ANNEX I

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. 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). The use of Artesunate Amivas in the first trimester is therefore not recommended unless the benefit to the mother outweighs the risk to the fetus.

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. As a precautionary measure, it is preferable to avoid the use of Artesunate Amivas during the second or third trimester of pregnancy.

Pregnancy registry
A pregnancy registry has been set up to monitor all pregnancies and their outcomes following treatment with Artesunate Amivas.

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		
Skin and Subcutaneous Tissue Disorders			Stevens-Johnson Syndrome, Pruritus, Rash, Urticaria	

Organ Systems	Very Common	Common	Uncommon	Not known
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 (South East 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

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

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

4 years

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 medicinal product does not require any special storage conditions.

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, 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, containing 12 mL of sterile 0.3 M sodium phosphate buffer for reconstitution.

Each pack contains 2 or 4 vials of artesunate powder and 2 or 4 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. MARKETING AUTHORISATION HOLDER

Amivas Ireland Ltd
Suite 5, Second Floor
Station House
Railway Square
Waterford
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1582/001
EU/1/21/1582/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22/11/2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

MIAS Pharma Limited,
Suite 1 Stafford House,
Strand Road,
Portmarnock,
Co. Dublin, Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (2 X 2 VIALS) (4 X 4 VIALS)

1. NAME OF THE MEDICINAL PRODUCT

Artesunate Amivas 110 mg powder and solvent for solution for injection
artesunate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients: monosodium phosphate monohydrate, disodium phosphate dihydrate, phosphoric acid, concentrated, sodium hydroxide, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

2 vials of artesunate powder and 2 vials of sodium phosphate buffer solvent
4 vials of artesunate powder and 4 vials of sodium phosphate buffer solvent

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.
Reconstitute before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Reconstituted solution must be used within 1.5 hours of preparation.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Amivas Ireland Ltd
Suite 5, Second Floor
Station House
Railway Square
Waterford
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1582/001
EU/1/21/1582/002

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

POWDER VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

Artesunate Amivas 110 mg powder for solution for injection
artesunate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of powder contains 110 mg of artesunate
After reconstitution, the solution for injection contains 10 mg artesunate per mL

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.
Reconstitute with 11 mL of enclosed solvent before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Reconstituted solution must be used within 1.5 hours of preparation

9. SPECIAL STORAGE CONDITIONS

Date and time of reconstitution: _/_/_

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Amivas Ireland Ltd
Suite 5, Second Floor
Station House
Railway Square
Waterford
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1582/001
EU/1/21/1582/002

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

SOLVENT VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

Artesunate Amivas 110 mg solvent for solution for injection
sodium phosphate buffer

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of solvent for reconstitution contains 12 mL of 0.3 M sodium phosphate buffer

3. LIST OF EXCIPIENTS

Excipients: monosodium phosphate monohydrate, disodium phosphate dihydrate, phosphoric acid, concentrated, sodium hydroxide, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solvent for solution for injection

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For reconstitution use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Amivas Ireland Ltd
Suite 5, Second Floor
Station House
Railway Square
Waterford
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

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EU/1/21/1582/002

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Artesunate Amivas 110 mg powder and solvent for solution for injection
artesunate

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Artesunate Amivas is and what it is used for

Artesunate Amivas contains the active substance artesunate. Artesunate Amivas is used to treat severe malaria in adults and children.

After treatment with Artesunate Amivas your doctor will complete your treatment for malaria with a course of anti-malarial medication that can be taken by mouth.

2. What you need to know before you are given Artesunate Amivas

Do not use Artesunate Amivas
- if you are allergic to artesunate, to any other antimalarial treatment that contains an artemisinin (e.g. artemether or dihydroartemisinin) or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
You may develop anaemia, a reduced number of red blood cells, or other blood changes after treatment with this medicine. Some changes to numbers of blood cells can occur while you are being treated and usually recover after stopping treatment for malaria. However, some individuals develop severe anaemia that can occur up to several weeks after completing treatment for malaria. In most cases, the anaemia recovers without any specific treatment. In a small number of cases the anaemia may be severe and require blood transfusion. Your doctor will carry out regular blood tests that can include a direct antiglobulin test to determine if treatment, e.g. with corticosteroids, is necessary and monitor your recovery for 4 weeks after you have completed your treatment for malaria. It is important you attend appointments for these check-ups. Talk to your doctor for more information.

