

Artesun[®]

Artesunate for Injection

1. NAME OF THE MEDICINAL PRODUCT

Artesun[®]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Artesun 30 mg box contains 1 vial of 30 mg artesunate powder for solution for injection, 1 ampoule of 0.5 ml sodium bicarbonate 50 mg/ml solution for injection and 1 ampoule of 2.5ml sodium chloride 9 mg/ml solution for injection;
Each Artesun 60 mg box contains 1 vial of 60 mg artesunate powder for solution for injection, 1 ampoule of 1 ml sodium bicarbonate 50 mg/ml solution for injection and 1 ampoule of 5 ml sodium chloride 9 mg/ml solution for injection;
Each Artesun 120 mg box contains 1 vial of 120 mg artesunate powder for solution for injection, 1 ampoule of 2 ml sodium bicarbonate 50 mg/ml solution for injection and 1 ampoule of 10 ml sodium chloride 9 mg/ml solution for injection;

3. PHARMACEUTICAL FORM

Artesunate for injection: White crystalline powder

Solvent (sodium bicarbonate injection): Clear, colourless liquid

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Artesun[®], 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

Dose:

Adults and children: Artesun[®] is administered at a dose of 2.4 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.

Artesun[®] 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 Artesun[®], and when able to tolerate oral medication, the patient should be switched to a complete treatment course of an oral combination antimalarial regimen. Relevant treatment guidelines should be consulted when selecting an appropriate regimen.

Preparation

Because of the instability of artesunate 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 needed should be determined prior to reconstituting the artesunate powder.

Reconstitution of the artesunate solution

Using a syringe, withdraw 1 vial 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

Using a syringe, add *either* 5% glucose for injection or sodium chloride 0.9% 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.

Artesun[®] should NOT be administered as an intravenous drip.

For intramuscular (IM) injection

Using a syringe, add 2 *either* 5% glucose for injection or sodium chloride 0.9% for injection to the vial containing the reconstituted artesunate solution. This will yield 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.*

Hepatic and renal impairment:

Dose adjustment is not necessary in patients with hepatic or renal impairment (see Sections 4.4 and 5.2).

4.3 Contraindications

Artesun[®] 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 Artesun[®] 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 Artesun[®]. Relevant treatment guidelines should be consulted.

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 (see Section 4.8).

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.

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 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 sulfadoxine-pyrimethamine. 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 of 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, pruritus, oedema, and/or dyspnoea.

More common minor side effects associated with IV administration have included dizziness, light-headedness, 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 (1/100–1/10), uncommon (1/1000–1/100), rare (1/10 000–1/1000), 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

Post-treatment anaemia

In general, despite transient decreases in reticulocyte counts, clinically significant anaemia attributed to IV artesunate has not been common in clinical trials in severe malaria. However, in a case-series of 25 patients in Europe who were treated with IV artesunate for severe malaria acquired in an endemic area, 6 patients developed significant post-treatment haemolytic anaemia, presenting as late as 3 weeks after treatment, and 5 of them required transfusion. The aetiology of the haemolysis remains unknown.

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 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: Antimalarial , ATC code: P01BE03

Mechanism 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.

Clinical efficacy and safety

In the SEAQUAMAT (South East Asian Quinine Artesunate Malaria Trial), an international randomised, open-label, multicenter trial conducted in Bangladesh, India, Indonesia and Myanmar, 1461 patients with severe malaria (including 1259 adults) were treated intravenously with either artesunate or quinine. Artesunate was administered at 2.4 mg/kg IV at 0, 12 and 24 h and then every 24 h until the patient could tolerate oral medication. Quinine was given IV at 20 mg/kg over 4 hours, followed by 10 mg/kg over 2-8 hours, 3 times daily until oral therapy could be started. Mortality in the artesunate group was 15% versus 22% in the quinine group, for a reduction in risk of death of 34.7% (p=0.0002). Subgroup analysis suggested a greater benefit of artesunate versus quinine in patients with parisitemia >10%. The reduction in mortality observed in the 202 paediatric patients (<15 years of age) appeared consistent with the overall results, however the number of children was too small to demonstrate statistical significance. IV artesunate was well tolerated, while quinine was associated with a substantially increased risk of hypoglycaemia.

Paediatrics

The AQUAMAT (African Quinine Artesunate Malaria Trial) was an international, randomized open-label multicenter trial which sought to extend the results of the SEAQUAMAT study by comparing parenteral artesunate versus IV quinine for severe malaria in 5425 African children (< 15 years) in 9 African countries. Dosing was similar to SEAQUAMAT, except that both artesunate and quinine could be administered either intravenously or intramuscularly, using the same doses for IM and IV administration for each drug. Roughly one third of patients received study drug by intramuscular injection. Mortality in the artesunate group was 8.5% compared to 10.9% in the quinine group, resulting in a relative risk reduction for death of 22.5% (p=0.0022); the risk reduction was similar for IV and IM administration. In addition, although the risk of neurological sequelae in survivors in both groups did not differ significantly by 28 days following treatment, in-hospital coma, convulsions, and

deterioration of coma were all less frequent in the artesunate-treated patients. As in the SEAQUAMAT, post-treatment hypoglycaemia was more common in the quinine-treated group.

