PACKAGE INSERT

▼ 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. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Artesunate Amivas 110 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder contains 110 mg of artesunate.
Each vial of solvent for reconstitution contains 12 mL of 0.3 M sodium phosphate buffer.
After reconstitution, the solution for injection contains 10 mg of artesunate per mL.

Excipient(s) with known effect:
After reconstitution, the solution for injection contains 13.4 mg sodium per mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

Powder: white or almost white, fine crystalline powder.
Solvent: clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Artesunate Amivas is indicated for the initial treatment of severe malaria in adults and children (see sections 4.2 and 5.1).

Consideration should be given to official guidance on the appropriate use of antimalarial agents.

4.2 Posology and method of administration

It is recommended that Artesunate Amivas should be used to treat patients with severe malaria only after consultation with a physician with appropriate experience in the management of malaria.

Posology

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

Adults and children (birth to less than 18 years)
The recommended dose is 2.4 mg/kg (0.24 mL of reconstituted solution for injection per kg body weight) by intravenous (IV) injection at 0, 12 and 24 hours (see sections 4.4 and 5.2).

After at least 24 hours (3 doses) treatment with Artesunate Amivas, patients unable to tolerate oral treatment may continue to receive intravenous treatment with 2.4 mg/kg once every 24 hours (from 48 hours after start of treatment).

Treatment with Artesunate Amivas should be stopped when patients can tolerate oral treatment. After stopping Artesunate Amivas, all patients should receive a complete treatment course of an appropriate oral combination antimalarial regimen.

Elderly
No dose adjustment is required (see sections 4.4 and 5.2).

Renal impairment
No dose adjustment is required (see section 5.2).

Hepatic impairment
No dose adjustment is required (see section 5.2).

Paediatric population
No dose adjustment is recommended based on age or weight (see sections 4.4 and 5.2).

Method of administration

Artesunate Amivas is for IV administration only. The reconstituted solution should be administered as a slow bolus injection over 1-2 minutes.

Artesunate Amivas must be reconstituted with the supplied solvent prior to administration. Because of the instability of artesunate in aqueous solutions the reconstituted solution must be used within 1.5 hours 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.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance, to any other artemisinin antimalarial agent or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity

Allergic reactions to intravenous artesunate, including anaphylaxis have been reported. Other reported allergic reactions include urticaria, rash and pruritus (see section 4.8).

Post-artesunate delayed haemolysis

Post-artesunate delayed haemolysis (PADH) is characterised 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 has been reported to occur very commonly after successful treatment of severe malaria that commenced with IV artesunate in returning travellers. The risk of PADH may be highest in patients with hyperparasitaemia and in younger children. Patients should be monitored for evidence of haemolytic anaemia for 4 weeks after starting artesunate treatment. Spontaneous recovery from PADH usually occurs within a few weeks. However, cases of post-artesunate haemolytic anaemia severe enough to require transfusion have been reported. Since a subset of patients with delayed haemolysis after artesunate therapy have evidence of immune haemolytic anaemia, performing a direct antiglobulin test should be considered to determine if therapy, e.g. with corticosteroids, is necessary. See section 4.8.

Reticulocytopenia

The artemisinins have shown direct inhibitory effects on human erythroid precursors *in vitro* and inhibit bone marrow responses (especially red blood cell precursors) in animal models. Both animal preclinical data and human data from clinical trials have suggested that reversible reticulocytopenia occurs at least commonly in association with treatment with intravenous artesunate (see section 4.8). The reticulocyte count recovers after cessation of treatment.

Malaria due to *Plasmodium vivax, Plasmodium malariae* or *Plasmodium ovale*

Artesunate Amivas has not been 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 (see section 5.1). It 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*. 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 clinical data to establish the safety and efficacy of Artesunate Amivas in infants below 6 months of age. Pharmacokinetic modelling and simulations indicate that after 2.4 mg/kg IV artesunate the dihydroartemisinin (DHA) plasma exposures in infants aged less than 6 months are likely to be higher than those in older infants and children (see section 5.2).

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 (see section 5.2).

Information about excipients

This medicinal product contains 193 mg sodium per the recommended single dose for a 60 kg adult, equivalent to 9.6 % of the WHO recommended maximum daily intake of 2 g sodium for an adult. As the first and second doses are recommended 12 hours apart, on days when two doses are given in a 24 hour period, then the dose would be 386 mg sodium per day, equivalent to 19.2 % of the WHO recommended maximum daily intake of 2 g 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 Amivas.