Other medicines and Artesunate Amivas
Tell your doctor if you are taking, have recently taken or might take any other medicines. This includes medicines not on prescription.

Some medicines should not be taken with artesunate because they could reduce its effect on malaria. Some examples include:

- rifampicin (to treat bacterial infections)
- ritonavir, nevirapine (anti-HIV medication)
- carbamazepine, phenytoin (to treat epilepsy)

Some medicines may increase blood levels of artesunate and may increase the risk of side effects. Some examples include:

- diclofenac (to treat pain or inflammation)
- axitinib, vandetanib and imatinib (used in the treatment of certain cancers)

Artesunate may increase or decrease the blood levels of some other medicines. Your doctor will advise you on taking any medicines during artesunate treatment.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, you should talk to your doctor before being given this medicine.

Your doctor will discuss with you the potential risk of taking Artesunate Amivas during pregnancy. Use in the first trimester of pregnancy is not recommended unless your doctor decides that the benefit of treatment for you outweighs the risk to your unborn child. In the later stages of pregnancy, you should only take Artesunate Amivas if your doctor feels that there are no suitable alternative medicines.

If you are or become pregnant during treatment with this medicine, the doctor will report your pregnancy to the manufacturer, who is keeping a record in order to understand any effects that the treatment may have on the pregnancy and the baby.

Traces of this medicine may be present in your breast milk. It is not known if these could have any effect on a breastfed baby. If you are planning to breastfeed, discuss with your doctor whether the benefits of breastfeeding to you and your baby outweigh the potential risk.

Driving and using machines
You should not drive or use machines if you feel tired or dizzy.

Artesunate Amivas contains sodium
This medicine contains 193 mg sodium (main component of cooking/table salt) in each single dose. This is equivalent to just under 10 % of the recommended maximum daily dietary intake of sodium for an adult.
As the first and second doses are recommended 12 hours apart, this would supply 386 mg sodium (nearly 20 %of your maximum daily intake).

3. How Artesunate Amivas is given

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

This medicine will be given to you by a slow injection directly into a vein. Your doctor or nurse will inject this medicine for you.

The dose of the medicine you are given is based on your weight and your doctor or nurse will work out the right amount to give you. The recommended dose is 2.4 mg for each kg of body weight. The dose per kg is the same for adults and children of all ages.

You will be given at least three doses of Artesunate Amivas, each dose given 12 hours apart. After three doses, if you still cannot take medicines by mouth, you will be given one dose of Artesunate Amivas every 24 hours (once a day) until you are able to take a different malaria treatment by mouth.

It is very important that you complete a full course of antimalarial treatment taken by mouth after you have had at least three doses of Artesunate Amivas by injection.

If you are given more Artesunate Amivas than you should
As this medicine will be given to you in a hospital, it is unlikely that you will be given too much. Tell your doctor if you have any concerns. Signs of an overdose include seizures, dark coloured stools, a blood test showing low blood cell counts, weakness, fatigue, fever and nausea. Your doctor will help to treat these symptoms if you are given too much of this medicine.

If a dose of Artesunate Amivas is forgotten
As this medicine will be given to you in a hospital, your doctor or nurse will manage your treatment and it is unlikley a dose will be forgotten. Should a dose be delayed, your doctor or nurse will give the required dose at the earliest opportunity and continue to give future doses 12 or 24 hours apart.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you experience any of the following side effects seek medical help immediately:
- difficulty breathing or swallowing, swelling of your face, mouth or throat. These are signs you may be having a severe allergic reaction. The frequency of very severe allergic reactions leading to loss of consciousness is unknown.

