Product Monograph

Including Patient Medication Information

PrAMIVAS-ARTESUNATE

Artesunate for Injection

Sterile Powder for Solution, 110 mg/vial,

For Intravenous use

Diluent for Solution, 12 mL of sterile 0.3 M sodium phosphate buffer

Manufacturer's Standard

Antimalarial Agent

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

Distributor
Phebra Canada Inc.
7171 Frederick-Banting, Suite 216
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Date of Initial Authorization:
[2025-MM-DD]

Control Number: 285622

Recent Major Label Changes

None at the time of the most recent authorization.	

Table of Contents

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Part 1 : Health Professional Information

1. Indications

AMIVAS-ARTESUNATE (artesunate) is indicated for:

- The initial treatment of severe malaria in adult and pediatric patients.

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

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

LIMITATIONS OF USE
Artesunate 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.*

1.1 Pediatrics

Pediatrics (> 6 months– 18 years old): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of AMIVAS-ARTESUNATE in pediatric patients older than 6 months of age has been established. Therefore, Health Canada has authorized an indication for pediatric use.

Pediatrics (birth - 6 months): There was no clinical data of AMIVAS-ARTESUNATE in pediatric patients less than 6 months of age. Pharmacokinetic modelling and simulations indicated that after receiving a dose of 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 7 Warnings and Precautions, 7.1.3 Pediatrics and 10.3 Pharmacokinetics).

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Available data for the use of AMIVAS-ARTESUNATE in patients older than 65 years of age is limited.

2. Contraindications

AMIVAS-ARTESUNATE is contraindicated in:

- Patients who are hypersensitive to this drug, to any other artemisinin antimalarial agent, or to any ingredient in the formulation or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition and Packaging.

3. Serious Warnings and Precautions Box

Post-treatment Hemolysis: Cases of post-treatment hemolytic anemia severe enough to require transfusion have been reported. Monitor patients for 4 weeks after treatment for evidence of hemolytic anemia (see 4 Dosage and Administration and 7 Warnings and Precautions).

Hypersensitivity: Serious hypersensitivity reactions including anaphylaxis have been reported. Discontinue if signs of serious hypersensitivity occur (see 7 Warnings and Precautions).

4. Dosage and Administration

4.2 Recommended Dose and Dosage Adjustment

- AMIVAS-ARTESUNATE is for IV administration only. The reconstituted solution should be administered as a slow bolus injection over 1-2 minutes.
- Do not administer AMIVAS-ARTESUNATE via continuous intravenous infusion.
- 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.
- After at least 24 hours (3 doses) treatment with AMIVAS-ARTESUNATE, 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 AMIVAS-ARTESUNATE should be stopped when patients can tolerate oral treatment. **After stopping AMIVAS-ARTESUNATE all patients should receive a complete treatment course of an appropriate oral combination antimalarial regimen**.
- In patients with severe malaria due to *Plasmodium vivax* (*P. vivax)* or *Plasmodium ovale* (*P. ovale)*, AMIVAS-ARTESUNATE should be administered with an antimalarial agent that is active against the hypnozoite liver stage forms of *Plasmodium*, such as an 8-aminoquinoline drug.
- Monitor hemoglobin weekly for 4 weeks post artesunate therapy (see 3 Serious Warnings and Precautions Box, and 7 Warnings and Precautions).
- Geriatrics: No dose adjustment is required (see 7.1.4 Geriatrics and 10.3 Pharmacokinetics).
- Renal impairment: No dose adjustment is required (see 10.3 Pharmacokinetics).
- Hepatic impairment: No dose adjustment is required (see 10.3 Pharmacokinetics).
- Pediatric population: No dosage adjustment is recommended based on age and weight (see 7.1.3 Pediatrics and 10.3 Pharmacokinetics).

4.3 Reconstitution

AMIVAS-ARTESUNATE must be reconstituted with the supplied diluent prior to administration (see Table 1).

To reconstitute AMIVAS-ARTESUNATE, withdraw 11 mL of the supplied 0.3 M sodium phosphate diluent with a needle and syringe and inject into the vial containing 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.

Table 1 - Reconstitution

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Concentration per mL
20 mL	11 mL	11 mL	10 mg/mL

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.

Discard the vial and any unused portion of the reconstituted medicinal product after use (see 11 Storage, Stability and Disposal).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements (see 11 Storage, Stability and Disposal).