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.

5.3 Preclinical safety data

General toxicity

Artesunate presents low acute toxicity. After repeated administration of 50 mg/kg/day in rats and 82.5 mg/kg/day in dogs, i.e. approximately 10 and 17 times the proposed maximal therapeutic dose in man, evidence of toxicity was observed in the haematopoietic organs, the immune system and response, the liver and kidneys.

Genotoxicity

Artesunate did not show any mutagenic or clastogenic potential in *in vitro* and *in vivo* tests (Ames, mouse micronucleus).

Carcinogenesis

No studies of the carcinogenic potential of artesunate have been conducted.

Reproductive toxicology studies

Oral artesunate caused dose-dependent foetal toxicity in rats, rabbits and monkeys, resulting in foetal resorption and abortion, as well as a low incidence of cardiac and skeletal defects. The no-observed-adverse-effect-level (NOAEL) was 12 mg/kg in pregnant monkeys (3 and 7 day exposures) and the no or low adverse effects level was 5-7 mg/kg in pregnant rats or rabbits (12 day exposures), both of which are above the therapeutic dose range (2.4-4.8 mg/kg) and expected duration of exposure for treatment of severe malaria in humans. In rats, the embryo-fetuses were most sensitive from gestational days 9-14; at other times embryotoxicity was significantly reduced.

Safety pharmacology studies

A slight sedative effect, decrease in body temperature, mild natriuretic effect and a decrease in creatinine clearance were observed with artesunate after single intravenous doses of 200 mg/kg (mice), 450 mg/kg (rats, rabbits and dogs) and following single oral doses of 180 mg/kg in male rats. Beagle dogs administered IV artesunate at 10, 20, 50, and 50 mg/kg for 14 days did not display significant clinical effects, including any signs of neurotoxicity, effects on body weight, ECG abnormalities (including QT interval changes), heart rate, blood pressure, or respiratory rate.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Solvent: Sodium bicarbonate and sodium chloride

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C. Protect from light.

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

6.5 Nature and contents of container

Artesunate for injection: The primary packs are colourless, type I glass vials with gray colored type I rubber stoppers and aluminium lid with a blue flip-off plastic cover.

Solvent (sodium bicarbonate injection 50mg/ml): The primary packs are colourless type I glass ampoules.

Pack size: A carton box containing one vial of artesunate for injection and one ampoule of the sodium bicarbonate solvent.

6.6 Special precautions for disposal

No special requirements

7. SUPPLIER

Guilin Pharmaceutical Co., Ltd.;

No. 43 Qilidian Road, Guilin 541004, Guangxi, China

Telephone: + 86 773 3841973 Fax: +86 773 3841973

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8. DATE OF REVISION OF THE TEXT

December 2012

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Artesunate for Injection

1. NAME OF THE MEDICINAL PRODUCT

Artesun[®]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Artesun 30 mg box contains 1 vial of 30 mg artesunate powder for solution for injection, 1 ampoule of 0.5 ml sodium bicarbonate 50 mg/ml solution for injection and 1 ampoule of 2.5ml sodium chloride 9 mg/ml solution for injection;
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Each Artesun 120 mg box contains 1 vial of 120 mg artesunate powder for solution for injection, 1 ampoule of 2 ml sodium bicarbonate 50 mg/ml solution for injection and 1 ampoule of 10 ml sodium chloride 9 mg/ml solution for injection;

3. PHARMACEUTICAL FORM

Artesunate for injection: White crystalline powder

Solvent (sodium bicarbonate injection): Clear, colourless liquid

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Artesun[®], 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

Dose:

Adults and children: Artesun[®] is administered at a dose of 2.4 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.

Artesun[®] 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 Artesun[®], and when able to tolerate oral medication, the patient should be switched to a complete treatment course of an oral combination antimalarial regimen. Relevant treatment guidelines should be consulted when selecting an appropriate regimen.

Preparation

Because of the instability of artesunate 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 needed should be determined prior to reconstituting the artesunate powder.

Reconstitution of the artesunate solution

Using a syringe, withdraw 1 vial 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

Using a syringe, add *either* 5% glucose for injection or sodium chloride 0.9% 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.

Artesun[®] should NOT be administered as an intravenous drip.

For intramuscular (IM) injection

Using a syringe, add 2 *either* 5% glucose for injection or sodium chloride 0.9% for injection to the vial containing the reconstituted artesunate solution. This will yield 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.*

Hepatic and renal impairment:

Dose adjustment is not necessary in patients with hepatic or renal impairment (see Sections 4.4 and 5.2).

4.3 Contraindications

Artesun[®] 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 Artesun[®] 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 Artesun[®]. Relevant treatment guidelines should be consulted.

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 (see Section 4.8).

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.

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 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 sulfadoxine-pyrimethamine. 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 of 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, pruritus, oedema, and/or dyspnoea.

More common minor side effects associated with IV administration have included dizziness, light-headedness, 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 (1/100–1/10), uncommon (1/1000–1/100), rare (1/10 000–1/1000), 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

Post-treatment anaemia

In general, despite transient decreases in reticulocyte counts, clinically significant anaemia attributed to IV artesunate has not been common in clinical trials in severe malaria. However, in a case-series of 25 patients in Europe who were treated with IV artesunate for severe malaria acquired in an endemic area, 6 patients developed significant post-treatment haemolytic anaemia, presenting as late as 3 weeks after treatment, and 5 of them required transfusion. The aetiology of the haemolysis remains unknown.

