SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Argesun ® 30mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains: Artesunate powder 30 mg
Each ampoule of 1.5 ml solvent contains:
Sodium Bicarbonate 8.4mg/ml;
Arginine 20mg/ml;
H_2O

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Artesunate for injection: White crystalline powder
Solvent (Sodium Bicarbonate and Arginine injection): Clear, colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication
Argesun ® 30mg, 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 weighing more 20 kg or more: **Argesun® 30mg** 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.

Children weighing less than 20 kg: **Argesun® 30mg** 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).

Argesun® 30mg 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 **Argesun® 30mg** and when able to tolerate oral medication, the patient should be switched to a complete treatment course of an oral antimalarial 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 for patients weighing more than 20 kg; or dose in mg = patient's weight in kg x 3 for children weighing less than 20 kg) and the number of vials of artesunate needed should be determined prior to reconstituting the artesunate powder.

Reconstitution of the artesunate solution
Following reconstitution, the solution must be diluted according to the method of injection, as described below.

For intravenous (IV) injection & intramuscular (IM) injection (20 mg/ml)

Using a syringe, withdraw 1.5 ml of the sodium bicarbonate and arginine solvent, and inject this into the vial containing the artesunate powder. Gently shake the vial for 3-5 minutes 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. The end concentration of the solution will be 20 mg artesunate per ml solvent. Thus, the volume in ml for administration to the patient will be equal to: (desired dose in mg)/20
Withdraw the required volume of artesunate solution from the vial with a syringe

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

Argesun® 30mg is contraindicated in patients with hypersensitivity to artesunate or other artemisinin derivatives.

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.*

Resistance to antimalarials
Local information on the prevalence of resistance to antimalarials should be considered in choosing the appropriate antimalarial regimen for use as follow-up treatment after **Argesun® 30mg**. Relevant treatment guidelines should be consulted such as those of the WHO and public health authorities (see reference section at end of this SmPC)

Post-treatment haemolytic anaemia
Delayed haemolytic anaemia following treatment with injectable artesunate has been observed in children in malaria endemic areas and in non-immune travellers presenting with severe falciparum malaria. The risk was most pronounced in patients with hyperparasitaemia and in younger children. Some cases have been severe and required blood transfusion. Vigilance for delayed onset anaemia is therefore advised, particularly in hyperparasitaemic patients and younger children, and prolonged follow-up should be considered (e.g., 14-28 days). As the overall benefit-risk ratio remains highly favourable for injectable artesunate in the treatment of severe malaria, WHO strongly recommends its continued use (see reference links under Section 4.4 at end of this document).

Hepatic / renal impairment
Data regarding artesunate pharmacokinetics in patients with hepatic and/or renal impairment are limited. Based on pharmacokinetic data from studies in patients with severe malaria, as well as on knowledge of artesunate metabolism and elimination (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 from the blood compartment is also rapid (half-life approximately 45 min). The potential for drug-drug interactions with other medicinal products is limited. *In vitro* drug-interaction studies have demonstrated minimal effects of artesunate on cytochrome P450 isoenzymes. In the limited number of clinical drug-drug interaction studies that have been performed, however, no clinically significant drug-drug interactions have been identified.

4.6 Pregnancy and lactation
Pregnancy
Severe malaria is a life-threatening disease for the mother during pregnancy. Therefore, in patients with severe malaria during pregnancy, the full dose parenteral artesunate treatment should be administered at any stage of pregnancy without delay.

In animal studies, artesunate has been associated with fetal toxicity during the first trimester of pregnancy. Limited clinical experience with the use of artesunate in the first trimester of pregnancy as well as clinical data from more than 4,000 pregnant women, treated with artemisinin derivatives in the second and third trimester, do not indicate adverse effects of artesunate on pregnancy or on the health of the fetus or newborn child.

