SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

For IM / IV use

1. NAME OF THE PRODUCT

ARCENATE™ (Artesunate) Injection 30mg

ARCENATE™ (Artesunate) Injection 60mg

ARCENATE™ (Artesunate) Injection 120mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ARCENATE™ Injection 30mg
Each vial contains:
Artesunate Ph. Int..... 30mg
(Sterile powder of Artesunate)

ARCENATE™ Injection 60mg
Each vial contains:
Artesunate Ph. Int..... 60mg
(Sterile powder of Artesunate)

ARCENATE™ Injection 120mg
Each vial contains:
Artesunate Ph. Int..... 120mg
(Sterile powder of Artesunate)

3. PHARMACEUTICAL FORM

Powder for solution for injection

Appearance:

ARCENATE™ Injection 30mg: Fine white crystalline powder.

ARCENATE™ Injection 60mg: Fine white crystalline powder.

ARCENATE™ Injection 120mg: Fine white crystalline powder.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

ARCENATE™ is indicated for the initial treatment of severe malaria in adults and children.

Limitations of Use:

ARCENATE™ injection does not treat the hypnozoite liver stage forms of *Plasmodium* and will therefore, not prevent relapses of malaria due to *Plasmodium vivax* or *Plasmodium ovale*.

Concomitant therapy with an antimalarial agent such as an 8-aminoquinoline drug is necessary for the treatment of severe malaria due to *P. vivax* or *P. ovale*. Consideration should be given to guidance on the appropriate use of antimalarial agents.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:

It is recommended that **ARCENATE™** should be used to treat patients with severe malaria only after consultation with a physician.

Initial treatment of severe malaria with artesunate should always be followed by a complete treatment course with appropriate oral antimalarial therapy.

Posology:

Adults and children weighing at least 20kg: **ARCENATE™** 30mg is administered at a dose of 2.4mg 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 20kg: **ARCENATE™** 30mg is administered at a dose of 3mg 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.

ARCENATE™ 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 **ARCENATE™** 30mg, and when able to tolerate oral medication, the patient should be switched to a complete treatment course of an oral combination antimalarial regimen.

Preparation: Because of the instability of artesunate in aqueous solutions the reconstituted solution must be used within one hour of preparation.

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 20kg, respectively) and the number of vials of artesunate needed should be determined prior to reconstituting the artesunate powder.

Direction for reconstitution:

Step 01:

- Using a syringe, withdraw 0.5ml for 30mg vial OR 1ml for 60mg vial OR 2ml for 120mg vial respectively of the supplied Sodium Bicarbonate Injection 5% solvent from the ampoule.
- Inject the Sodium Bicarbonate Injection 5% 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.

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

Step 02:

Dilution for intravenous (IV) injection (10mg/ml):

- Using a syringe, add 2.5ml for 30mg vial OR 5ml for 60mg vial OR 10ml for 120mg vial respectively of Sodium Chloride Injection 0.9% to the vial containing the reconstituted artesunate solution. This will yield 3ml for 30mg vial OR 6ml for 60mg vial OR 12ml for 120mg vial respectively of a solution containing artesunate 10mg/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 of the solution required (ml) will be: Volume (ml) = [dose (mg)] ÷ 10
- Withdraw the required volume of artesunate solution from the vial with a syringe. Then inject slowly intravenously, over 1-2 minutes.

ARCENATE™ should not be administered as an intravenous drip.

Dilution for intramuscular (IM) injection (20mg/ml):

- Using a syringe, add 1ml for 30mg vial OR 2ml for 60mg vial OR 4ml for 120mg vial respectively of Sodium Chloride Injection 0.9% to the vial containing the reconstituted artesunate solution. This will yield 1.5ml for 30mg vial OR 3ml for 60mg vial OR 6ml for 120mg vial respectively of a solution containing artesunate 20mg/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 of the solution required (ml) will be: Volume (ml) = [dose (mg)] ÷ 20
- 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.

Elderly: No dose adjustment is required.

Renal and hepatic impairment: No dose adjustment is required.

Paediatric population: No dose adjustment is recommended based on age or weight.

4.3. CONTRAINDICATIONS:

Hypersensitivity to the active substances, or to any other artemisinin antimalarial agent.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Hypersensitivity: Allergic reactions including anaphylaxis, are known to be reported. Other reported allergic reactions include urticaria, rash and pruritus. Discontinue artesunate injection administration and continue therapy with another antimalarial drug.