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 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: Antimalarial , ATC code: P01BE03

Mechanism 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.

Clinical efficacy and safety

In the SEAQUAMAT (South East Asian Quinine Artesunate Malaria Trial), an international randomised, open-label, multicenter trial conducted in Bangladesh, India, Indonesia and Myanmar, 1461 patients with severe malaria (including 1259 adults) were treated intravenously with either artesunate or quinine. Artesunate was administered at 2.4 mg/kg IV at 0, 12 and 24 h and then every 24 h until the patient could tolerate oral medication. Quinine was given IV at 20 mg/kg over 4 hours, followed by 10 mg/kg over 2-8 hours, 3 times daily until oral therapy could be started. Mortality in the artesunate group was 15% versus 22% in the quinine group, for a reduction in risk of death of 34.7% (p=0.0002). Subgroup analysis suggested a greater benefit of artesunate versus quinine in patients with parisitemia >10%. The reduction in mortality observed in the 202 paediatric patients (<15 years of age) appeared consistent with the overall results, however the number of children was too small to demonstrate statistical significance. IV artesunate was well tolerated, while quinine was associated with a substantially increased risk of hypoglycaemia.

Paediatrics

The AQUAMAT (African Quinine Artesunate Malaria Trial) was an international, randomized open-label multicenter trial which sought to extend the results of the SEAQUAMAT study by comparing parenteral artesunate versus IV quinine for severe malaria in 5425 African children (< 15 years) in 9 African countries. Dosing was similar to SEAQUAMAT, except that both artesunate and quinine could be administered either intravenously or intramuscularly, using the same doses for IM and IV administration for each drug. Roughly one third of patients received study drug by intramuscular injection. Mortality in the artesunate group was 8.5% compared to 10.9% in the quinine group, resulting in a relative risk reduction for death of 22.5% (p=0.0022); the risk reduction was similar for IV and IM administration. In addition, although the risk of neurological sequelae in survivors in both groups did not differ significantly by 28 days following treatment, in-hospital coma, convulsions, and

deterioration of coma were all less frequent in the artesunate-treated patients. As in the SEAQUAMAT, post-treatment hypoglycaemia was more common in the quinine-treated group.

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.

5.3 Preclinical safety data

General toxicity

Artesunate presents low acute toxicity. After repeated administration of 50 mg/kg/day in rats and 82.5 mg/kg/day in dogs, i.e. approximately 10 and 17 times the proposed maximal therapeutic dose in man, evidence of toxicity was observed in the haematopoietic organs, the immune system and response, the liver and kidneys.

Genotoxicity

Artesunate did not show any mutagenic or clastogenic potential in *in vitro* and *in vivo* tests (Ames, mouse micronucleus).

Carcinogenesis

No studies of the carcinogenic potential of artesunate have been conducted.

Reproductive toxicology studies

Oral artesunate caused dose-dependent foetal toxicity in rats, rabbits and monkeys, resulting in foetal resorption and abortion, as well as a low incidence of cardiac and skeletal defects. The no-observed-adverse-effect-level (NOAEL) was 12 mg/kg in pregnant monkeys (3 and 7 day exposures) and the no or low adverse effects level was 5-7 mg/kg in pregnant rats or rabbits (12 day exposures), both of which are above the therapeutic dose range (2.4-4.8 mg/kg) and expected duration of exposure for treatment of severe malaria in humans. In rats, the embryo-fetuses were most sensitive from gestational days 9-14; at other times embryotoxicity was significantly reduced.

Safety pharmacology studies

A slight sedative effect, decrease in body temperature, mild natriuretic effect and a decrease in creatinine clearance were observed with artesunate after single intravenous doses of 200 mg/kg (mice), 450 mg/kg (rats, rabbits and dogs) and following single oral doses of 180 mg/kg in male rats. Beagle dogs administered IV artesunate at 10, 20, 50, and 50 mg/kg for 14 days did not display significant clinical effects, including any signs of neurotoxicity, effects on body weight, ECG abnormalities (including QT interval changes), heart rate, blood pressure, or respiratory rate.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Solvent: Sodium bicarbonate and sodium chloride

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C. Protect from light.

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

6.5 Nature and contents of container

Artesunate for injection: The primary packs are colourless, type I glass vials with gray colored type I rubber stoppers and aluminium lid with a blue flip-off plastic cover.

Solvent (sodium bicarbonate injection 50mg/ml): The primary packs are colourless type I glass ampoules.

Pack size: A carton box containing one vial of artesunate for injection and one ampoule of the sodium bicarbonate solvent.

