SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

GARSUN 60 mg (powder and solvent for solution for injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 60 mg artesunate.

Each ampoule of solvent contains sodium bicarbonate 50 mg/ml, 1 ml.

Each ampoule of diluent contains sodium chloride 9 mg/ml, 5ml.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

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 any delay.

Adults and children weighing 20 kg or more:

GARSUN is administered at a dose of 2,4 mg of artesunate/kg body weight, by intravenous (IV) injection or intramuscular (IM) injection, at 0, 12 and 24 hours, then once daily until oral treatment can be substituted.

Children weighing less than 20 kg:

GARSUN is administered at a dose of 3 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 (see section 5.1).

Special populations

Hepatic and renal impairment:

Currently available data do not allow dosing recommendations in hepatic and renal impairment (see sections 4.4 and 5.2).

Method of administration

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 section 4.4).

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) or dose in mg = patient's weight in kg x 3 for children weighing less than 20 kg, respectively) and the number of vials of GARSUN needed should be determined prior to reconstituting the powder.

For reconstitution and dilution according to the method of injection see section 6.6 below.

GARSUN should NOT be administered as an intravenous infusion.

4.3 Contraindications

Known hypersensitivity to artesunate or to any of the excipients of GARSUN listed in 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

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 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 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 haemolytic 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 section 4.8).

The etiology of haemolysis remains unknown.

Vigilance for delayed onset anaemia is therefore advised, particularly in hyperparasitaemic patients and younger children. Given the persistent uncertainties regarding the risk of delayed haemolysis, a minimum follow-up should be strictly observed until day 28 (see section 4.8).

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.

Paediatric population

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

4.5 Interaction with other medicines and other forms of interaction

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Severe malaria is especially hazardous during pregnancy, therefore full dose parenteral GARSUN treatment should be administered at any stage of pregnancy without delay.

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

Limited clinical experience with the use of artesunate in the first trimester of pregnancy as well as clinical

data from pregnant women treated with artemisinin derivatives in the second and third trimester, do not indicate adverse effects of GARSUN on pregnancy or on the health of the foetus /newborn child.

In addition, an observational study conducted in pregnant women with first-trimester falciparum malaria showed no differences in the risk of miscarriage or major congenital malformation in artemisinin derivatives compared to other antimalarial medicines.

Lactation

The active metabolite of GARSUN, namely dihydroartemisinin, is excreted in breast milk.

The medicine levels are not expected to cause any adverse effects in breastfed infants. The amount of medicine 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.

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 or operate machinery.

GARSUN can cause dizziness and light-headedness (see section 4.8) which can affect the ability to perform or execute activities requiring mental alertness or coordination.

4.8 Undesirable effects

a. Summary of the safety profile

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

A potentially serious delayed haemolysis (Post-Artesunate Delayed Haemolysis, PADH) has been reported frequently in travellers and in children. See section c) below.

Common side effects associated with IV administration have included dizziness, light-headedness, rash, and

taste alteration (metallic/bitter taste). Transient elevation in liver transaminases, nausea, vomiting, anorexia and diarrhoea have also been commonly reported, however it is uncertain whether such events have been symptoms of severe malaria. Refer to section c) below.

b. Tabulated summary of adverse reactions

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

Very common:	Post-treatment haemolytic anaemia in travellers, mild and transient decrease in reticulocyte count.
Common to very common:	Post-treatment haemolytic anaemia in endemic areas.
Uncommon:	neutropenia and anaemia (both occasionally severe), thrombocytopenia, agranulocytosis, reticulocytopenia, erythroblastopenia.
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).

Cardiac disorders

Uncommon:	Rhythm and conduction disorders.
Rare:	Arterial ischaemia.

Vascular disorders

Rare:	Hypertensive retinopathy.

Respiratory, thoracic, and mediastinal disorders

Common:	Cough and/or 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, calculous cholecystitis.

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.

c. Description of selected adverse reactions

Post-Artesunate Delayed Haemolysis (PADH)

A delayed haemolysis was detected in prospective studies with a frequency ranging from 7 to 27 % of patients treated with artesunate. This adverse event has been observed both in travellers (15 %) and among young African children (7-22 %) in cases of severe malaria. The best-known cases of delayed haemolysis have been reported in travellers (including non-immune tourists and "visiting friends and relatives" persons). The pathophysiology of this phenomenon has not been fully elucidated but may include various combinations of delayed destruction of different subpopulations of erythrocytes and an immune-mediated aetiology. All patients treated with parenteral artesunate should be followed for at least 4 weeks to detect signs of haemolysis and enable appropriate treatment.

Cardiac disorders

Some cases of cardiac adverse events and particularly rhythm (bradycardia, sinus dysrhythmia) and conduction disorders (OTc lengthening, abnormal sinoatrial conduction) have been recently described. One case of cardiac arrest has been reported in a context of severe malaria with multi-organ failure but the causality by GARSUN has not been established. Whether or not cardiovascular events should be attributed to GARSUN or to severe malaria is not known, but considering that other artemisinin derivatives (arthemeter, arteether) have been associated with QT prolongation in pre-clinical data, EKG should be monitored before and during treatment, especially in patients with a history of cardiovascular impairment or having risk factors.

Paediatric population:

The safety profile of injectable GARSUN 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. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.2.6 Medicines against protozoa

Pharmacotherapeutic group: Antimalarial, ATC code: P01BE03

Mechanism of action

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 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, sporozoites, 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 (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.

Intramuscular

Artesunate is rapidly absorbed following intramuscular injection, and peak plasma levels are generally achieved within 30 minutes of administration. After IM injection of 2,4 mg/kg of artesunate, absorption was rapid in children and adults, with T_{max} values of 8 and 12 minutes, respectively. The corresponding artesunate $t_{1/2}$ values were estimated to be 48 minutes in children and 41 minutes in adults, and C_{max} values were 1,7 and 2,3 µmol/L, for children and adults, respectively.

After IM injection artesunate C_{max} 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, 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of 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)

6.2 Incompatibilities

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

6.3 Shelf life

36 months

6.4 Special precautions for storage

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.

6.5 Nature and contents of the container

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, paper box, and paper carton.

6.6 Special precautions for disposal and other handling

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 (10 mg/ml)

Using a syringe, add 5 ml of 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.

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

Using a syringe, add 2 ml of 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)/20 ml.

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.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd

100 Sovereign Drive, Route 21 Corporate Park

Nellmapius Drive, Irene, Pretoria

8. REGISTRATION NUMBER

48/20.2.6/0866

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02 June 2017

10. DATE OF REVISION OF THE TEXT

03 April 2024