4.4 Administration

AMIVAS-ARTESUNATE must be reconstituted before administration (see 4.3 Reconstitution).

Because of the instability of artesunate in aqueous solutions the reconstituted solution must be used within 1.5 hours of preparation (see 11 Storage, Stability and Disposal). 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.

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

AMIVAS-ARTESUNATE must not be mixed with other medicinal products.

4.5 Missed Dose

Should a dose be missed or delayed, AMIVAS-ARTESUNATE should be administered at the earliest opportunity and continue to give the remaining doses 12 or 24 hours apart.

5. Overdose

Experience of acute overdose with artesunate is limited. One fatal overdose case has been reported in a 5-year-old child administered rectal artesunate at 88 mg/kg/day for 4 days (almost 8-fold over the highest recommended dose). Clinical signs included pancytopenia, melena, seizures, and multiorgan failure before death.

In cases of suspected overdosage, symptomatic and general supportive therapy should be given as appropriate.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition and Packaging

Table 2 - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Powder for Solution, 110 mg Solution 12 mL of sterile 0.3 M sodium phosphate buffer	Concentrated phosphoric acid, disodium phosphate dihydrate, monosodium phosphate monohydrate, sodium hydroxide, water for injection

Description

AMIVAS-ARTESUNATE is a white or almost white, fine crystalline powder available in a Type I glass vial capped with a latex-free bromobutyl rubber stopper and an aluminium seal.

Each vial of powder contains 110 mg of artesunate. After reconstitution (see 4.3 Reconstitution), each mL contains 10 mg of artesunate.

The diluent consists of a clear and colourless sodium phosphate buffer for reconstitution available in a Type I glass vial capped with a latex-free bromobutyl rubber stopper and aluminium seal.

Each vial of diluent contains 12 mL of 0.3 M sodium phosphate buffer.

After reconstitution, each mL contains 13.4 mg of sodium.

7. Warnings and Precautions

See 3 Serious Warnings and Precautions Box

General

Malaria due to *P. vivax, Plasmodium malariae* (*P. malariae*) or *P. ovale*

AMIVAS-ARTESUNATE has not been evaluated in the treatment of severe malaria due to *P. vivax, P. malariae* or *P. ovale.* Available data indicates that it is effective against all *Plasmodium* species (see 1 Indications, 4.2 Recommended Dose and Dosage Adjustment and 15 Microbiology). It does not treat the hypnozoite liver stage forms of *Plasmodium* and will therefore not prevent relapses of malaria due to *P. vivax* or *P. 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*.

Hematologic

Post-artesunate delayed hemolysis

Post-artesunate delayed hemolysis (PADH) is characterised by decreased hemoglobin with laboratory evidence of hemolysis (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 hyperparasitemia and in younger pediatric patients. Patients should be monitored for evidence of hemolytic anemia for 4 weeks after starting artesunate treatment (see 3 Serious Warnings and Precautions Box and 7 Warnings and Precautions: Monitoring and Laboratory Tests). Spontaneous recovery from PADH usually occurs within a few weeks. However, cases of post-artesunate hemolytic anemia severe enough to require transfusion have been reported. Since a subset of patients with delayed hemolysis after artesunate therapy have evidence of immune hemolytic anemia, performing a direct antiglobulin test should be considered to determine if therapy, e.g. with corticosteroids, is necessary.

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 commonly in association with treatment with intravenous artesunate. The reticulocyte count recovers after cessation of treatment.

Immune

Hypersensitivity

Allergic reactions to intravenous artesunate, including anaphylaxis, have been reported. Other reported allergic reactions include Stevens-Johnson syndrome, urticarial rash and pruritus (see 8.1 Adverse Reactions Overview).

Monitoring and Laboratory Tests

Monitor hemoglobin on Days 7, 14, 21 and 28 post artesunate therapy. If a decrease in hemoglobin is detected, additional laboratory tests for hemolysis could include haptoglobin, lactate dehydrogenase and direct antiglobulin (see 3 Serious Warnings and Precautions Box, 4 Dosage and Administration and PADH in Hematologic above).

Reproductive Health

- **Fertility**
  No fertility data are available in humans. Animal studies have reported effects on the male reproductive organs (see section 16 Non-Clinical Toxicology).