Very common side effects (may affect more than 1 in 10 people)
a lack of healthy red blood cells, which can make you feel tired and weak (anaemia); this can develop at least 7 days or sometimes several weeks after treatment has finished.

Common side effects (may affect up to 1 in 10 people)
- inflammation of a vein
- altered sense of taste
- raised body temperature or fever
- very dark yellow or reddish brown coloured urine
- reduced kidney function, including low urine output
- bruising easily or slow clotting of any cuts or wounds.
- abnormal levels of liver enzyme levels detected in blood tests
- yellowing of the skin (jaundice)
- diarrhoea
- abdominal pain
- vomiting
- slow heart rate
- low blood pressure
- cough
- rhinitis (blocked and/or runny nose)
- feeling dizzy or weak
- headache

Uncommon (affecting less than 1 in 100 patients)
- tiredness
- feeling sick
- constipation
- pain at injection site
- painful widespread rash with blisters especially near mouth, nose, eyes and genitals, flu-like symptoms for several days (Stevens-Johnson syndrome or SJS)
- loss of appetite
- rash
- itching
- swelling and reddening of the face
- flushing

Not known (frequency cannot be estimated from the available data)
- a lack of healthy red blood cells caused by your immune system (immune haemolytic anaemia)
- abnormal electrical activity of the heart that affects its rhythm (Prolonged electrocardiogram QT)

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Artesunate Amivas

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label on the carton after EXP.

This medicine does not require any special storage conditions.

The reconstituted solution must be used within 1.5 hours of preparation.

6. Contents of the pack and other information

What Artesunate Amivas contains
- The active substance is artesunate.
- 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.
- The other ingredients in the 0.3 M sodium phosphate buffer solvent are monosodium phosphate monohydrate, disodium phosphate dihydrate (see section 2 “Artesunate Amivas contains sodium”) and phosphoric acid, concentrated (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

After reconstitution with 11 mL of the solvent provided, the solution for injection contains 10 mg of artesunate per mL.

What Artesunate Amivas looks like and contents of the pack
Artesunate Amivas 110 mg powder and solvent for solution for injection.
The powder is white or almost white, fine crystalline powder in a glass vial.
The solvent is a clear, colourless liquid in a glass vial.

Each pack contains 2 or 4 vials of Artesunate Amivas powder and 2 or 4 vials of sodium phosphate buffer solvent.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Amivas Ireland Ltd, Suite 5, Second Floor, Station House, Railway Square, Waterford, Ireland

Manufacturer
MIAS Pharma Limited, Suite 1, Stafford House, Strand Road, Portmarnock, Co. Dublin, Ireland

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu

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The following information is intended for healthcare professionals only:

Preparation and Administration

The required dose of Artesunate Amivas should be calculated prior to reconstitution:

Dose mg = patient's weight in kg x 2.4

Only the required number of vials of Artesunate Amivas should be reconstituted when preparing the dose. Remaining unopened vials can be stored in the carton ready for use at the next scheduled dose.

To reconstitute, withdraw 11 mL of the supplied solvent (0.3 M sodium phosphate buffer) with a needle and syringe. Inject into the vial containing the artesunate powder (the final concentration of artesunate is 10 mg/mL when reconstituted). Swirl gently for 5 to 6 minutes until the powder is fully dissolved. Do not shake.

Visually inspect the solution within the vial to ensure that no visible particles remain and there is no discolouration. Do not administer if solution is discoloured or contains visible particles.

Inject the reconstituted drug solution IV as a slow bolus over 1-2 minutes. Do not administer via continuous IV infusion.

The recommended dosage schedule is at 0, 12, 24 and 48 hours, then once daily until alternative oral anti-malarial medication can be tolerated.

Artesunate Amivas also contains 193 mg sodium per the recommended single dose in 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.

Storage of reconstituted Artesunate Amivas solution

Once reconstituted, the Artesunate Amivas solution should be administered within 1.5 hours of preparation. Discard any unusued solution in accordance with local guidelines.