6.6 Special precautions for disposal

No special requirements

7. SUPPLIER

Guilin Pharmaceutical Co., Ltd.;

No. 43 Qilidian Road, Guilin 541004, Guangxi, China

Telephone: + 86 773 3841973 Fax: +86 773 3841973

Email: glpharma@public.gljptt.gx.cn

8. DATE OF REVISION OF THE TEXT

December 2012

Artesun®

Artesunate injectable

1. NOM DU MEDICAMENT

Artesun®
2. COMPOSITION QUALITATIVE ET QUANTITATIVE
Chaque Artesun 30 mg boîte contient 1 flacon de 30 mg de poudre d’artsuante pour solution d’injection, 1 ampoule de 0,5 ml de la solution pour injection de bicarbonate de sodium de 50 mg/ml et 1 ampoule de 2,5 ml de la solution pour injection de chlorure de sodium de 9 mg/ml;
Chaque Artesun 60 mg boîte contient 1 flacon de 60 mg de poudre d’artsuante pour solution d’injection, 1 ampoule de 1 ml de la solution pour injection de bicarbonate de sodium de 50 mg/ml et 1 ampoule de 5 ml de la solution pour injection de chlorure de sodium de 9 mg/ml;
Chaque Artesun 120 mg boîte contient 1 flacon de 120 mg de poudre d’artsuante pour solution d’injection, 1 ampoule de 2 ml de la solution pour injection de bicarbonate de sodium de 50 mg/ml et 1 ampoule de 10 ml de la solution pour injection de chlorure de sodium de 9 mg/ml;

3. FORME PHARMACEUTIQUE

Artesunate injectable: poudre cristalline blanche

Solvant (sodium bicarbonate injection): Liquide clair, incolore

4. DONNEES CLINIQUES

4.1 Indication thérapeutique

Artesun®, administré par voie intraveineuse ou intramusculaire, est indiqué pour le traitement du paludisme grave causé par le *Plasmodium falciparum*, chez les adultes et les enfants.

4.2 Posologie et mode d’adminstration

Dosage:

Adultes et enfants: Artesun® est administré à une dose de 2,4 mg d’artsunate / kg, par voie intraveineuse (IV) ou intramusculaire (IM), à 0, 12 et 24 heures, puis une fois quotidiennement jusqu’à ce qu’un traitement par voie orale puisse être administré.

Artesun® doit être administré pendant une période minimale de 24 heures (3 doses), indépendamment de la capacité antérieure du patient à tolérer un traitement oral. Après au moins 24 heures de Artesun®, et lorsque le patient est en mesure de tolérer un traitement oral, le patient devra suivre un traitement complet avec antipaludéens oraux combinés. Les directives de traitement pertinentes doivent être consultées lors de la sélection d’un régime approprié.

Préparation

En raison de l’instabilité de l’artsunate dans des solutions aqueuses, la solution reconstituée doit être utilisée dans l’heure suivant la préparation. Par conséquent, la dose nécessaire d’artsunate doit être calculée (dose en mg = poids du patient en kg x 2,4) et le nombre de flacons d’artsunate nécessaires doit être déterminé avant la reconstitution de la poudre d’artsunate.

Reconstitution de la solution d’Artesunate

En utilisant une seringue, retirer 1 flacon du solvant de bicarbonate de sodium fourni avec l’ampoule et l’injecter dans le flacon contenant la poudre d’artsunate. Agiter le flacon pendant quelques minutes pour bien mélanger jusqu’à ce que la poudre soit complètement dissoute et la solution claire. Si la solution est trouble ou si un précipité est présent, elle doit être jetée. La solution reconstituée d’artsunate doit toujours être utilisée immédiatement et jetée si non utilisée dans l’heure suivante.

Après reconstitution, la solution doit être diluée selon la méthode d’injection, tel que décrit ci-dessous.

Par voie intraveineuse (IV)

À l’aide d’une seringue, ajouter soit glucose à 5% pour l’injection ou de chlorure de sodium injectable à 0,9% dans le flacon contenant la solution reconstituée d’artsunate. Ceci donnera d’une solution contenant 10 mg / ml d’artsunate Agiter pour bien mélanger, en s’assurant que la solution obtenue est encore claire. Si la solution est trouble ou si un précipité est présent, elle doit être jetée.

Le volume requis sera égal à: (dose désirée en mg) / 10 ml

Prélever le volume nécessaire de solution d’artsunate dans le flacon avec une seringue et l’injecter ensuite lentement par voie intraveineuse, pendant 1-2 minutes.

Artesun® ne doit PAS être administré par perfusion intraveineuse.

Pour administration intramusculaire (IM)

En utilisant une seringue, ajouter soit glucose à 5% pour injection ou de chlorure de sodium injectable à 0,9% dans le flacon contenant la solution reconstituée d’artsunate. Ceci donnera d’une solution contenant 20 mg / ml d’artsunate. Agiter pour bien mélanger, en s’assurant que la solution obtenue est encore claire. Si la solution est trouble ou si un précipité est présent, elle doit être jetée.

Le volume requis sera égal à: (dose désirée en mg) / 20 ml

Prélever le volume nécessaire de solution dans le flacon d’artsunate avec une seringue et l’injecter ensuite par voie intramusculaire. La cuisse antérieure est habituellement préférée pour l’injection. Si le volume total de solution à injecter par voie intramusculaire est grand, il peut être préférable de diviser le volume et l’injecter à plusieurs endroits, par exemple, dans les deux cuisses.