7.1 Special Populations

7.1.1 Pregnancy

The use of AMIVAS-ARTESUNATE in the first trimester is not recommended unless the benefit to the mother outweighs the risk to the fetus. There is limited clinical experience with the use of AMIVAS-ARTESUNATE in the first trimester of pregnancy. A risk to the fetus cannot be excluded. Animal studies have shown reproductive toxicity (see 16 Non-Clinical Toxicology).

A moderate amount of clinical data on pregnant women (between 300-1,000 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 AMIVAS-ARTESUNATE during the second or third trimester of pregnancy.

Delaying treatment of severe malaria in pregnancy may result in serious morbidity and mortality to the mother and fetus.

Advise women who are exposed to AMIVAS-ARTESUNATE during pregnancy that there is a pregnancy safety study that monitors pregnancy outcomes. Encourage these patients to report their pregnancy to Amivas, Inc. at 1-855-526-4827 (1-855-5AMIVAS) or www.amivas.com/our-products.

7.1.2 Breastfeeding

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.

7.1.3 Pediatrics

The safety and effectiveness of AMIVAS-ARTESUNATE have been established in pediatric patients **older than 6** months of age. This indication is supported by evidence from clinical studies in adults and pediatric patients with additional pharmacokinetic and safety data in pediatric patients aged 6 months and older (see 8 Adverse Reactions and 14 Clinical Trials).

There was insufficient clinical data to establish the safety and effectiveness of AMIVAS-ARTESUNATE in infants below 6 months of age. Pharmacokinetic modelling and simulations indicate that after receiving a dose of 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 10.3 Pharmacokinetics).

7.1.4 Geriatrics

There are limited clinical data regarding the safety and efficacy of AMIVAS-ARTESUNATE in patients 65 years and older (see 10.3 Pharmacokinetics).

8. Adverse Reactions

8.1 Adverse Reaction Overview

The most common adverse drug reaction reported in clinical trials has been anemia. Reticulocytopenia that resolves after completion of treatment with IV artesunate occurs commonly or very commonly (see section 7 Warnings and Precautions).

Patients in clinical trials for artesunate were assessed for neurologic sequelae at the time of hospital discharge. Numerically, a greater number of patients in the artesunate arm of these trials had neurological sequalae at discharge from the hospital than the number in the quinine arm and the neurologic sequelae included loss of balance, hemiplegia/ paresis, ataxia, neuropsychiatric symptoms, tremor, generalized weakness, and confusion and restlessness.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Tables 3 and 4 summarize the adverse reactions occurring in > 2% in artesunate arm vs. the quinine comparator arm, in the 2 pivotal trials (see 14.1 Clinical Trials by Indication).

Table 3 - Summary of Artesunate Adverse Drug Reactions by Organ System – Trial 1

System organ class/preferred term	Artesunate n = 730 (%)	Quinine n = 731 (%)
Infection and Infestation		
Blackwater fever	49 (6.7)	33 (4.5)
Renal		
Dialysis	60 (8.2)	48 (6.6)

Note: Blackwater fever is a clinical scenario characterized by intravascular hemolysis, hemoglobinuria (with dark brown or red urine) and renal failure.

Table 4 - Summary of Artesunate Adverse Drug Reactions by Organ System – Trial 2

System organ class/preferred term	Artesunate n = 2712 (%)	Quinine n = 2713 (%)
Blood and Lymphatic Tissue Disorders		
Acute anemia	155 (5.7)	125 (4.6)
Nervous system disorder		
Coma	138 (5.1)	95 (3.5)
Convulsions	274 (10.1)	225 (8.3)
Investigations		
Hypoglycemia	76 (2.8)	49 (1.8)

The following clinically significant adverse reactions occurred in at least 2% of healthy volunteers or patients.

Blood and Lymphatic system disorders: leukopenia, reduced reticulocytes

Gastrointestinal disorders: abdominal pain, vomiting

General disorders and administration site conditions: pyrexia

Hepatic/Biliary/Pancreatic disorders: hyperbilirubinemia

8.3 Less Common Clinical Trial Adverse Reactions:

The following clinically significant adverse reactions occurred in less than 2% of healthy volunteers or patients.