Effect of other medicinal products on artesunate and/or dihydroartemisinin (DHA)

After intravenous administration, artesunate is converted to DHA by esterases and by CYP2A6. DHA is converted to inactive glucuronide conjugates primarily by UGT1A9.

Co-administration of intravenous artesunate with strong inhibitors of UGT enzymes (e.g. axitinib, vandetanib, imatinib, diclofenac) may increase plasma exposures to DHA. Co-administration should be avoided if possible.

Co-administration of Artesunate Amivas with UGT inducers (e.g. nevirapine, ritonavir, rifampicin, carbamazepine, phenytoin) may decrease DHA exposures, leading to a reduction in, or loss of, efficacy. Co-administration should be avoided.

Effect of artesunate and/or DHA on other medicinal products

Limited data from in-vitro studies and from clinical drug-drug interaction studies with oral artesunate and/or oral DHA have indicated that DHA induces CYP3A and inhibits CYP1A2. Caution is advised when co-administering intravenous artesunate with substrates of CYP3A4 or CYP1A2 that have narrow therapeutic windows.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited clinical experience with the use of Artesunate Amivas in the first trimester of pregnancy. A risk to the fetus cannot be excluded. Animal studies have shown reproductive toxicity (see section 5.3).

A moderate amount of clinical data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or feto/neonatal toxicity of artesunate when given IV in their second or third trimester.

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 breastfeeding 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.

Animal studies have reported effects on the male reproductive organs, however studies on female rats show no effect on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients should be warned not to drive or use machines if they feel tired or dizzy.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse drug reaction reported in clinical trials has been anaemia. While anaemia occurs very commonly in patients with severe malaria as a result of the disease and effective treatment, anaemia that was not dose-related was also reported in healthy subjects in clinical pharmacology studies with IV artesunate.

Post-Artesunate Delayed Haemolysis (PADH) has been reported very commonly following effective treatment of severe malaria with IV artesunate in travellers and in children (see section 4.4).

Reticulocytopenia that resolves after completion of treatment with IV artesunate occurs commonly or very commonly (see section 4.4).

Tabulated list of adverse reactions

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) and unknown (frequency cannot be determined) (Table 1).

Table 1. Summary of adverse drug reactions by organ system and frequency

Organ Systems	Very Common	Common	Uncommon	Not known
Infections and Infestations		Rhinitis		
Blood and Lymphatic System Disorders	Anaemia Reduced reticulocyte count Post-artesunate delayed haemolysis			Immune haemolytic anaemia
Metabolism And Nutrition Disorders			Anorexia	
Nervous System Disorders		Dizziness, Dysgeusia, Headache		
Cardiac Disorders		Bradycardia		Electrocardiogram QT prolonged
Vascular Disorders		Hypotension, Phlebitis	Flushing	
Respiratory, Thoracic and Mediastinal Disorders		Cough		
Gastrointestinal Disorders		Abdominal Pain, Diarrhoea, Vomiting	Nausea, Constipation	
Hepatobiliary Disorders		Hyperbilirubinaemia Jaundice		

Organ Systems	Very Common	Common	Uncommon	Not known
Skin and Subcutaneous Tissue Disorders			Stevens-Johnson Syndrome, Pruritus, Rash, Urticaria	
Renal and Urinary Disorders		Haemoglobinuria Acute renal failure		
General Disorders and Administration Site Conditions		Pyrexia	Fatigue, Pain at injection site	
Immune System Disorders				Anaphylaxis
Investigations		ALT increased, AST increased		

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 professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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.

Clinical efficacy
In SEAQUAMAT (Southeast Asian Quinine Artesunate Malaria Trial), an open-label, multicentre trial conducted in Bangladesh, India, Indonesia and Myanmar, 1461 patients (1259 adults and 202 children <15 years) with severe falciparum malaria were randomised to initial intravenous treatment with artesunate or quinine until oral medication could be tolerated. Artesunate was administered at 2.4 mg/kg IV at 0, 12 and 24 hours and then every 24 hours. Quinine was given IV at 20 mg/kg over 4 hours, followed by 10 mg/kg thrice daily over 2-8 hours. Mortality in the intention to treat population was 14.7% (107 of 730) in the artesunate group compared to 22.4% (164 of 731) in the quinine group, a reduction in the odds of death adjusted by study site of 40% (95% CI: 21%, 55%; p=0.0002). Mortality in patients with severe malaria in the artesunate group was 19.8% (101 of 509) compared to 28.1% (152 of 541), a reduction in the odds of death adjusted by study site of 35% (95% CI: 13%, 52%; p=0.003).