Ne pas utiliser d’eau injectable pour la reconstitution de la poudre d’artsunate ou la dilution de la solution obtenue avant l’injection.

Insuffisance hépatique et rénale:

Aucun ajustement posologique n’est nécessaire chez les patients ayant une insuffisance hépatique ou rénale (voir sections 4.4 et 5.2).

4.3 Contre-indications

Artesun® est contre-indiqué chez les patients présentant une hypersensibilité à l’artsunate ou autres artémisines.

4.4 Mises en garde spéciales et précautions d’emploi

Malaria due à d’autres espèces de Plasmodium

L’artsunate n’a pas été évalué dans le traitement du paludisme grave dû à *Plasmodium vivax*, *Plasmodium malariae* ou *Plasmodium ovale*.

Communtat au régime de traitement par voie orale

Le traitement du paludisme à falciparum aigu sévère avec Artesun® doit toujours être suivi d’un traitement complet par association médicamenteuse orale appropriée. (voir section 4.2)

Résistance aux antipaludiques

L’information locale sur la prévalence de la résistance aux antipaludiques doit être considérée dans le choix du schéma d’association antipaludique approprié pour une utilisation avec Artesun®. Les directives de traitement pertinentes doivent être consultées.

Anémie post-traitement

Malgré une diminution transitoire du nombre de réticulocytes, une anémie cliniquement significative associée à l’artsunate IV n’a pas été commune dans les essais cliniques. Cependant, des cas occasionnels d’anémie hémolytique d’après-traitement assez graves pour nécessiter une transfusion ont été rapportés (voir section 4.8).

Insuffisance hépatique/rénale

Les données concernant la pharmacocinétique de l’artsunate chez les patients avec une insuffisance hépatique ou rénale sont limitées. Basé sur des données provenant d’études chez des patients atteints de paludisme grave, ainsi que le métabolisme connu de l’artsunate (voir section 5.2), aucune adaptation posologique n’est jugée nécessaire chez les patients avec insuffisance hépatique ou rénale.

Population pédiatrique

Dans les essais cliniques, l’efficacité et l’innocuité de l’artsunate par voies intraveineuse et intramusculaire ont été similaires chez les populations adultes et pédiatriques.

4.5 Interactions avec d’autres médicaments et autres formes d’interactions

L’artsunate est rapidement et largement transformé en dihydroartémisinine (DHA), le métabolite actif, principalement par des estérases plasmatiques et érythrocytaires. L’élimination du DHA est également rapide (demi-vie d’environ 45 min) et le potentiel d’interactions médicamenteuses semble limité. Des études d’interactions médicamenteuses in vitro ont démontré des effets minimes de l’artsunate sur le cytochrome P450. Peu d’études cliniques sur les interactions médicamenteuses ont été réalisées, mais aucune interaction cliniquement significative n’a été identifiée.

4.6 Grossesse et allaitement

Grossesse

Le paludisme grave est particulièrement dangereux pendant la grossesse, donc une dose complète de traitement antipaludique parentéral doit être administrée sans délai. Peu d’expériences cliniques ont été effectuées avec l’utilisation de l’artsunate dans la période de grossesse. Dans les études animales, l’artsunate a été associé à une toxicité foetale durant le premier trimestre de la grossesse. À ce jour, les données cliniques concernant la sécurité dans le premier trimestre n’ont pas indiqué un risque accru de nuire au fœtus. Le traitement par artesunate ne doit pas être exclu au cours du premier trimestre, si cela peut potentiellement sauver la vie de la mère. Comme dans d’autres populations, la preuve que l’artsunate réduit le risque de décès par paludisme grave par rapport à d’autres traitements doit être pris en compte. Dans une étude menée sur 461 femmes enceintes thaïlandaises (44 dans leur premier trimestre) qui ont été traitées avec des dérivés de l’artémisinine (artsunate principalement), il n’y avait pas de preuve évidente d’effets indésirables parmi les 414 femmes pour qui l’issue des grossesses était connue. Les taux observés d’avortement, de mortinatalité, d’anomalies congénitales et de faible poids de naissance étaient comparables aux taux communautaires.

Au cours d’essais cliniques menés de 1999 à 2006, 2045 femmes enceintes en Thaïlande, en Gambie et au Soudan ont été traitées avec de l’artsunate, seul ou en combinaison avec d’autres antipaludiques, notamment la quinine, la méfloquine, l’atovaquone-proguanil et la sulfadoxine-pyriméthamine. Chez ces patientes, dont la plupart étaient dans leur deuxième ou troisième trimestres de grossesse, aucune différence significative par rapport à la communauté en général n’a été observée concernant le poids à la naissance, la durée de gestation, le poids du placenta, ou les taux d’anomalies congénitales, ou dans la croissance et les paramètres de développement des nourrissons suivis pendant un an.

Allaitement maternel / allaitement

Des informations limitées indiquent que la dihydroartémisinine, le métabolite actif de l’artsunate, est présente en faibles concentrations dans le lait maternel. Le taux de médicament ne devrait pas causer d’effets indésirables chez les nourrissons allaités au sein. La quantité de médicament dans le lait maternel ne protège pas l’enfant contre le paludisme.