Blood and Lymphatic system disorders: thrombocytopenia, lymphopenia, neutropenia, disseminated intravascular coagulation, leukocytosis

Ear/Nose/Throat disorders: cough, tinnitus, rhinitis

Gastrointestinal disorders: nausea, constipation, diarrhea,

General disorders and administration site conditions: fatigue, pain at injection site

Immune system disorders: Immune hemolytic anemia, Stevens-Johnson syndrome

Metabolism and Nutrition disorders: anorexia

Monitoring and Laboratory Tests: transaminase increased, elevated creatinine

Neurologic disorders: headaches, dizziness, dysgeusia

Renal disorders: acute renal failure, hemoglobinuria

Respiratory disorders: acute respiratory distress syndrome, pneumonia, pulmonary edema

Skin and subcutaneous tissue disorders: pruritus, rash, urticaria

Vascular disorders: flushing, hypotension, phlebitis

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during use of parenteral artesunate. Because the reactions are reported voluntarily from a population of uncertain size, it is not possible to estimate their frequency reliably or to establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: delayed hemolysis, immune hemolytic anemia, hemolysis

Gastrointestinal disorders: pancreatitis

General disorders and administration site conditions: drug resistance, general physical health deterioration, treatment failure

Immune system disorders: hypersensitivity, anaphylaxis

9. Drug Interactions

9.2 Drug Interactions Overview

After intravenous administration, artesunate is converted to DHA by esterases and by CYP2A6. DHA is converted to inactive glucuronide conjugates by UGT1A9 and UGT2B7.

Co-administration of AMIVAS-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 AMIVAS-ARTESUNATE 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.

Limited data from *in vitro* studies and from published studies with oral artesunate and/or oral DHA have indicated that DHA may induce CYP3A and inhibit CYP1A2. Caution is advised when co-administering AMIVAS-ARTESUNATE with substrates of CYP3A4 or CYP1A2 that have narrow therapeutic windows.

9.3. Drug-Behaviour Interactions

The interaction of AMIVAS-ARTESUNATE with individual behavioural risks (e.g. cigarette smoking, cannabis use, and/or alcohol consumption) has not been studied.

9.4 Drug-Drug Interactions

No clinical drug-drug interactions studies have been conducted with AMIVAS-ARTESUNATE.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. Clinical Pharmacology

10.1 Mechanism of Action

AMIVAS-ARTESUNATE is an antimalarial drug (see 15 Microbiology).

10.2 Pharmacodynamics

Cardiac Electrophysiology:

No definitive QT study was conducted.

At the approved intravenous dose of 2.4 mg/kg artesunate, artesunate and DHA do not cause large mean increases (i.e., 20 msec) in the QTc interval.

10.3 Pharmacokinetics

Absorption

The pharmacokinetic parameters of artesunate and DHA in patients with severe malaria following intravenous administration of 2.4 mg/kg artesunate as a bolus injection over 3-4 minutes are shown in Table 5.

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 *in vitro*

have been reported to contain very high DHA concentrations compared to plasma levels (e.g. 300-fold vs. mean plasma concentrations).

Metabolism

Artesunate is converted to DHA by cytochrome 2A6 and blood esterases. In human hepatocyte incubations of DHA, DHA-glucuronide was the main 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.

Table 5 - Summary of Median (Range) Pharmacokinetic Parameters in Patients with Severe Malaria (N=14)

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)
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		

Special populations and conditions: See also 4 Dosage and Administration

- **Pediatrics**

  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 7.1.3 Pediatrics).

- **Geriatrics**

  There are no pharmacokinetic data available after AMIVAS-ARTESUNATE dosing in patients aged 65 years or older with severe malaria (see 4.2 Recommended Dose and Dosage Adjustment and 7 Warnings and Precautions).

- **Hepatic Insufficiency**

  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.

- **Renal Insufficiency**

  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.

11. Storage, Stability and Disposal

Store at 15°C - 30°C. Do not freeze. Protect from light.

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

Keep out of the sight and reach of children.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Part 2: Scientific Information

13. Pharmaceutical Information

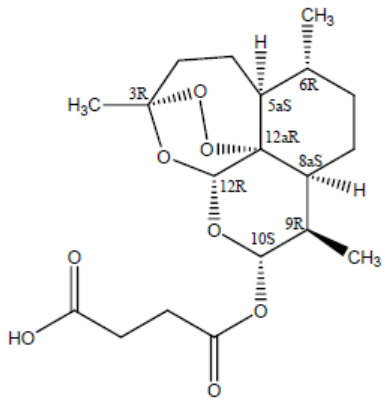
Drug Substance

Proper name: Artesunate

Chemical name(s): Butanedioic acid, [3R-(3α,5aβ,6β,8aβ,9α,10β,12β,12a R*)] mono(decahydro-3,6,9-trimethyl- 3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin-10-yl) ester

Molecular formula and molecular mass: $C_{19}H_{28}O_{8,}$ M_r = 384.43

Structural formula:



Physicochemical properties: Artesunate is a fine, white to almost white crystalline powder. Artesunate is very soluble in dichloromethane, soluble in ethyl acetate, freely soluble in ethanol and acetone, very slightly soluble in water, and insoluble in hexane.