AQUAMAT (African Quinine Artesunate Malaria Trial) was an open-label multicentre trial in which African children aged < 15 years (n=5425) with severe falciparum malaria were randomised to parenteral artesunate or parenteral quinine using the same dose as in SEAQUAMAT. Mortality in the intent to treat population was 8.5% (230 of 2712) in the artesunate group compared to 10.9% (297 of 2713) in the quinine group, a reduction in the odds of death adjusted by study site of 25% (95% CI: 10%, 37%; p=0.0022). Mortality in children with severe malaria in the artesunate group was 9.9% (226 of 2280) compared to 12.4% (291 of 2338) in the quinine group, a reduction in the odds of death adjusted by study site of 23% (95% CI: 7%, 36%; (p=0.0055).

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 in Table 2.

Table 2: Summary of pharmacokinetic parameters in patients with severe malaria

PK Parameter	Artesunate	DHA
C_{max} (mcg/mL)	3.3 (1.0-164)	3.1 (1.7-9.5)
AUC (mcg-h/mL)	0.7 (0.3-111.3)	3.5 (2.2-6.3)
Distribution		
Volume of Distribution (L)	68.5 (0.2-818)	59.7 (26-117)
Protein Binding	Approximately 93%	
Elimination		
Half-life (hours)	0.3 (0.1-1.8)	1.3 (0.9-2.9)
Clearance (L/h)	180 (1-652)	32.3 (16-55)
In vitro Metabolism		
Primary Pathway	Blood Esterases	Glucuronidation
Metabolite	DHA	α-DHA-β-glucuronide
Excretion		
Urine	Unknown	Unknown
PK=pharmacokinetics, AS=artesunate, DHA=dihydroartemisinin, C_{max}=maximum concentration, AUC=area under the concentration-time curve		

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 (see sections 4.2 and 4.4).

Renal impairment
No pharmacokinetic data are available for patients with impaired renal function. Clinical trial data from patients with severe malaria and accompanying renal impairment at start of treatment indicate that no dose modifications are necessary.

Hepatic impairment
No pharmacokinetic data are available for patients with impaired hepatic function. Clinical trial data from patients with severe malaria and accompanying hepatic impairment at start of treatment indicate that no dose modifications are necessary.

Paediatric population
There are limited PK data on the use of IV artesunate in neonates and infants. Physiologically-based PK modelling and simulations predict that plasma exposures are likely to be higher in infants below 6 months of age compared to infants aged more than 6 months (see section 4.4).

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, an *in vivo* mouse bone marrow micronucleus assay using oral administration, and in an *in vivo* micronucleus assay in rats when administered intravenously. 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
In a fertility and early embryonic development study IV administration of artesunate to rats at between 1-2 times the clinical dose (based on body surface area comparisons) did not affect female fertility, or early embryonic development. Oral administration of artesunate during organogenesis in rats, rabbits, and monkeys induces a dose-dependent increase in embryolethality and fetal 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 fetal 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
Solvent:
Monosodium phosphate monohydrate
Disodium phosphate dihydrate
Phosphoric acid, concentrated (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

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

6.3 Shelf life
The expiry date can be found on the packaging

Chemical and physical in-use stability has been demonstrated for 1.5 hours at 25°C.
From a microbiological point of view, unless the method of opening/reconstituting/dilution precludes the risks of microbial contamination, the product should be used immediately.
If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage
This medicine should be stored at or below 30°C but above freezing temperatures and protected from the light

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container
The powder is supplied in a Type I glass vial capped with a latex-free bromobutyl rubber stopper and aluminium seal, with a royal blue flip-off cap, containing 110 mg of artesunate.

The solvent is supplied in a Type I glass vial capped with a latex-free bromobutyl rubber stopper and aluminium seal, with a royal blue flip-off cap, containing 12 mL of sterile 0.3 M sodium phosphate buffer for reconstitution.

Each pack contains 2 vials of artesunate powder and 2 vials of sodium phosphate buffer solvent.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Instructions for reconstitution
Withdraw 11 mL of the supplied 0.3 M sodium phosphate buffer with a needle and syringe and inject into the vial containing Amivas Artesunate powder for injection (the final concentration of artesunate is 10 mg/mL when reconstituted). Swirl gently (do not shake) for up to 5 to 6 minutes until the powder is fully dissolved and no visible particles remain.

Instructions for use and disposal
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.

7. Product Owner
Amivas Ireland Ltd
Suite 5, Station House, Railway SQ, Waterford, Ireland

8. MARKETING AUTHORISATION NUMBER(S)
SINxxxx

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Mock-up Leaflet