4.7 Effets sur l’aptitude à conduire et à utiliser des machines

Aucune information n’est disponible sur l’effet de l’artsunate sur la capacité à conduire ou à utiliser des machines. L’état clinique du patient doit être considéré lors de l’évaluation la capacité à conduire ou à faire fonctionner des machines.

4.8 Effets indésirables

L’effet indésirable le plus important rapporté de l’artsunate est une rare réaction allergique grave (risque estimé à environ 1 sur 3000 patients), impliquant une éruption urticairennne ainsi que d’autres symptômes, dont l’hypotension, le prurit, l’oedème et/ou la dyspnée.

Des effets secondaires mineurs associés à l’administration intraveineuse incluent des vertiges, des étourdissements, des éruptions cutanées et une altération du goût (métallique / amer). Des nausées, des vomissements, des symptômes d’anorexie et de diarrhée ont également été signalés, mais il n’est pas sûr que de tels événements aient été des symptômes de paludisme grave.

Les événements indésirables considérés comme au moins possiblement liés à l’artsunate sont énumérés ci-dessous, par système, par classe d’organe et par fréquence absolue. Les fréquences sont définies comme: très fréquent (≥1 / 10), fréquent (1/100-1/10), peu fréquent (1/1000-1/100), rare (1 / 10 000-1/1000), et très rare (<1 / 10 000).

Troubles des systèmes sanguin et lymphatique

Peu fréquent: Neutropénie et anémie (toutes deux parfois sévères), thrombocytopénie

Très rare: Cas d’érythroblastopénie

Fréquence inconnue: Anémie post-traitement (voir ci-dessous), une diminution légère et transitoire de la numération des réticulocytes

Troubles du système nerveux

Fréquent: vertiges, étourdissements, céphalées, insomnie, acouphènes (avec ou sans diminution de la fonction auditive)

Très rare: Neuropathie périphérique (ou paresthésie)

Troubles respiratoires

Fréquent: Toux, symptômes nasaux

Troubles gastro-intestinaux

Fréquent: altération du goût, des nausées, vomissements, douleurs ou crampes abdominales, diarrhée

Rare: amylosémie élevée, pancréatite

Troubles hépatobiliaires

Peu fréquent: élévation transitoire des transaminases hépatiques (ASAT, ALAT)

Rare: Hépatite

Troubles cutanés et sous-cutanés

Fréquent: rougeurs, alopecie

Troubles musculosquelettiques et du tissu conjonctif

Fréquent: Arthralgies, troubles musculaires

Troubles généraux et troubles concernant le site d’administration

Fréquent: Fatigue, malaise, fièvre, douleur au site d’injection

Troubles du système immunitaire

Peu fréquent : hypersensibilité

Anémie post-traitement

En général, malgré une diminution transitoire du nombre de réticulocytes, l’anémie cliniquement significative attribuée à l’artsunate IV n’a pas été commune dans les essais cliniques de paludisme grave. Cependant, dans une série de cas de 25 patients, en Europe, qui ont été traités avec l’artsunate IV pour un paludisme grave acquis dans une région endémique, 6 patients ont développé une anémie hémolytique significative post-traitement, se présentant aussi tard que trois semaines après le traitement, et 5 d’entre eux ont nécessité une transfusion. L’étiologie de l’hémolyse demeure inconnue.

4.9 Surdosage

La possibilité de surdosage aigu avec l’artsunate est limitée. Un cas de surdosage a été documenté chez un enfant de 5 ans auquel on a administré par erreur de l’artsunate à la dose de 88 mg / kg / jour pendant 4 jours, ce qui représente une dose plus de 7 fois plus élevée que la dose maximale d’artsunate recommandée. Le surdosage a été associé à une pancytopénie, du méléna, des convulsions, une défaillance multiviscérale et le décès.

Le traitement du surdosage doit comporter des mesures de support général.

5. PROPRIETES PHARMACOLOGIQUES

5.1 Propriétés pharmacodynamiques

Groupe pharmacothérapeutique: antipaludiques, code ATC: P01BE03

Mécanisme d’action

L’artsunate est un dérivé hémisuccinate de la dihydroartémisinine, qui est elle-même formée par la réduction de l’artémisinine. L’artémisinine est une lactone sesquiterpène endoperoxyde extraite du Qinghao (*armoise, Artemisia annua L.*), une plante qui a été utilisé pendant des siècles en médecine traditionnelle chinoise. Le mécanisme d’action de l’artémisinine implique vraisemblablement un clivage du pont interne endoperoxyde par réaction avec l’hème dans les érythrocytes infectés, générant ainsi des radicaux libres qui alkylent des protéines parasitaires vitales. Toutefois, l’artémisinine a été signalée comme inhibant une calcium adenosine triphosphatase parasitaire essentielle.

Les artémisines se distinguent des autres antipaludiques par leur capacité à tuer tous les stades érythrocytaires du parasite du paludisme, y compris le stade anneau, relativement inactif et schizontes tardifs, ainsi que les gamétocytes responsables de la transmission du paludisme. L’artsunate et l’artémisinine sont les plus antipaludiques agissent le plus rapidement, et ils ont aussi démontré améliorer la clairance splénique des érythrocytes infectés par la réduction de la cytoadhérence. *In vitro*, la dihydroartémisinine (DHA), le métabolite actif de l’artsunate, montre une puissance similaire contre les clones de P. falciparum résistants à la chloroquine et les clones sensibles à la chloroquine. L’artsunate et autres artémisines sont inactifs contre les formes extra-érythrocytaires, les sporozoïtes, les schizontes hépatiques ou les mérozoïtes.