Breastfeeding / lactation
Limited information indicates that dihydroartemisinin, the active metabolite of artesunate, is present at low concentrations in breast milk. The drug levels are not expected to cause any adverse effects in breastfed infants, except in case of pre-existing allergies to artemisinins in the infant. The amount of drug 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. In a reproduction toxicity study in rats, testicular and epididymal lesions were seen, but no effects on fertility were observed (see section 5.3). The relevance of this finding for human fertility is unknown.

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 can present as an urticarial rash or more severe allergic symptoms, including hypotension, pruritus, oedema, and/or dyspnoea.

More common minor side effects described in association with parenteral administration of artesunate include dizziness, light-headedness, rash, and taste alteration (metallic/ bitter taste). Nausea, vomiting, anorexia and diarrhea have also been reported; however, it is uncertain whether these are attributable to the drug or to the disease 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 haemolytic anaemia*, 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*
Cases of delayed haemolytic anaemia have been identified in non-immune travellers

following treatment of severe malaria with injectable artesunate. Some were severe and required blood transfusions. In a study in African children aged 6 months to 10 years of age in malaria endemic areas, 5 out of 72 children (7%) experienced delayed haemolytic anaemia following treatment with injectable artesunate, and one child required transfusion. Risk was increased with hyperparasitaemia in all age groups and with younger age in children. Onset of haemolysis and anaemia was evident by 14-28 days after artesunate treatment. Vigilance for recognizing this adverse event is advised (see section 4.4).

Paediatric population:
The safety profile of injectable artesunate is similar in children and adults.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare providers are asked to report any suspected adverse reactions to the marketing authorization holder or if available via the national reporting system (See details below);

Paper based reporting: TMDA yellow card
Online reporting: https://sqrt.tmda.go.tz/
*USSD reporting: send a simple short text message to report any suspected Adverse Drug Reaction by dialing *152*00# and follow the instructions*

4.9 Overdose
Information on acute overdosing 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, multi-organ failure and death. Treatment of accidental overdose of artesunate consists of general supportive measures.

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*USSD reporting: send a simple short text message to report any suspected Adverse Drug Reaction by dialing *152*00# and follow the instructions.*

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 in the molecule through reaction with heme within the infected erythrocyte, thereby generating free radicals which alkylate vital parasite proteins. However, other studies have described specific target proteins in the parasite as mechanism of action.

The artemisinins are distinguished from other antimalarials by their ability to kill all erythrocytic stages of the malaria parasite, including the ring stage and schizonts, as well as the early-stage gametocytes, the sexual stage of the parasite responsible for malaria transmission. Artesunate and the artemisinins are currently the most rapidly acting of the antimalarials.

In vitro, dihydroartemisinin (DHA), the active metabolite of artesunate, exhibits similar potency against chloroquine-resistant and chloroquine-sensitive strains of *P. falciparum.*

Artesunate and the other artemisinins are not active against pre-erythrocytic parasite stages including sporozoites and liver schizontes, or against mature stage gametocytes.

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 a dose of 2.4 mg/kg at 0, 12 and 24 h and then every 24 h until the patient could tolerate oral medication. Quinine was given as a loading dose of 20 mg/kg over 4 hours, followed by a dose of 10 mg/kg administered 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 parasitaemia >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 reach statistical significance. Post-treatment hypoglycaemia was more common in the quinine-treated group.