14. Clinical Trials

14.1. Clinical Trials by Indication

Trial Design and Study Demographics

Table 6 – Summary of Patient Demographics for Clinical Trials in the Treatment of Severe Malaria

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Gender
Trial 1 (Dondorp 2005)	Open-label, multicentre, randomized	Artesunate 2.4 mg/kg IV at 0, 12 and 24 hours and then every 24 hours for artesunate Quinine 20 mg/kg IV over 4h, followed by 10 mg/kg infused over 2-8h thrice (3) daily for quinine	Artesunate (730) Quinine (731)	Artesunate: 27.9 years (2 - 85) Quinine: 27.9 years (2 - 87)	1,075 males 386 females
Trial 2 (Dondorp 2010)	Open-label, multicentre, randomized	Artesunate 2.4 mg/kg IV at 0, 12 and 24 hours and then every 24 hours for artesunate Quinine 20 mg/kg IV over 4h, followed by 10 mg/kg infused over 2-8h thrice (3) daily for quinine	Artesunate (2712) Quinine (2713)	Artesunate: 2.8 years (1.7 - 4.3) Quinine: 2.9 years (1.6 - 4.2)	2,815 males 2,610 females

In Trial 1 (Dondorp 2005), an open-label, multi-centre trial conducted in Bangladesh, India, Indonesia and Myanmar, 1,461 patients (1,259 adults and 202 pediatric patients <15 years) with severe falciparum malaria were randomized 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

Trial 2 (Dondorp 2010) was an open-label multi-centre trial in which African pediatric patients aged < 15 years (n=5425) with severe falciparum malaria were randomized to parenteral artesunate or parenteral quinine using the same dose as in Trial 1.

Table 7 - Results of Trial 1 (Dondorp 2005) and Trial 2 (Dondorp 2010) in Malaria

	Trial 1			Trial 2		
	Artesunate (N = 730)	**Quinine (N = 731)**	**Treatment difference (95% CI)[a]**	**Artesunate (N = 2712)**	**Quinine (N = 2713)**	**Treatment difference (95% CI) [a]**
Primary endpoint						
Mortality in Intent-to-Treat (ITT) population	14.7 %	22.4%	OR 0.59 (0.45, 078) p=0.0002	8.5%	10.9%	OR 0.75, (0.63–0.90) p= 0.0022[b]
Mortality in patients with severe malaria (SM)	19.8%	28.1%	OR: 0.63 (0.48, 0.84) p=0.0031	9.9 %	12.4%	OR 0.77, (0.64–0.93) p= 0.0055[b]

a. Based on Odds Ratio (OR) stratified by study site b. Statistically significant under multiplicity control for artesunate vs quinine comparison

15. Microbiology

Mechanism of Action: Artesunate is rapidly metabolized into an active metabolite, DHA. Artesunate and DHA, like other artemisinins contain an endoperoxide bridge that is activated by heme iron leading to oxidative stress, inhibition of protein and nucleic acid synthesis, ultrastructural changes as well as a decrease in parasite growth and survival.

Both artesunate and DHA are active against the asexual forms of the *Plasmodium* parasites and clear parasites within 48 to 72 hours.

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*).

Antimicrobial activity: Artesunate and DHA are active against the blood-stage asexual parasites and gametocytes of *Plasmodium* species. However, artesunate and DHA are not active against the hypnozoite liver stage forms of *P. vivax* and *P. ovale.*

Artemisinin resistance: Decreases in 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.

16. Non-Clinical Toxicology

Carcinogenicity

Carcinogenicity studies have not been conducted with artesunate.

Genotoxicity

Artesunate was negative in an *in vitro* bacterial reverse mutation assay, an *in vitro* Chinese hamster ovary chromosome aberration assay, and in an *in vivo* rat peripheral blood micronucleus assay using intravenous administration.