L’efficacité clinique et la sécurité

Dans le SEAQUAMAT (*South East Asian Quinine Artesunate Malaria Trial*), un essai randomisé, international, ouvert multicentrique, mené au Bangladesh, en Inde, en Indonésie et au Myanmar, 1461 patients atteints de paludisme grave (y compris 1259 adultes) ont été traités par voie intraveineuse soit avec de l’artsunate ou de la quinine. L’artsunate a été administré à 2,4 mg / kg IV à 0 , 12 et 24 h, puis toutes les 24 h jusqu’à ce que le patient puisse tolérer un traitement oral. La quinine a été donnée en IV de 20 mg / kg sur 4 heures, puis 10 mg / kg pendant 2-8 heures, 3 fois par jour jusqu’à ce que le traitement par voie orale puisse être démarré. La mortalité dans le groupe artsunate était de 15% contre 22% dans le groupe quinine, pour une réduction du risque de décès de 34,7% (p = 0,0002). L’analyse de sous-groupe a

suggéré un plus grand bénéfice avec l’artsunate par rapport à la quinine chez les patients atteints de parasitemie à > 10%. La réduction de la mortalité observée dans les 202 patients pédiatriques (<15 ans) est apparue cohérente avec les résultats d’ensemble, cependant le nombre d’enfants étant trop petit pour démontrer une signification statistique. L’artsunate IV a été bien toléré, tandis que la quinine a été associée à un risque considérablement accru d’hypoglycémie.

Pédiatrie

L’AQUMAT (*African Quinine Artesunate Malaria Trial*) était une étude internationale, randomisée, ouverte multicentrique qui avait pour but d’étendre les résultats de l’étude SEAQUAMAT en comparant l’artsunate parentéral contre la quinine IV pour le paludisme grave chez 5425 enfants africains (<15 ans) dans 9 pays africains. La posologie a été similaire à SEAQUAMAT, sauf que l’artsunate et la quinine pouvaient être administrés soit par voie intraveineuse ou intramusculaire, en utilisant les mêmes doses d’IM et de l’administration IV pour chaque médicament. Environ un tiers des patients ont reçu les médicaments de l’étude par injection intramusculaire. La mortalité dans le groupe artsunate était de 8,5% comparativement à 10,9% dans le groupe quinine, résultant en une réduction du risque relatif de décès de 22,5%(p = 0,0022), la réduction du risque était similaire pour l’administration IV et IM. En outre, bien que le risque de séquelles neurologiques chez les survivants dans les deux groupes ne diffère pas significativement dans les 28 jours suivant le traitement, à l’hôpital, le coma, les convulsions, et la détérioration du coma étaient tous moins fréquents chez les patients traités avec l’artsunate. Comme dans le SEAQUAMAT, l’hypoglycémie post-traitement est plus fréquente dans le groupe traité avec la quinine.

5.2 Propriétés pharmacocinétiques

Par voie intraveineuse

Après une injection intraveineuse, l’artsunate est très rapidement transformé en son métabolite actif, la dihydroartémisinine (DHA). En conséquence, la demi-vie (t ½) de l’artsunate est estimée à moins de 5 minutes. Après une dose intraveineuse unique de 2,4 mg / kg, les concentrations plasmatiques maximales d’artsunate (Cmax) ont été estimées à 77 µmol / L dans une étude chez les enfants gabonais atteints de paludisme grave, et 42 et 36 µmol / L dans deux études chez les adultes vietnamiens atteints de paludisme sans complications.

Des concentrations élevées de DHA sont observées dans les 5 minutes suivant l’administration de l’artsunate IV. Dans les études ci-dessus (adulte et pédiatrique), les fourchettes de valeurs pour l’heure estimée de la concentration maximale (Tmax) et t½ pour DHA étaient de 0,5 à 15 minutes et 21 à 64 minutes, respectivement, tandis que les valeurs pour la DHA Cmax variaient de 5.3 à 10.6 µmol / L.

Intramusculaire

L’artsunate est rapidement absorbé après injection intramusculaire, et les concentrations plasmatiques de pointe sont généralement atteintes dans les 30 minutes suivant l’administration. Ainsi, après une injection intramusculaire de 2,4 mg / kg d’artsunate, l’absorption est rapide chez les enfants gabonais et adultes vietnamiens, avec des valeurs Tmax de 8 et 12 minutes respectivement. Les valeurs correspondantes d’artsunate t ½ ont été estimées à 48 minutes chez les enfants et 41 minutes chez les adultes, et Cmax ont été de 1,7 et 2.3µmol / L, pour les enfants et les adultes, respectivement.

Après une injection IM, les valeurs d’artsunate Cmax ont donc été inférieures d’environ 45 fois plus chez les enfants et 20 fois chez les adultes par rapport à l’injection IV. Toutefois, les taux d’élimination de l’artsunate chez les enfants et les adultes étaient de 32 fois et 1.3 fois plus lents, respectivement, après une injection IM, par rapport à l’administration IV.