Paediatric patients

The AQUAMAT (African Quinine Artesunate Malaria Trial) was an international, randomized open-label multicenter trial was a follow-up study of SEAQUAMAT, comparing parenteral artesunate versus IV quinine for severe malaria in 5425 African children (< 15 years) in 9 African countries (Mozambique, The Gambia, Ghana, Kenya, Tanzania, Nigeria, Uganda, Rwanda, and Democratic Republic of the Congo). Dosing was similar to SEAQUAMAT, except that according to the study site the study drugs were administered either intravenously or intramuscularly, using the same doses for IM and IV administration for each drug. Roughly one third of patients received the study drug by intramuscular injection. Mortality in the artesunate group was 8.5% compared to 10.9% in the quinine group, translating to 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 administration
After intravenous bolus injection, artesunate is rapidly and completely hydrolyzed to its active metabolite, dihydroartemisinin (DHA). A detailed pharmacokinetic study with the current artesunate product was performed in 72 healthy Thai adults. Following a single IV bolus injection of 2.4 mg/kg, the median (range) maximum artesunate plasma concentration (Cmax) was 6705 ng/mL (2260 to 26800 ng/mL); the volume of distribution (V_d) was 60.75 L (20.57 to 145.33 L); the elimination clearance rate (CL) was 197.72 L/h (75.65 to 466.38 L/h) with a plasma half-life ($t_{1/2}$) of 0.21 h (0.10 to 0.77 h), and an area under the concentration-time curve from time zero to infinity (AUC_{inf}) of 688.80 h*ng/mL (317.00 to 2273.41 h*ng/mL). For DHA the Cmax was 1735 ng/mL (702 to 3460 ng/mL), the time to maximum DHA concentration (Tmax) was 0.25 h (0.08 to 0.50 h), the V_d was 143.36 L (75.87 to 398.31 L); the CL was 95.91 L/h (28.42 to 95.91 L/h) with a plasma $t_{1/2}$ of 1.88 h (1.01 to 5.66 h), and an AUC_{inf} of 1983.09 h*ng/mL (1064.32 to 3254.88 h*ng/mL).

Intramuscular
Artesunate is rapidly absorbed following intramuscular injection, and peak plasma levels are generally achieved within 30 minutes of administration. A detailed pharmacokinetic study with the current artesunate product was performed in 72 healthy Thai adults. Following a single IM bolus injection of 2.4 mg/kg, the median (range) maximum artesunate plasma concentration (Cmax) was 1230.00 ng/mL (577.00 to 2500.00 ng/mL); the time to maximum artesunate concentration (Tmax) was 0.25 h (0.08 to 0.75 h); the volume of distribution (V_d) was 101.69 L (45.58 to 252.57 L); the elimination clearance rate (CL) was 147.57 L/h (103.83 to 247.68 L/h) with a plasma half-life ($t_{1/2}$) of 0.46 h (0.25 to 1.11 h), and an area under the concentration-time curve from time zero to infinity (AUC_{inf}) of 997.69 h*ng/mL (581.83 to 1307.27 h*ng/mL). For DHA the Cmax was 748.50 ng/mL (320.00 to 1040.00 ng/mL), the Tmax was 0.75 h (0.50 to 1.50 h), the Vd was 152.03 L (49.02 to 427.93 L); the CL was 62.39 L/h (29.42 to 100.53 L/h) with a plasma $t_{1/2}$ of 1.65 h (1.11 to 3.63 h), and an AUC_{inf} of 1714.65 h*ng/mL (1010.25 to 2816.19 h*ng/mL).

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. 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. A study of artesunate administered to male rats daily for 6 weeks noted testicular and epididymal lesions, although these lesions did not affect fertility. The lesions were reversible after cessation of treatment.

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 Arginine.

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 colorless, type I glass vials with gray colored type I rubber stoppers and aluminum lid with a blue flip-off plastic cover.
Solvent *(*sodium bicarbonate 8.4mg/ml and arginine 20mg/ml injection*):* The primary packs are colorless type II glass ampoules.
Pack size: A small box containing one vial of artesunate for injection, one ampoule of the sodium bicarbonate and arginine solution (solvent).

6.6 Special precautions for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Name and address of the MAH holder
Name: Shanghai Fosun Pharmaceutical Development Co., Ltd.;
Address: Room 350, No.5 Kangshi Road, Kangqiao Town, Pudong New District (Kangqiao), Shanghai, China.
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8. Marketing Authorisation Number
TAN 20 HM 0417

9. Date of First Authorisation / Renewal of The Authorisation
25/09/2020

10. DATE OF REVISION / APPROVAL OF THE TEXT