However, the published literature indicates that artesunate induced DNA damage, as detected by Comet assay, in human lymphocytes and HepG2 liver cells *in vitro* and in the spermatozoa of intraperitoneally treated mice. The published literature also indicates that artesunate increased micronuclei formation in human lymphocytes *in vitro*.

Reproductive and Developmental Toxicology

Animal reproduction studies in several species have demonstrated fetal harm from oral and intravenously administered artesunate. The clinical relevance of the animal data is uncertain.

A single dose of intravenous artesunate at 1.5 mg/kg (approximately 0.1 times the clinical dose based on body surface area [BSA] comparisons) administered to pregnant rats during early organogenesis on gestation day (GD) 11 resulted in complete postimplantation loss. A mass balance study conducted in pregnant rats administered a single dose of 5 mg/kg intravenous ^{14}C-artesunate on GD 11 (corresponding to 0.3 times the recommended clinical dose based on BSA comparisons) showed distribution of radiolabeled artesunate (approximately 7% of detected radioactivity) to feto-placental tissues.

Pregnant rats dosed orally during organogenesis (GD 6 through 17) with 6, 10 and 16.7 mg/kg/day artesunate (approximately 0.4- to 1.1-times the clinical dose based on BSA comparisons) showed dose-dependent postimplantation losses, with surviving fetuses displaying cardiovascular (ventricular septal defects, abnormal origin of subclavian artery) and skeletal (e.g., bent and/or shortened scapulae, humeri, femurs, and fibulae) malformations in the absence of maternal toxicity. Oral dosing in pregnant rabbits during organogenesis (GD 7 through GD 19) at doses of 5, 7, and 12 mg/kg/day artesunate (0.7- to 1.6-times the clinical dose based on BSA comparisons) resulted in cardiovascular (ventricular septal defects, abnormal origin of subclavian artery), skeletal (e.g., cleft sternebrae, shortened and/or displaced ribs) and brain (dilated ventricles, pons absent) malformations in the absence of maternal toxicity. Additionally, administration of artesunate at 12 mg/kg/day to pregnant rabbits during organogenesis resulted in abortions and postimplantation loss. Oral administration of artesunate to pregnant cynomolgus monkeys during organogenesis (GD 20 to GD 50) at 12 mg/kg/day (approximately 1.6-times the clinical dose based on BSA comparisons) resulted in increased embryonic death with skeletal malformations (i.e., decrease in absolute length of the ulna) observed in surviving fetuses.

In a fertility and early embryonic development study, intravenous administration of artesunate to female rats at between 1-2 times the clinical dose (based on BSA comparisons) for two weeks before mating, during mating, and through implantation (up to GD 7) did not affect fertility, or early embryonic development.

No significant changes in male reproductive organs (i.e., gross, microscopic or histologic lesions or organ weights) or sperm motility, counts or morphology were observed in rats and dogs following 28 days of repeated dosing with intravenously administered artesunate in Good Laboratory Practice (GLP) studies.

In published literature, male rats and mice administered oral or intraperitoneal artesunate as a single dose or repeated doses (3 days to 6 weeks) displayed histopathological changes of the seminiferous tubules and altered spermatogenesis (increased percentage of abnormal sperm and/or decreased sperm motility and viability) at doses ranging from approximately 0.2- to 1.3-times the clinical dose based on BSA comparisons.

Juvenile Toxicity

No juvenile toxicity studies have been conducted with artesunate alone.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]AMIVAS-ARTESUNATE

Artesunate for Injection

Read this carefully before you are given **AMIVAS-ARTESUNATE**. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **AMIVAS-ARTESUNATE**.

Serious warnings and precautions box

AMIVAS-ARTESUNATE may cause serious side effects, including:

- **Hemolytic anemia** which is a condition where red blood cells in your body are destroyed faster than they can be made. This leads to a lack of red blood cells. Your healthcare professional will monitor you for signs of hemolytic anemia while you are receiving AMIVAS-ARTESUNATE and for 4 weeks after you started your treatment. Talk to your healthcare professional if you get any symptoms of hemolytic anemia while you are receiving AMIVAS-ARTESUNATE. See "**Serious side effects and what to do about them**" for symptoms.
- **Severe allergic reactions**. Stop taking AMIVAS-ARTESUNATE and get immediate medical help if you get any symptoms of a severe allergic reaction. **See "Serious side effects and what to do about them"** for symptoms.