Post-artesunate delayed haemolysis (PADH): Characterized by decreased haemoglobin with laboratory evidence of haemolysis (such as decreased haptoglobin and increased lactate dehydrogenase) with onset at least 7 days and sometimes several weeks after initiating artesunate treatment.

PADH is known to occur very commonly after successful treatment of severe malaria that commenced with IV artesunate in returning travelers. The risk of PADH may be highest in patients with hyper-parasitemia and in younger children.

Patients should be monitored for evidence of haemolytic anemia for 4 weeks after starting artesunate treatment. Spontaneous recovery from PADH usually occurs within a few weeks. Some patients require transfusion.

Reticulocytopenia: Both, known animal preclinical data and known human data from clinical trials have suggested that reversible reticulocytopenia occurs at least commonly in association with treatment with artesunate. The reticulocyte count recovers after cessation of treatment.

Malaria due to *Plasmodium vivax, Plasmodium malariae* or *Plasmodium ovale*: Artesunate is not known to be evaluated in the treatment of severe malaria due to *Plasmodium vivax*, *Plasmodium malariae* or *Plasmodium ovale*. Available data indicates that it is effective against all *Plasmodium* species. Patients treated initially with artesunate for severe malaria due to *P. vivax* or *P. ovale* should receive an antimalarial agent that is active against the hypnozoite liver stage forms of *Plasmodium*.

Infants aged less than 6 months: There are insufficient known clinical data to establish the safety and efficacy of artesunate in infants below 6 months of age.

Elderly: There are insufficient clinical data to establish the safety and efficacy of intravenous artesunate in patients aged 65 years and older with severe malaria.

Sodium: When given by intravenous injection (into the vein). This medicine contains 31.40mg sodium in each intravenous injection. This is equivalent to 1.6% of the recommended maximum daily dietary intake of sodium for an adult.

When given by intramuscular injection (into the muscle). This medicine contains 20.77mg sodium in each intramuscular injection. This is equivalent to1.06% of the recommended maximum daily dietary intake of sodium for an adult.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:
No clinical drug-drug interactions studies have been conducted with artesunate.
Effect of other medicinal products on artesunate and/or dihydroartemisinin (DHA): Co-administration of artesunate with strong inhibitors of UGT enzymes (e.g. axitinib, vandetanib, imatinib, diclofenac) may increase plasma exposures to DHA and should be avoided if possible.
Co-administration of artesunate with UGT inducers should be avoided (e.g. nevirapine, ritonavir, rifampicin, carbamazepine, phenytoin) may decrease DHA exposures, leading to a reduction or loss of efficacy.
Effect of artesunate and/or DHA on other medicinal products: Caution is advised when co-administering artesunate with substrates of CYP3A4 or CYP1A2 that have narrow therapeutic windows.

4.6. PREGNANCY AND LACTATION:
Pregnancy: There is limited clinical experience with the use of artesunate in the first trimester of pregnancy. A risk to the foetus cannot be excluded. The use of artesunate in the first trimester is therefore, not recommended unless the benefit to the mother outweighs the risk to the foetus.
As a precautionary measure, it is preferable to avoid the use of artesunate during the second or third trimester of pregnancy.
Breast-feeding: DHA, a metabolite of artesunate, is present in human milk. There are no data on the effects of artesunate or DHA on the breastfed infant or on milk production. The benefits of breast-feeding to mother and infant should be weighed against potential risk from infant exposure to DHA through breast milk.
Fertility: No fertility data are available in humans.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
No studies on the effects on the ability to drive and use machines are known to be performed. Patients should be warned not to drive or use machines if they feel tired or dizzy.

4.8. UNDESIRABLE EFFECTS:
Very Common: Anemia, reduced reticulocyte count, post-artesunate delayed haemolysis.
Common: Rhinitis, dizziness, dysgeusia, headache, bradycardia, hypotension, phlebitis, cough, abdominal pain, diarrhoea, vomiting, hyperbilirubinemia, jaundice, haemoglobinuria, acute renal failure, pyrexia, ALT increased, AST increased.
Uncommon: Anorexia, flushing, nausea, constipation, Stevens-Johnson syndrome, pruritus, rash, urticaria, fatigue, pain at injection site.
Unknown: Anaphylaxis.

