhoea have also been reported.

Side effects considered at least possibly related to **GARSUN** are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (≥ 1/10), common (1/100 to 1/10), uncommon (1/1000 to 1/100), rare (1/10 000 to 1/1000), and very rare (< 1/10 000).

Blood and lymphatic system disorders

Uncommon: neutropenia and anaemia (both occasionally severe), thrombocytopenia

Very rare: pure red cell aplasia, post-treatment anaemia (see below), mild and transient decrease in reticulocyte count

Immune system disorders

Uncommon: hypersensitivity

Nervous system disorders

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

Very rare: peripheral neuropathy (or paraesthesia)

Respiratory, thoracic, and mediastinal disorders

Common: cough, nasal symptoms

Gastrointestinal disorders

Common: altered taste, nausea, vomiting, abdominal pain or cramps, diarrhoea

Rare: raised serum amylase, pancreatitis

Hepato-biliary 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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Experience of acute overdose with **GARSUN** is limited. Treatment of overdose should be symptomatic and should consist of general supportive measures.

IDENTIFICATION

GARSUN is a white crystalline powder. After reconstitution, the resulting solution is clear to colourless and essentially free of visible particles.

The solvent and diluent are clear, colourless solutions.

PRESENTATION

GARSUN is supplied in kits containing:

- A single-use vial with lyophilised powder (7 ml Type I clear, colourless glass vial closed with grey bromobutyl rubber stopper and aluminium lid with a blue flip-off plastic cover).
- One ampoule with 1 ml of 5 % sodium bicarbonate solution for injection (Type I clear colourless glass ampoule).
- One ampoule with 5 ml of 0,9 % sodium chloride solution for injection (Type I clear colourless glass ampoule).

The Artesunate powder + solvent + diluent are co-packaged into a plastic tray and paper carton.

STORAGE INSTRUCTIONS

Prior to reconstitution:

Store at or below 30 °C.

Keep the vial and ampoules in the outer carton until required for use.

After Reconstitution:

After reconstitution, from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior use are the responsibility of the user.

If not used immediately, the reconstituted solution could be stored at or below 30 °C for one hour. If not used within one hour, the solution must be discarded.

KEEP OUT OF REACH AND SIGHT OF CHILDREN

REGISTRATION NUMBERS

48/20.2.6/0866

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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DATE OF PUBLICATION OF THE PACKAGE INSERT

02 June 2017

Namibia
Scheduling: NS2
Registration nr.: 20/20.2.6/0102