Répartition

Selon les études, le DHA s’accumule de façon substantielle dans les érythrocytes infectés par P. falciparum. Une liaison de la dihydroartémisinine avec les protéines plasmatiques a été établie à 93% chez les patients et 88% chez des volontaires sains.

Métabolisme et élimination

L’artsunate est largement et rapidement hydrolysé par les estérases plasmatiques, avec une contribution minimale possible par le CYP2A6. Le principal métabolite, la dihydroartémisinine, est responsable de la la plupart de l’activité in vivo antipaludique de l’artsunate par voie orale. Cependant, après l’administration IV d’artsunate, l’artsunate peut y contribuer de manière plus significative. Le DHA est ensuite métabolisé dans le foie par glucuronidation et est excrété dans l’urine; le α-dihydroartémisinine-β-glucuronide a été identifié comme le principal produit urinaire chez les patients atteints de paludisme avec le *P. falciparum*.

Population particulière

Aucune donnée pharmacocinétique n’est disponible pour les patients présentant une insuffisance rénale ou hépatique. Toutefois, sur la base des mécanismes connus du métabolisme et l’élimination de l’artsunate, combinées avec des données cliniques provenant de patients atteints de paludisme grave et d’une insuffisance rénale et / ou hépatique de différents degrés, aucune modification de dose n’est considérée nécessaire en cas d’insuffisance rénale ou hépatique.

5.3 Données de sécurité précliniques

Toxicité générale

L’artsunate présente une faible toxicité aiguë. Après l’administration répétée de 50 mg / kg / jour chez les rats et 82,5 mg / kg / jour chez les chiens, soit environ 10 et 17 fois la dose maximale thérapeutique proposée chez l’homme, aucune preuve de toxicité n’a été observée dans les organes hématopoïétiques, le système immunitaire, le foie et les reins.

Génotoxicité

L’artsunate n’a montré aucun potentiel mutagène ou clastogène lors de tests in vitro et in vivo (Ames, micronoyau chez la souris).

Cancérogenèse

Aucune étude sur le potentiel carcinogène de l’artsunate n’ont été menées.

Les études de toxicologie de la reproduction

L’artsunate oral a causé une toxicité foetale dose-dépendante chez des rats, des lapins et des singes, entraînant une résorption foetale et l’avortement, ainsi qu’une faible incidence d’anomalies cardiaques et squelettiques. La concentration sans effet indésirable observé (NOAEL) était de 12 mg / kg chez la femelle singe enceinte (3 et 7 jours d’exposition) et le niveau d’effets indésirables nul ou faible a été de 5 à 7 mg / kg chez les femelles rats enceintes ou des lapins (12 expositions par jour), qui sont tous deux au-dessus des doses thérapeutiques (2,4 à 4,8 mg / kg) et la durée prévue de l’exposition pour le traitement du paludisme grave chez les humains. Chez le rat, le fœtus embryon a été le plus sensible lors des jours de gestation 9-14; à d’autres moments, l’embryotoxicité a été significativement réduite.

Les pharmacologies de sécurité

Un léger effet sédatif, diminution de la température du corps, léger effet natriurétique et une diminution de la clairance de la créatinine ont été observées avec l’artsunate, après une dose unique intraveineuse de 200 seule mg / kg (souris), 450 mg / kg (rats, lapins et chiens) et après des doses orales de 180 mg / kg chez les rats mâles. Des chiens beagle auxquels on a administré l’artsunate IV à 10, 20, 50 et 50 mg / kg pendant 14 jours n’ont pas affiché d’importants effets cliniques, c’est-à-dire aucun signe de neurotoxicité, d’effet sur le poids corporel, d’anomalies de l’ECG (y compris les modifications de l’intervalle QT), d’effet sur la fréquence cardiaque, la pression sanguine, ou la fréquence respiratoire.

6. DONNEES PHARMACEUTIQUES

6.1 Liste des excipients

Solvants: Bicarbonate de sodium et chlorure de sodium

6.2 Incompatibilités

En l’absence d’études de compatibilité, ce médicament ne doit pas être mélangé avec d’autres médicaments.

6.3 Durée de conservation

36 mois

6.4 Précautions particulières de conservation

Conservér en-dessous de 30°C. Protéger de la lumière.

La solution reconstituée doit être conservée en-dessous de 30°C et devrait être utilisée dans l’heure.

6.5 Nature et contenu de l’emballage

L’artsunate injectable: les emballages primaires sont des ampoules en verre de type I, munis de bouchons en caoutchouc de type I recouverts d’aluminium avec un couvercle de plastique amovible bleu.

Solvant (bicarbonate de sodium injectable 50mg/ml): les emballages primaires sont des ampoules en verre de type I incolores.

Conditionnement: Une boîte en carton contenant un flacon d’artsunate injectable et une ampoule de solvant de bicarbonate de sodium.

6.6 Précautions particulières d’élimination

Aucune exigence particulière.

7. FOURNISSEUR

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8. DATE DE MISE A JOUR DU TEXTE

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