4.9. OVERDOSE:
In cases of suspected overdosage symptomatic and supportive therapy should be given as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:
Pharmacotherapeutic group: Antiprotozoals, artemisinin and derivatives. **ATC code:** P01BE03.
Mechanism of action: The antimalarial mechanism of action of artesunate is generally thought to depend upon activation involving iron-mediated cleavage of the endoperoxide bridge of DHA to generate an unstable organic free radical followed by alkylation, where the free radical binds to malarial proteins leading to destruction of parasite membranes.
In-vitro activity: Available in-vitro data indicate that artesunate 50% inhibitory concentrations (IC_{50} values) are broadly comparable for *P. falciparum* and for the other *Plasmodium* species that cause malaria in humans (*P. vivax, P. ovale, P. malariae, P. knowlesi*).
Artemisinin resistance: Decreased susceptibility to artesunate and other artemisinins, manifesting clinically as slower rates of parasite clearance is associated with mutation in the K13 gene, which encodes the parasite's Kelch propeller protein Kelch13.

5.2. PHARMACOKINETIC PROPERTIES:
Absorption: Following intravenous administration of artesunate as a bolus injection over 1-2 minutes, the pharmacokinetics of artesunate and dihydroartemisinin in plasma are shown below:

Parameter	Artesunate	DHA
C_{max} (ng/mL)	1020-3260	2060-3140
V (L/kg)	1.3	0.75 (median value)
CL (L/kg/h)	3.4	1.1
$t_{½}$ (min)	15	80
AUC (ng-h/mL)	727-750	2017-3492

Following intramuscular administration, artesunate is rapidly absorbed. Time to reach peak plasma concentration: Within 15 minutes (DHA).
Distribution: Artesunate and DHA distribute into the extracellular body fluid. DHA is approximately 93% protein-bound in patients with uncomplicated malaria infection. Erythrocytes infected with *Plasmodia* have been reported to contain very high DHA concentrations compared to plasma levels (e.g. 300-fold vs. mean plasma concentrations).
Biotransformation: Artesunate is converted to DHA by cytochrome 2A6 and blood esterases. In human liver microsomal incubations of DHA, DHA-glucuronide was the only metabolite found. In urine from patients, α-DHA-β-glucuronide (α-DHA-G) and a variable amount of the tetrahydrofuran isomer of α-DHA-G was identified. DHA itself was present only in very small amounts.
Elimination: Artesunate is very rapidly eliminated from blood (within a few minutes) via conversion to DHA. DHA is eliminated from blood within a few hours after an intravenous dose, mainly via urinary excretion of glucuronides.
Special populations:
Elderly: There are no pharmacokinetic data available after intravenous artesunate dosing in patients aged 65 years or older with severe malaria.
Renal and hepatic impairment: No pharmacokinetic data are available for patients with impaired renal and hepatic function.
Paediatric population: There are limited PK data on the use of IV artesunate in neonates and infants.

5.3. PRECLINICAL SAFETY DATA:
Artesunate was negative in an in vitro bacterial reverse mutation assay, an in vitro Chinese hamster ovary chromosome aberration assay, and an in vivo mouse bone marrow micronucleus assays. Carcinogenicity studies have not been conducted with artesunate. Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:
Reproductive and developmental toxicity: Animal reproduction studies show a single IV administration of artesunate to rats early in gestation results in embryolethality. Oral administration of artesunate during organogenesis in rats, rabbits, and monkeys induces a dose-dependent increase in embryolethality and foetal malformations (including cardiovascular, brain, and/or skeletal) at 0.3 to 1.6-times the clinical dose based on body surface area (BSA) comparisons. Although animal reproduction studies in several species have demonstrated foetal harm from oral and IV administered artesunate and other artemisinin class drugs, the clinical relevance of the animal data is uncertain. Studies in the literature indicate that artesunate oral administration in the male rat can cause a dose and duration dependent effect on the epididymis and testes with reversible decreases in the production of viable sperm at near clinical doses. No such effects were noted in rats or dogs in 28-day Good Laboratory Practice (GLP) studies conducted using IV dosing.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:
Not applicable.

6.2. INCOMPATIBILITIES:
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal product.

6.3. SHELF LIFE:
See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:
Do not store over 30°C, and protect from heat, light and moisture. Do not store in a refrigerator or freezer.
Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:
ARCENATE™ Injection 30mg: ***Powder for Injection:*** Clear glass vial (USP Type-I) with bromobutyl rubber stopper, sealed with flip off seal. ***0.5ml Sodium Bicarbonate Injection 5% w/v:*** Clear 1ml glass ampoule (USP Type-I). ***2.5ml Sodium Chloride Injection 0.9% w/v:*** Clear 3ml glass ampoule (USP Type-I), pack size is 1 vial & 2 ampoules.
ARCENATE™ Injection 60mg: ***Powder for Injection:*** Clear glass vial (USP Type-I) with bromobutyl rubber stopper, sealed with flip off seal. ***1ml Sodium Bicarbonate Injection 5% w/v:*** Clear 1ml glass ampoule (USP Type-I). ***5ml Sodium Chloride Injection 0.9% w/v:*** Clear 5ml glass ampoule (USP Type-I), pack size is 1 vial & 2 ampoules.
ARCENATE™ Injection 120mg: ***Powder for Injection:*** Clear glass vial (USP Type-I) with bromobutyl rubber stopper, sealed with flip off seal. ***2ml Sodium Bicarbonate Injection 5% w/v:*** Clear 2ml glass ampoule (USP Type-I). ***10ml Sodium Chloride Injection 0.9% w/v:*** Clear 10ml glass ampoule (USP Type-I), pack size is 1 vial & 2 ampoules.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:
Visually inspect the solution within the vial to ensure that no visible particles remain and there is no discolouration of the solution. Do not administer if the solution is discoloured or contains particulate matter. Inject the reconstituted solution IV as a slow bolus over 1-2 minutes. Do not administer via continuous IV infusion. Discard the vial and any unused portion of the medicinal product after use. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:
Ph. Int. Specs.

7. MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, Off Hub River Road, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com
Mfg. Lic. No. 000072

8. MARKETING AUTHORISATION NUMBER(S)
ARCENATE™ Injection 30mg: 100927
ARCENATE™ Injection 60mg: 100928
ARCENATE™ Injection 120mg: 100929

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
ARCENATE™ Injection 30mg: 19th December 2019
ARCENATE™ Injection 60mg: 19th December 2019
ARCENATE™ Injection 120mg: 19th December 2019

10. DATE OF REVISION OF THE TEXT

آرسی نیٹ™ انجکشن

(آرٹی سونیٹ)

دوا تیار کرنے کا طریقہ:

مرحلہ ۱: وائل میں 5% Sodium Bicarbonate Injection درج ذیل مقدار میں ڈالیں
اور پاؤڈر کے مکمل حل ہو جانے تک اچھی طرح ہلائیں۔

مرحلہ ۲:

برائے وریدی استعمال: مرحلہ ا سے تیار شدہ وائل میں 0.9% Sodium Chloride Injection درج ذیل مقدار میں ڈالیں
اور اچھی طرح ہلا کر شفاف سلوشن تیار کر لیں (تیار شدہ سلوشن کو IV drip میں ہرگز مت ڈالیں)۔

برائے عضلاتی استعمال: مرحلہ ا سے تیار شدہ وائل میں 0.9% Sodium Chloride Injection درج ذیل مقدار میں ڈالیں اور اچھی طرح ہلا کر شفاف سلوشن تیار کر لیں۔

Steps	Route Of Administration	Diluent	For ARCENATE™ Injection 30mg	For ARCENATE™ Injection 60mg	For ARCENATE™ Injection 120mg
Step 1	For IV / IM	Sodium Bicarbonate Injection 5%	0.5ml	1ml	2ml
Step 2	For IV	Sodium Chloride Injection 0.9%	2.5ml	5ml	10ml
	For IM		1ml	2ml	4ml

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔ بچوں کی پہنچ سے دور رکھیں۔
دوا کو ۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں، گرمی، روشنی اور نمی سے محفوظ رکھیں۔
ریفریجریٹر یا فریزر میں رکھنے سے گریز کریں ورنہ دوا خراب ہو جائیگی۔
تیار شدہ محلول کو فوری استعمال کر لیں۔