What AMIVAS-ARTESUNATE is used for:

- AMIVAS-ARTESUNATE is used for the initial treatment of severe malaria in adults and children.
- After treatment with AMIVAS-ARTESUNATE, you will be given oral medicines to fully treat your malaria.
- AMIVAS-ARTESUNATE does not treat malaria caused by certain types of parasites. You may also be given other medicines while you are receiving AMIVAS-ARTESUNATE. Your healthcare professional will decide if AMIVAS-ARTESUNATE is right for you.

How AMIVAS-ARTESUNATE works:

AMIVAS-ARTESUNATE belongs to a group of medicines known as "antimalarial agents". It destroys the membrane of the parasite that causes malaria which leads to its death.

The ingredients in AMIVAS-ARTESUNATE are:

Medicinal ingredient: artesunate.

Non-medicinal ingredients (diluent): disodium phosphate dihydrate, monosodium phosphate monohydrate, phosphoric acid, concentrated, sodium hydroxide, water for injection.

AMIVAS-ARTESUNATE comes in the following dosage forms:

Powder for solution: 110 mg per vial of artesunate.

AMIVAS-ARTESUNATE is provided as a 110 mg of powder in a vial and must be dissolved in the supplied diluent solution before it is injected. The concentration of the solution to be injected is 10 mg of artesunate per mL.

Do not use AMIVAS-ARTESUNATE if:

- you are allergic to artesunate, to any other treatment for malaria that contains an artemisinin such as artemether or dihydroartemisinin
- you are allergic to any of the other ingredients in AMIVAS-ARTESUNATE or to any part of the container

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take AMIVAS-ARTESUNATE. Talk about any health conditions or problems you may have, including if you:

- have a condition called anemia where you have a low amount of healthy red blood cells.

Other warnings you should know about:

Pregnancy:
Tell your healthcare professional before taking AMIVAS-ARTESUNATE if you are pregnant, think you may be pregnant or are planning to become pregnant. AMIVAS-ARTESUNATE could harm an unborn baby. However, not treating severe malaria in a pregnant woman can seriously harm the mother and unborn baby. Talk to your doctor about the treatment of severe malaria in pregnancy. If you are pregnant and receive AMIVAS-ARTESUNATE, your healthcare professional will tell you about a pregnancy registry. This registry monitors the effects of taking AMIVAS-ARTESUNATE when pregnant. Your healthcare professional will encourage you to report your pregnancy to Amivas, Inc. at 1-855-526-4827 (1-855-5AMIVAS) or at www.amivas.com/our-products.

Breastfeeding:
Tell your healthcare professional before taking AMIVAS-ARTESUNATE if you are breastfeeding or planning to breastfeed. This is because AMIVAS-ARTESUNATE may pass into your breastmilk and harm your baby. Your healthcare professional will tell you if can breastfeed your baby while you are receiving taking AMIVAS-ARTESUNATE.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with AMIVAS-ARTESUNATE:

- rifampicin, a medicine used to treat bacterial infections
- ritonavir and nevirapine, medicines used to treat HIV infection
- carbamazepine and phenytoin, medicines used to treat epilepsy
- diclofenac, a medicine used to treat pain or inflammation
- axitinib, vandetanib and imatinib , medicines used to treat certain cancers

AMIVAS-ARTESUNATE may increase or decrease the blood levels of some other medicines. Your healthcare professional will advise and monitor you on the medicines you take during your treatment.

How to take AMIVAS-ARTESUNATE:

- AMIVAS-ARTESUNATE will be given to you by a healthcare professional.
- Your healthcare professional will make sure that AMIVAS-ARTESUNATE is prepared correctly before it is given to you.
- It will be given to you by a slow injection directly into a vein.
- You will be given at least three doses of AMIVAS-ARTESUNATE. Each dose will be given 12 hours apart. After three doses, if you still cannot take medicines by mouth, you will be given one dose of AMIVAS-ARTESUNATE once a day (every 24 hours) until you are able to take a different malaria treatment by mouth.
- It is very important that you take oral medicines to fully treat your malaria after you have received at least three doses of AMIVAS-ARTESUNATE.
- During your treatment, your healthcare professional will closely monitor your health.
- Follow all instructions given to you by your healthcare professional.

Usual dose:

Your healthcare professional will decide how much AMIVAS-ARTESUNATE you will receive. It will be based on your weight.

Overdose:

If you think that you have received too much AMIVAS-ARTESUNATE, tell your healthcare professional right away. Your healthcare professional will take appropriate measures to treat any overdosage.

If you think you, or a person you are caring for, has been given too much AMIVAS-ARTESUNATE, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

Your healthcare professional will manage your treatment and will avoid missing a dose. If a dose is missed, your healthcare professional will give you the missed dose as soon as possible. They will continue giving your remaining doses 12 or 24 hours apart.

Possible side effects from using AMIVAS-ARTESUNATE:

These are not all the possible side effects you may have when taking AMIVAS-ARTESUNATE. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Diarrhea
- Stomach pain
- Inflammation of a vein

- Altered sense of taste
- Blocked or runny nose
- Headache
- Constipation
- Pain at injection site
- Flushing

Serious side effects and what to do about them			
Frequency / Side Effect / Symptom	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Anemia (low amount of healthy red blood cells): tiredness, weakness, pale skin, dizziness, shortness of breath	**X**		
Blackwater fever (sudden destruction of red blood cells): dark red or brown urine, yellowing of the skin or eyes, fever, chills, fast heart beat			**X**
Coma (being unconscious for a prolonged time): closed eyes, no response to pain or stimuli, no reflexes, low heart beat, irregular breathing			**X**
Convulsions (rapid, involuntary muscle contractions): uncontrollable shaking or limb movement		**X**	
Kidney failure (kidneys not working properly, which may require a medical procedure called dialysis):peeing less often or with less urine, swelling of the legs, ankles or feet, tiredness, loss of appetite, nausea, confusion			**X**
UNCOMMON			
Hypotension (low blood pressure): Light-headedness, dizziness, weakness, blurred vision, fatigue or tiredness, fainting	**X**		
Leukocytosis (high amount of white blood cells): fever, pain, difficulty breathing, hives and itching, weight loss, vision problems, bleeding form the intestines or mouth		**X**	
Leukopenia (low amount of white blood cells): fever, fatigue, weakness, frequent infections, mouth sores or ulcers, sore throat, flu-like symptoms		**X**	
Stevens-Johnson syndrome (severe skin reaction): redness, blistering or peeling of the skin or inside of the lips, eyes, mouth, nasal passages or genitals, fever, chills, headache, cough, body aches or swollen glands.		**X**	

Serious side effects and what to do about them			
Frequency / Side Effect / Symptom	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Thrombocytopenia (low amount of platelets in blood): easy bruising, bleeding for longer than usual, red or purple dots or spot on the skin, bleeding gums, blood in stool or urine		**X**	
UNKNOWN			
Acute respiratory distress syndrome (lung injury when fluids build up in the lungs): severe shortness of breath, difficulty breathing, cough, chest pain, fast breathing, rapid heart beat, lips and fingernails turning bluish			**X**
Disseminated intravascular coagulation (serious condition that causes abnormal blood clotting): uncontrollable bleeding, blood in stool or urine, bruising, confusion, memory loss, difficulty breathing, fever		**X**	
Hemolytic anemia (a condition where red blood cells in your body are destroyed faster than they can be made): dark-coloured urine, dizziness or confusion, yellowing of the skin (jaundice), pale skin, muscle pain, nausea, vomiting, weakness or fatigue, shortness of breath, heart beats fast.		**X**	
Liver problems (liver being damaged or not working properly): yellowing of the skin and eyes , abdominal pain, dark urine, fatigue, nausea, vomiting, itching		**X**	
Neurological sequelae (problems with the brain or the nerves): trouble walking or staying steady, weakness or paralysis on one side of the body, shaking, change in mood or behavior, generalized weakness, confusion, agitation		**X**	
Pneumonia (infection of the lung): fever, chills, cough, chest pain, shortness of breath, fatigue		**X**	
Pulmonary edema (fluids in the lung): shortness of breath especially when lying down, wheezing, cough, rapid heart beat, feeling of anxious		**X**	
Severe allergic reaction: difficulty breathing or swallowing, swelling of your face, mouth, tongue or throat, reddening of the face, rash or hives, loss of consciousness.			**X**

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

AMIVAS-ARTESUNATE will be stored by your healthcare professional between 15°C and 30°C.

Keep out of reach and sight of children.

If you want more information about AMIVAS-ARTESUNATE:

- Talk to your healthcare professional.
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (Drug Product Database: Access the database); the manufacturer's website, amivas.com, or by calling 1-866-333-5458.

This leaflet was prepared by Amivas Ireland Ltd.

Date of Authorization: