PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrARGATROBAN
(argatroban for injection)
Concentrate Solution, 100 mg/mL (250 mg/ 2.5 mL) argatroban
(as argatroban monohydrate), Intravenous Injection

PrARGATROBAN
(argatroban injection)
Ready to use Solution, 1 mg/mL (50 mg/ 50 mL) argatroban
(as argatroban monohydrate), Intravenous Injection

Manufacturer's Standard

Antithrombotic

Sandoz Canada Inc.
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Boucherville, QC, J4B 1E6

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RECENT MAJOR LABEL CHANGES

4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations	06/2024
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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Argatroban is indicated as anticoagulant therapy in patients with heparin-induced thrombocytopenia syndrome, who, in the opinion of their attending physician, require anticoagulation.

1.1 Pediatrics

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Argatroban in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Evidence from clinical studies and experience suggests that use of Argatroban in the geriatric population is not associated with differences in safety or effectiveness.

2 CONTRAINDICATIONS

Argatroban is contraindicated in patients

- with active major bleeding (for example: overt bleeding in a critical organ/area or bleeding causing a fall in hemoglobin level ≥ 2g/dL or leading to a transfusion of ≥ 2 units)
- who are hypersensitive to the drug or to any ingredient in the formulation
- with hereditary fructose intolerance

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Argatroban concentrate (100 mg/mL) must be diluted prior to its infusion. Argatroban concentrate should not be mixed with other drugs prior to dilution in a suitable intravenous fluid (see 4.3 RECONSTITUTION).

Argatroban Ready to use (RTU) (1 mg/mL) solution **does not require any dilution** prior to its infusion. The vial can be inverted for use with medical infusion set**.**

4.2 Recommended Dose and Dosage Adjustment

Initial Dosage for Patients with Heparin-Induced Thrombocytopenia: Discontinue heparin therapy and obtain baseline aPTT. The recommended initial dose of Argatroban for adult patients without hepatic impairment is 2 mcg/kg/min, administered as a continuous infusion (see Table 1).

Table 1. Standard Infusion Rates for 2.0 mcg/kg/min Dose.

(1 mg/mL final concentration)

Body Weight (kg)	Infusion Rate (mL/hr)
50	6
60	7
70	8
80	10
90	11
100	12
110	13
120	14
130	16
140	17

Monitoring therapy: In general, therapy with Argatroban is monitored using the aPTT. Anticoagulant effects (including the aPTT) typically attain steady-state levels within 2.5 hours following initiation of Argatroban or with dosage adjustment. Check the aPTT two hours after initiation of therapy to confirm that the patient has attained the desired therapeutic range.

Dosage adjustment: The dose can be adjusted as clinically indicated (not to exceed 10 mcg/kg/min), until the steady-state aPTT is 1.5 to 3.0 times the initial baseline value (not to exceed 100 seconds).

Patients with Hepatic Impairment: For patients with heparin-induced thrombocytopenia with hepatic impairment, the initial dose of Argatroban should be reduced. For patients with moderate hepatic impairment, an initial dose of 0.5 mcg/kg/min is recommended, based on the approximate four-fold decrease in Argatroban clearance relative to those with normal hepatic function. The aPTT should be monitored closely and the dosage should be adjusted as clinically indicated.
Achievement of a steady state aPTT levels may take longer and require more Argatroban dose adjustments in patients with moderate hepatic impairment compared to patients with normal hepatic functions. Also, upon cessation of Argatroban infusion in the patients with moderate hepatic impairment, full reversal of anticoagulant effects may require longer than four (4) hours due to decreased clearance and increased elimination half life of Argatroban.

Argatroban should be used with caution in patients with severely impaired hepatic function. For these patients, the initial suggested dose is not to exceed 0.05 mcg/kg/min; the aPTT should be monitored closely and the dosage adjustment should be performed as clinically indicated.

Patients with Renal Impairment: In a study of over 20 patients with renal impairment, and some who required dialysis, dosage adjustment was not necessary and dosages up to 5.0 mcg/kg/min were administered with no medically significant safety concerns.

Use in Pediatrics (<18 years of age): The safety and efficacy of Argatroban have not been established in children and adolescent patients <18 years of age. Health Canada has not authorized an indication for pediatric use.

Use in Geriatrics (≥65 years of age): In the prospective study in HIT and HITTS, the effectiveness of Argatroban was not affected by patient age. Dosage adjustment is not necessary in patients 65 years of age and older.

Conversion to oral anticoagulant therapy:

Initiating Oral Anticoagulant Therapy: When converting to oral anticoagulant therapy, a loading dose of warfarin **should not** be used because of the potential for combined effects on INR by the combination of Argatroban and warfarin. Initiate therapy using the expected daily dose of warfarin.

Co-Administration of Warfarin and Argatroban at Doses up to 2 mcg/kg/min: The concomitant use of Argatroban with warfarin results in prolongation of INR beyond that produced by warfarin alone. Therefore, the previously established relationship between INR and bleeding risk are altered (for details, see 10 CLINICAL PHARMACOLOGY). INR should be measured daily while Argatroban and warfarin are co-administered. In general, with doses of Argatroban up to 2 mcg/kg/min, Argatroban can be discontinued when the INR is >4.0. After Argatroban is discontinued, repeat the INR measurement in 4 to 6 hours. If the repeat INR is below the desired therapeutic range, resume the infusion of Argatroban and repeat the procedure daily until the desired therapeutic range on warfarin alone is reached. The relationship between INR on combined therapy and warfarin alone is dependent on both the dose of Argatroban and the thromboplastin reagent used.

Co-Administration of Warfarin and Argatroban at Doses Greater than 2 mcg/kg/min: For doses greater than 2 mcg/kg/min, the relationship between INR on warfarin alone, and warfarin plus Argatroban is less predictable. In this case, in order to predict the INR on warfarin alone, temporarily reduce the dose of Argatroban to 2 mcg/kg/min. Repeat the INR on Argatroban and warfarin 4 to 6 hours after Argatroban reduction and follow the process outlined above for dosing Argatroban at up to 2 mcg/kg/min.

4.3 Reconstitution of the concentrate (100 mg/mL) formulation

Preparation for Intravenous Administration: Argatroban concentrate (100 mg/mL) should be diluted in 0.9% Sodium Chloride Injection, USP; 5% Dextrose injection, USP or Lactated Ringer's Injection, USP; to a final concentration of 1 mg/mL (see Table 2). Use 1 vial (for 2.5 mL total) per 250 mL diluent bag, or 2 vials (for 5.0 mL total) per 500 mL diluent bag. The constituted solution must be mixed by repeated inversion of the diluent bag for one minute. Upon preparation, the solution may show slight but brief haziness due to the formation of microprecipitates that rapidly dissolve upon mixing. Use of diluents at room temperature is recommended. Colder temperatures can slow down the rate of dissolution of precipitates. The final solution must be clear before use. The pH of the intravenous solution prepared as recommended is 3.2-7.5.

Table 2. Intravenous Preparations

N x Vial size	Volume of diluent	Recommended diluents*	Final Concentration
1 x 2.5 mL (100 mg/mL)	250 mL	0.9% Sodium Chloride Injection, USP; or 5% Dextrose injection, USP; or Lactated Ringer's Injection	1 mg/mL
2 x 2.5 mL (100 mg/mL)	500 mL	Same recommended diluents as listed above	1 mg/mL

***The constituted solution must be mixed by repeated inversion of the diluent bag for one minute.

The diluted solutions are stable for 24 hours at 15-25°C in ambient indoor light, and stable for 48 hours at 2-8°C in the dark (see 11 STORAGE, STABILITY AND DISPOSAL).

The Ready to use (1 mg/mL) solution **DOES NOT** need reconstitution.

5 OVERDOSAGE

Symptoms/Treatment: Excessive anticoagulation, with or without bleeding, may be controlled by discontinuing Argatroban or by decreasing the Argatroban infusion dosage. In clinical trials, anticoagulation parameters generally returned to baseline within 2 to 4 hours after discontinuation of the drug (although this may take longer for those with hepatic impairment). Argatroban infusion doses of up to 40 mcg/kg/min have been administered to healthy subjects up to four hours without drug-related adverse events.

No specific antidote to Argatroban is available; if life-threatening bleeding occurs and excessive plasma levels of Argatroban are suspected, the following steps should be followed:

- Stop or reduce Argatroban administration immediately;
- Determine activated partial thromboplastin time (aPTT) and other coagulation indices as appropriate;
- Provide symptomatic and supportive therapy.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Route of Administration	Dosage Form/Strength/Composition	Non-medicinal Ingredients
Intravenous	Concentrate solution 250 mg / 2.5 mL vial (100 mg/mL)	D-sorbitol, dehydrated alcohol, water for injection

Route of Administration	Dosage Form/Strength/Composition	Non-medicinal Ingredients
Intravenous	Ready to use solution 50 mg / 50 mL vial (1 mg/mL)	Sodium chloride, sorbitol, water for injection

Argatroban Concentrate Solution (100 mg/mL)

Argatroban Concentrate Solution (100 mg/mL) is supplied as 2.5 mL solution in single-use vials at the concentration of 100 mg/mL. Each vial contains 250 mg of Argatroban.

Composition: Argatroban Concentrate Solution (100 mg/mL) is a sterile clear, colorless to pale yellow, slightly viscous solution. Each mL of sterile, nonpyrogenic solution contains 100 mg Argatroban.

Argatroban Ready to use Solution (1 mg/mL)

Argatroban Ready to use Solution (1 mg/mL) is supplied as 50 mL solution in single-use vials at the concentration of 1 mg/mL. Each vial contains 50 mg of Argatroban.

Composition: Argatroban Ready to use Solution (1 mg/mL) is a sterile clear, colorless solution in sodium chloride. Each mL of sterile solution contains 1 mg of Argatroban.

7 WARNINGS AND PRECAUTIONS

General

Argatroban is intended for use as an anticoagulant in patients with heparin-induced thrombocytopenia (HIT) syndrome. Hemorrhage can occur, especially in patients with disease states associated with a risk of bleeding. All patients should be carefully monitored.

Argatroban is intended for intravenous administration. All parenteral anticoagulants must be discontinued before administration of Argatroban.

Cardiovascular

Hemorrhage: Hemorrhage can occur at virtually any site in the body in patients receiving Argatroban. An unexplained fall in hematocrit, fall in blood pressure, or any other unexplained symptom should lead to serious consideration of a hemorrhagic event. Argatroban should be used with extreme caution in disease states and other circumstances in which there is an increased danger of hemorrhage. These include severe hypertension; immediately following lumbar puncture; spinal anesthesia; major surgery especially involving the brain, spinal cord, or eye; hematologic conditions associated with increased bleeding tendencies such as hemophilia, gastrointestinal lesions such as ulcerations.

Hepatic/Biliary/Pancreatic

Caution should be exercised when administering Argatroban to patients with hepatic disease, by starting with a lower dose and carefully titrating until the desired level of anticoagulation is achieved. Achievement of steady state aPTT levels may take longer and require more Argatroban dose adjustments

in patients with moderate hepatic impairment compared to patients with normal hepatic function. The aPTT should be closely monitored and the dosage should be adjusted as indicated clinically. Argatroban should be used with caution in patients with severely impaired hepatic function, and only if the clinical benefit outweighs the risk. Close monitoring and dosage adjustment should be done as clinically indicated. Also, upon cessation of Argatroban infusion in patients with hepatic impairment, full reversal of anticoagulant effects may require longer than 4 hours due to decreased clearance and increased elimination half-life of Argatroban (See 4 DOSAGE AND ADMINISTRATION).

Monitoring and Laboratory Tests

Anticoagulation effects associated with Argatroban infusion at doses up to 40 mcg/kg/min are well-correlated with the activated partial thromboplastin time (aPTT). If aPTT monitoring is problematic (such as for those having antiphospholipid antibodies), other global clot-based tests sensitive to Argatroban include the prothrombin time (PT), the International Normalized Ratio (INR), the activated clotting time (ACT) and thrombin time (TT). Plasma Argatroban concentrations also correlate well with anticoagulant effects (see 10 CLINICAL PHARMACOLOGY).

The concomitant use of Argatroban and warfarin results in prolongation of the PT and INR beyond that produced by warfarin alone. Alternative approaches for monitoring concurrent Argatroban and warfarin therapy are described in a subsequent section (see 9 DRUG INTERACTIONS and 4 DOSAGE AND ADMINISTRATION).

Renal

Dosage adjustment was not necessary in patients with renal impairment and dosages up to 5.0 mcg/kg/min were administered with no medically significant safety concerns (see 4 DOSAGE AND ADMINISTRATION).

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well controlled studies in which pregnant women have received Argatroban. Although animal reproductive studies have not revealed harm to the fetus (see 16 NON-CLINICAL TOXICOLOGY), these studies are not always predictive of the effects of a drug in humans. Argatroban should only be used in pregnancy if the benefits outweigh the risks.

7.1.2 Breast-feeding

Nursing women should discontinue breast feeding while taking Argatroban because of the potential risk for serious adverse reactions in nursing infants. Although it is not known whether this drug is excreted in human milk, experiments in rats show that Argatroban is detected in milk.

7.1.3 Pediatrics

The safety and effectiveness of Argatroban in patients below the age of 18 years have not been established. Therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Dosage adjustment is not necessary in patients 65 years of age and older.

8 ADVERSE REACTIONS

8.1 Adverse Drug Reaction Overview

Adverse events occurring with Argatroban are those which are anticipated for patients presenting with HIT or HITTS (heparin-induced thrombocytopenia with thrombosis) syndrome. The incidence of any of the primary efficacy endpoints of death, amputations or new thrombosis has been considered as the most serious adverse events.

The most common adverse event was bleeding, but major bleeding events with Argatroban did not occur more frequently than in historical controls.

Other common adverse reactions included diarrhea, dyspnea, hypotension, apnea, chest pain, sepsis, dizziness, fever ventricular tachycardia and nausea and vomiting.

8.2 Clinical Trial Adverse Drug 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.

The following safety information is based upon the 568 patients treated with Argatroban in the prospective pivotal clinical studies in patients with heparin-induced thrombocytopenia with and without thrombosis syndrome.

568 adult patients were treated with Argatroban and 193 adult patients made up the historical control group. Patients were required to have a clinical diagnosis of heparin-induced thrombocytopenia, either without thrombosis (HIT) or with thrombosis (HITTS) and be males or non-pregnant females between the age of 18 and 80 years old. HIT/HITTS was defined by a fall in platelet count to less than 100,000/μL or a 50% decrease in platelets after the initiation of heparin therapy with no apparent explanation other than HIT. Patients with HITTS also had presence of an arterial or venous thrombosis documented by appropriate imaging techniques or supported by clinical evidence such as acute myocardial infarction, stroke, pulmonary embolism, or other clinical indications of vascular occlusion. Patients who required anticoagulation with documented histories of positive HIT antibody test were also eligible in the absence of thrombocytopenia or heparin challenge (e.g., patients with latent disease).

Serious Adverse Events: Study Days 0-37: Table 3 shows the incidence of the primary efficacy endpoints [death (all cause), amputations (all cause), or new thrombosis, during study days 0-37; recorded as the most severe event] in the prospective and follow-on trials combined. These events qualify as (Serious Adverse Events). Table 3 illustrates the safety profile of Argatroban with regard to these serious outcomes as compared to a historical control group.

Table 3. Serious Adverse Events

	HIT		HITTS	
	Argatroban	Historical Control	Argatroban	Historical Control
	n=285	n=147	n=283	n=46
Death, n(%)	48 (17)	32 (22)	61 (22)	13 (28)
Amputation, n(%)	9 (3)	3 (2)	32 (11)	4 (9)
New Thrombosis, n (%)	16 (6)	22 (15)	27 (10)	9 (20)

Bleeding Event Frequency: In the first prospective pivotal trial, no statistically significant differences in the incidence of major bleeding were observed between the historical control group and the Argatroban group in either the HIT arm (8.2% versus 3.1%; p=0.0784) or HITTS arm (2.2% versus 10.4%; p=0.124). In the second pivotal trial, no statistically significant differences in the incidence of major bleeding were observed between the historical control group and the Argatroban group in either the HIT arm (8.2% vs. 3.2%; p=0.1190) or HITTS arm (2.2% vs. 4.3%; p=0.683). No clinically significant difference in minor bleed incidence was observed in either trial comparing Argatroban treated patients to historical controls. There were no cases of drug-related intracranial hemorrhage noted in either trial.

Most Common Reported Adverse Events in the Prospective Pivotal Clinical Trials:
The adverse events reported in this section are consistent with those which would be anticipated for a severely ill patient population who present with HIT/HITTS syndrome. In general, these patients had a mean age of 60+ years and were on complex concomitant medications. No clinically significant safety trends with regard to Argatroban exposure are apparent from both pivotal trials adverse event data. There may be some evidence of a clinical trend for treated patients to experience milder gastrointestinal disturbances, such as nausea, or diarrhea.

Comparative Summary of Adverse Events for Prospective Pivotal Clinical Trials:
The following is a comparative summary of non-hemorrhagic adverse events in pivotal studies that were experienced in heparin-induced thrombocytopenia (HIT) patients treated with Argatroban. All adverse events occurring with frequency of ≥5% in treated patients, in either trial, are listed in descending order of frequency as they occurred in the first pivotal trial.

Table 4. Comparative Summary of Adverse Events – HIT

Adverse Event	ARG-911 n = 160	ARG-915 n = 125	Historic Control; n = 147
≥5%	%	%	%
Diarrhea	11	2	2
Dyspnea	8	9	9
Hypotension	7	5	3

Adverse Event	ARG-911 n = 160	ARG-915 n = 125	Historic Control; n = 147
Apnea	6	0	5
Chest Pain	6	2	2
Sepsis	6	3	14
Dizziness	5	2	0
Vomiting	5	3	0
Fever	4	6	2
Nausea	4	6	0
Tachycardia Ventricular	3	7	3

The following is a comparative summary of non-hemorrhagic adverse events in pivotal studies that were experienced in heparin-induced thrombocytopenia with thrombotic syndrome (HITTS) patients treated with Argatroban. All adverse events occurring with frequency of ≥5% in treated patients, in either trial, are listed in descending order of frequency as they occurred in the first pivotal trial.

Table 5. Comparative Summary of Adverse Events – HITTS

Adverse Event	ARG-911 n = 149	ARG-915 n = 139	Historic Control n = 46
≥5%	%	%	%
Hypotension	9	8	0
Pain	9	3	4
Apnea	8	0	7
Cardiac Arrest	8	8	9
Constipation	8	1	2
Fever	8	9	2
Peripheral Ischemia	8	6	7
Urinary Tract Infection	8	4	4
Infection	7	4	4
Pulmonary	7	4	13

Adverse Event	ARG-911 n = 149	ARG-915 n = 139	Historic Control n = 46
Embolism			
Rash	7	4	2
Thrombophlebitis	7	0	2
Confusion	6	1	0
Sepsis	6	8	9
Thrombophlebitis (Deep)	6	4	15
Vomiting	6	3	0
Peripheral Gangrene	5	1	4
Pleural Effusion	5	3	4
Dyspnea	4	12	9
Diarrhea	4	7	0
Tachycardia Ventricular	4	5	4
Acute Renal Failure	3	5	7
Nausea	3	6	2
Pneumonia	2	5	15
Respiratory Insufficiency	1	6	0
Cardiac Failure	0	5	0

Adverse Events Resulting from Repeated or Chronic Administration: Adverse event rates in patients receiving multiple courses of Argatroban were similar to rates observed in patients receiving short courses of the drug. Patients receiving chronic administration (greater than 14 days of continuous therapy) of Argatroban had adverse event rates at a similar frequency to those receiving shorter courses of Argatroban.

8.5 Post-Market Adverse Drug Reactions

Table 6. Summary of Post-Market Adverse Drug Reactions

System Organ Class	Adverse Event
Blood and lymphatic system:	coagulopathy, Evans syndrome, hypofibrinogenemia, thrombocytopenia
Cardiac:	acute myocardial infarction, arrhythmia, heart failure, cardiomyopathy, coronary artery occlusion
Congenital, familial and genetic:	atrial septal defect, ventricular septal defect
Ear and labyrinth:	deafness
Eye:	conjunctival hemorrhage, pupils unequal
Gastrointestinal:	hemorrhage, pancreatitis, retroperitoneal hematoma, intestinal ischemia, hematochezia, diverticulum intestinal hemorrhagic
General disorders and administration site conditions:	drug resistance, injection site hemorrhage, mucosal hemorrhage, multi-organ failure, necrosis, procedural complications
Hepatobiliary:	hepatic failure, hepatic function abnormal, hepatitis, hepatotoxicity, ischemic hepatitis, liver disorder
Immune system:	anaphylactic shock, anaphylactoid reaction, drug hypersensitivity, transplant rejection
Infections and infestations:	chronic hepatitis C, perihepatic abscess, septic shock
Investigations:	aPTT abnormal, bleeding time prolonged, blood fibrinogen decreased, blood pressure decreased, coagulation time abnormal, fibrin D dimer increased, fibrinolysis granulocyte count decreased, hemoglobin decreased, INR abnormal, laboratory test abnormal, lipase increased, liver function test abnormal, platelet count abnormal, prothrombin time abnormal, thyroid function abnormal, white blood cell count decreased
Metabolism and nutrition:	enzyme abnormality, hyperkalemia, hypoglycemia, hypoproteinanemia, lactic acidosis
Musculoskeletal and connective tissue:	arthritis, compartment syndrome, myopathy, rhabdomyolysis
Neoplams benign, malignant and unspecified:	pancreatic carcinoma metastatic
Nervous system:	aphasia, basilar migraine, brain injury, brain oedema, cerebrovascular accident, cerebral hemorrhage, convulsion, hemorrhage, loss of consciousness, paralysis, transient ischemic attack, unresponsive to stimuli
Psychiatric:	agitation
Renal and urinary:	hematuria, renal failure, renal impairment
Reproductive system and breast:	vaginal hemorrhage
Respiratory, thoracic and mediastinal:	acute pulmonary oedema, asthma, epistaxis, hemoptysis, pneumonia aspiration, pulmonary hemorrhage, respiratory failure
Skin and subcutaneous tissue:	panniculitis, skin burning sensation, skin necrosis, Stevens-Johnson syndrome, urticaria
Vascular:	aneurysm ruptured, aortic thrombosis, circulatory collapse, embolism, hematoma, hemorrhagic infarction, labile blood

	pressure, peripheral vascular disorder, shock hemorrhagic, thrombosis

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

There is a potential for drug-drug interactions between Argatroban and anticoagulant medications. Bleeding risks are variable depending on the co-administered drug. Therefore, patients should be carefully monitored for aPTT, PT, and INR values.

9.3 Drug-Behavioural Interactions

Interactions with individual behaviours have not been established.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Drug Interaction	Effect	Clinical comment
Aspirin/Acetaminophen	There are no pharmacokinetic or pharmacodynamic drug-drug interactions between Argatroban and concomitantly administered aspirin or acetaminophen.	
Digoxin	In 12 healthy volunteers, a 5 day intravenous infusion of Argatroban (2 mcg/kg/min) did not affect the steady-state pharmacokinetics of oral digoxin (0.375 mg daily for 15 days).	
Erythromycin	In 10 healthy subjects, orally administered erythromycin (both a substrate for and a potent inhibitor of CYP3A4/5) at 500 mg QID for 7 days had no effect on the pharmacokinetics of Argatroban at a dose of 1 mcg/kg/min for 5 hours.	These data suggest oxidative metabolism by CYP3A4/5 is not an important elimination pathway *in vivo* for Argatroban. Based on these results, other CYP3A4/5 inhibitors such as ketoconazole and itraconazole are unlikely to inhibit the metabolism of Argatroban. As there has been no clinical experience with the co-administration of Argatroban and other CYP3A4/5 - metabolized drugs, such as fluconazole, indinavir, ritonavir, cyclosporine, simvastatin, nefazodone

Drug Interaction	Effect	Clinical comment
		or their analogues, the potential for possible interaction is unknown.
Heparin (Heparin is contraindicated in patients with heparin-induced thrombocytopenia; therefore, co-administration of Argatroban and heparin is unlikely)	Contraindicated due to bleeding risk	If Argatroban is to be initiated after cessation of heparin therapy, sufficient time should be allowed for the effects of heparin on the aPTT to decrease prior to the initiation of Argatroban therapy. As the half-life of heparin is highly variable, the maximum being about 2 hours, a period of time equal to two half-lives, or 4 hours is recommended. Nevertheless, because of the variability in heparin metabolism, aPTT should always be the primary indicator as to when Argatroban therapy may be initiated.
Lidocaine	Argatroban did not inhibit the metabolism of concomitantly administered lidocaine using a 1.5 mg/kg bolus plus 2 mg/kg/hour infusion for 16 hours.	
Thrombolytic agents	No clinically significant safety concern.	Argatroban at doses up to 3 mcg/kg/min has been administered in two clinical studies with either rt-PA or streptokinase.
Warfarin	There are no pharmacokinetic drug-drug interactions with argatroban. However, the concomitant use of Argatroban and warfarin results in prolongation of the prothrombin time (PT) and International Normalized Ratio (INR).	Previously established relationships between PT/INR and bleeding risk no longer apply (see 10 CLINICAL PHARMACOLOGY and 4 DOSAGE AND ADMINISTRATION).

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

Argatroban is an antithrombotic agent, which is highly specific for thrombin. The co-administration of Argatroban with warfarin produces a combined effect on prothrombin time (PT) and International Normalized Ratio INR values (see 9 DRUG INTERACTIONS). Previously established relationships between PT/INR and bleeding risk no longer apply (see 10 CLINICAL PHARMACOLOGY).

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Argatroban is a small-molecule, direct thrombin inhibitor that reversibly binds to the thrombin active site. Its mechanism of action is distinct from heparin, an indirect thrombin inhibitor, which requires the co-factor antithrombin III for antithrombotic activity. Argatroban exerts its anticoagulant effects by inhibiting thrombin-catalyzed or induced reactions, including fibrin formation; activation of coagulation factor XIII, factor V, factor VIII, and protein C; and platelet aggregation.

Argatroban is highly selective for thrombin with an inhibitory constant (K_i) of 5-39 nM. At therapeutic concentrations, Argatroban has no or minimal effect on related serine proteases (trypsin, factor Xa, plasmin, and kallikrein).

Argatroban is also capable of inhibiting the action of clot-associated thrombin. In contrast, the heparin-antithrombin III complex is incapable of inhibiting clot-associated thrombin.

Experience in a limited number of patients who received multiple doses of Argatroban indicates no antibody formation.

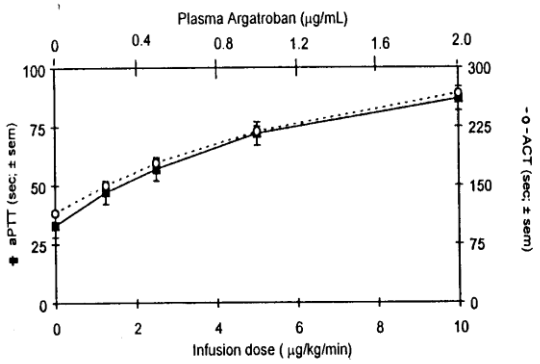
10.2 Pharmacodynamics

Argatroban is a potent and selective thrombin inhibitor with anticoagulant properties both “in vitro” and “in vivo”. Its activity does not depend upon the presence of antithrombin III. Unlike heparin, Argatroban is able to inhibit both the amidolytic and platelet activities of clot-associated thrombin. Pharmacological studies have shown that Argatroban is a potent antithrombotic agent when administered as an intravenous infusion in a wide variety of animal models both of erythrocyte-rich (venous) and platelet-rich (arterial) thrombosis, although the doses required to inhibit arterial thrombosis are higher than those necessary to inhibit venous thrombosis in experimental models. In addition, Argatroban has been shown to enhance experimental thrombolysis and maintain vascular recanalization when administered with either rt-PA, streptokinase or sc-UPA (Saruplase).

Argatroban is highly specific in that it has no effect on a battery of other proteases or other platelet activating agents except at concentrations several orders of magnitude greater than those required to inhibit thrombin. Argatroban caused a slight increase in the largely predominant anticoagulant effect of heparin using the aPTT as the coagulant parameter, but the effect of the combination was not statistically significant when compared to heparin alone and is not relevant in the context of the use of Argatroban in the indication HIT/HITTS. When co-administered with anticoagulant doses of Argatroban via the same venous catheter in the rat, rt-PA has no inhibitory effect on the anticoagulant effect of Argatroban. Moreover, there is no significant loss of fibrinolytic activity of rt-PA. The concomitant administration of Argatroban with aspirin, indomethacine, sulfinpyrazone, quinidine, ouabain, tolbutamide, clofibrate,

furosemide, or ticlopidine did not affect the anticoagulant properties of Argatroban in the rat. However, administration of Argatroban to rats 24 hours after oral warfarin increased the anticoagulant effect of the latter. None of the general pharmacological tests suggest that Argatroban has any potential adverse effects at pharmacologically relevant doses.

Figure 1. Relationship at Steady State between Argatroban Dose, Plasma Argatroban and Anticoagulant Effect.

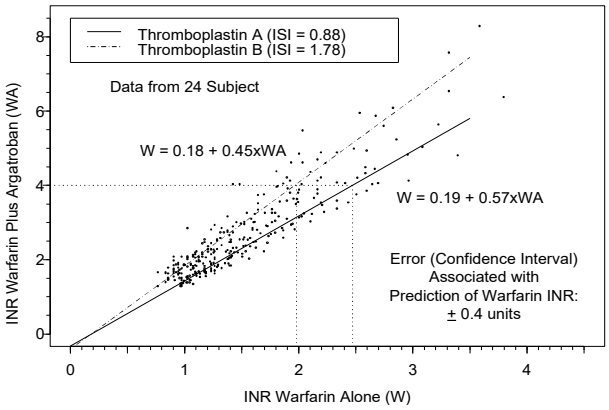


When Argatroban is administered by continuous infusion, anticoagulant effects and plasma concentrations of Argatroban follow similar, predictable temporal response profiles, with low intersubject variability. Immediately upon initiation of Argatroban infusion, anticoagulant effects are produced as plasma Argatroban concentrations begin to rise. Steady-state levels of both drug and anticoagulant effect are typically attained in 1-3 hours and are maintained until the infusion is discontinued or the dosage adjusted. Steady-state Argatroban plasma concentrations increase proportionally with dose (for infusion doses up to 40 mcg/kg/min in healthy subjects) and are well-correlated with steady-state anticoagulant effects. For infusion doses up to 40 mcg/kg/min, Argatroban increases, in a dose-dependent fashion, the activated partial thromboplastin time (aPTT), the activated clotting time (ACT), the prothrombin time (PT) and International Normalized Ratio (INR), and the thrombin time (TT). Representative steady-state plasma Argatroban concentrations and anticoagulant effects are shown in Figure 1 for Argatroban infusion doses up to 10 mcg/kg/min.

Effect on International Normalized Ratio (INR): Because Argatroban is a direct thrombin inhibitor, co-administration of Argatroban and warfarin produces a combined effect on the laboratory measurement of the INR. However, concurrent therapy, compared to warfarin monotherapy, exerts no additional effect on vitamin-K-dependent factor Xa activity. It is anticipated that there will be no enhanced bleeding risk resulting from the combined effect on INR lab value.

The relationship between INR on co-therapy and warfarin alone is dependent on both the dose of Argatroban and the thromboplastin reagent used. This relationship is influenced by the International Sensitivity Index (ISI) of the thromboplastin. Data for two commonly utilized thromboplastins with ISI values of 0.88 (Innovin, Dade) and 1.78 (Thromboplastin C Plus, Dade) are presented in Figure 2 for an Argatroban dose of 2 mcg/kg/min. Thromboplastins with higher ISI values than shown result in higher INRs on combined therapy of warfarin and Argatroban. These data are based on results obtained in normal individuals (see 9 DRUG INTERACTIONS and 4 DOSAGE AND ADMINISTRATION, Conversion to Oral Anticoagulant Therapy).

Figure 2. Relationship of Argatroban and Warfarin on International Normalized Ratio (INR)



Predicted INR for warfarin alone from a co-therapy INR of 4.0 is demonstrated by Figure 2. To calculate INR for warfarin alone (INR_W), based on INR for co-therapy of warfarin and Argatroban (INR_{WA}), use the equation next to the appropriate curve. Example: At a dose of 2 mcg/kg/min and an INR performed with Thromboplastin A, the equation 0.19 + 0.57 (INR_{WA}) = INR_W would allow a prediction of the INR on warfarin alone (INR_W). Solving for an INR_{WA} value of 4.0 on combined therapy: INRw =0.19 +0.57 (4)=2.47 as the value for INR on warfarin alone. The error associated with a prediction is +/- 0.4 units.

10.3 Pharmacokinetics

Metabolism, Excretion, and Protein Binding: Using human liver microsomes and whole cell preparations *in vitro*, four oxidative metabolites were detected (M1, M2, M3 and trace amounts of M4). The formation of each of these metabolites was catalyzed *in vitro* by the human liver microsomal cytochrome P450 enzymes CYP3A4/5. The M1 oxidative metabolite was not quantifiable in plasma of volunteers who received drug. These data together with the lack of effect of erythromycin (a potent CYP3A4/5 inhibitor) on Argatroban pharmacokinetics suggest that CYP3A4/5 mediated metabolism is not an important elimination pathway *in vivo*.

The major route of excretion of Argatroban is via fecal elimination, presumably via biliary secretion. In a study in which [^{14}C]Argatroban (5 mcg/kg/min) was infused for 4 hours to healthy subjects, the majority of the radioactivity was recovered in the feces (approximately 65% of the administered dose) over 7 days and urine (approximately 22% of the administered dose) within 6 days. Unchanged Argatroban accounted for the majority (approximately 16% of the administered dose) of the radioactivity in urine. The precise composition of the remainder of the radioactivity in urine and feces was not fully evaluated. Plasma radioactivity was undetectable by 24 hours. Argatroban is 54% bound to human serum proteins, with binding to albumin and α_1-acid glycoprotein being 20% and 34%, respectively.

The pharmacokinetic profile of Argatroban is well characterized by a two-compartment model with first-order elimination. Total body clearance is approximately 5.1 mL/min/kg (0.31 L/hr/kg) for infusion doses up to 40 mcg/kg/min, and the volume of the central compartment and the volume of distribution are

approximately 84 and 174 mL/kg, respectively. Upon cessation of Argatroban infusion, plasma Argatroban concentrations rapidly decline with α and β elimination half-lives of approximately 7 and 54 minutes, respectively. After four hours, little or no Argatroban remains in plasma.

The plasma clearance of the *R* and *S* stereoisomers is similar. *In vivo*, the plasma concentration ratio of *R* to *S* stereoisomers remains essentially constant over time and is approximately equal to the dose ratio (65:35). Hepatic impairment appears to equally affect the plasma concentration of the *R* and *S* stereoisomers since their ratio in plasma remains unchanged relative to that observed in healthy subjects. The less common *S* isomer is approximately twice as potent as the *R* isomer.

Special Populations and Conditions:

Age/Gender: The pharmacokinetics of Argatroban have been evaluated by age and gender in healthy subjects and in special populations including those with renal impairment, hepatic impairment, unstable angina, or patients undergoing coronary interventional procedures. There are no effects of age or gender on the pharmacokinetic parameters of Argatroban, with exception of clearance in elderly males being about 80% of that in elderly females.

Hepatic Impairment: Moderate hepatic impairment is associated with a four-fold decreased clearance for Argatroban as well as an increased elimination half-life of 2.5 hours (see 4 DOSAGE AND ADMINISTRATION).

Renal Impairment: Renal dysfunction did not affect the pharmacokinetic or pharmacodynamic parameters of Argatroban.

11 STORAGE, STABILITY AND DISPOSAL

Argatroban Concentrate Solution (100 mg/mL)

Vials of Argatroban concentrate solution are stable until the date indicated on the package when stored at 15-25°C in original package. Do not refrigerate or freeze. Store in carton until use. PROTECT FROM LIGHT. If the solution is cloudy, or if an insoluble precipitate is noted, the vial should be discarded.

Reconstituted solutions: Solutions prepared as recommended (see 4 DOSAGE AND ADMINISTRATION) are stable at 15-25°C in ambient indoor light for 24 hours; therefore, light resistant measures such as foil protection for intravenous lines are unnecessary. Solutions are physically and chemically stable for up to 48 hours when stored at 2 to 8°C in the dark. Prepared solutions should not be exposed to direct sunlight. No significant potency losses have been noted following simulated delivery of the solution through intravenous tubing.

Argatroban Ready to use Solution (1 mg/mL)

Vials of Argatroban ready to use solution are stable until the date indicated on the package when stored at 15-30°C in original package. Store in carton until use. PROTECT FROM LIGHT. Do not use if the solution is cloudy, contains particulate matter or precipitates, shows discoloration or if the container is damaged.

Special instructions for both dosage forms: As with all parenteral drug products, intravenous admixtures

should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used. Discard unused portion.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug substance

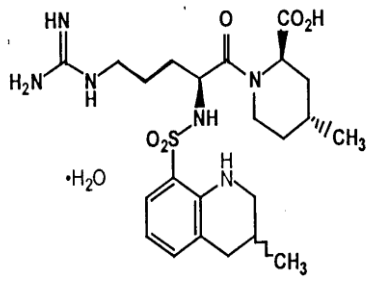
Common Name: Argatroban

Chemical Name: 1-[5-[(aminoiminomethyl)amino]-1-oxo-2[[(1,2,3,4-tetrahydro-3-methyl-8-quinolinyl)sulfonyl]amino]pentyl]-4-methyl-2-piperidinecarboxylic acid, monohydrate.

Molecular Formula
$C_{23}H_{36}N_6O_5S.H_20$

Molecular Mass:
526.66

Structural Formula:



Physicochemical Properties:
Argatroban is a synthetic, small-molecule, direct thrombin inhibitor derived from L-arginine. Argatroban has 4 asymmetric carbons. One of the asymmetric carbons has an *R* configuration (stereoisomer Type I) and an *S* configuration (stereoisomer Type II). Argatroban consists of a mixture of *R* and *S* stereoisomers at a ratio of approximately 65:35.

Argatroban is a white, odorless crystalline powder that is freely soluble in glacial acetic acid, slightly soluble in ethanol, and insoluble in acetone, ethyl acetate and ether.

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Acute Toxicity Studies

Species/ strains	No. per group	Route	Compound	Dose level (mg/kg)	Observations
Mice: ddY	10 4-5 4-5	IV PO IP	Argatroban	174-230 NS NS	LD_{50}: 211.4 mg/kg LD_{50}: 6200 mg/kg LD_{50}: 600-800 mg/kg
Rat: Wistar	29 4-5 4-5	IV PO IP	Argatroban	100-200 NS NS	LD_{50}: 138 mg/kg
Dog: Beagle	3 4	IV PO	Argatroban	30-65.8 NS	LD_{50}: > 65.8 mg/kg LD_{50}: > 1000 mg/kg
Rabbit: Japanese White	9	IV	Argatroban	100-200	LD_{50}: 100-150 mg/kg
Mice: ddY	10	PO IV IP SC	Argatroban	15 g/kg 81 167-1307 108-14860	LD_{50}: > 15 g/kg LD_{50}: > 81 mg/kg LD_{50}: M: 474 mg/kg F: 640 mg/kg LD_{50}: M: 3750 mg/kg F: 3900 mg/kg
Rat: Wistar	10	PO IV IP SC	Argatroban	15 g/kg 81 68-726: M 141-726: F 50-7000: M 50-5000: F	LD_{50}: > 15 g/kg LD_{50}: > 81 mg/kg LD_{50}: M: 320 mg/kg F: 409 mg/kg LD_{50}: M: 620 mg/kg F: 1565 mg/kg
Rat: Sprague-Dawley	5	IV	Argatroban	16.7, 50, 150	Dose related increase in aPTT and PT reversible by end of study.
Rat: Wistar-slc	5	IV	Argatroban	180-540	LD_{50}: 304 mg/kg
Rat: Wistar-slc	5	IV	Product G Product H	450 60	LD_{50}: > 450 mg/kg LD_{50}: > 60 mg/kg
Dog: Beagle	1	IV	Argatroban	100, 200	1 M and 1 F died at 200 mg/kg Hind limb paralysis at 100 and 200 mg/kg Increase in WBC, GPT, GOT
Dog: Beagle	2	IV	Argatroban	M: 3.3, 9.6,	No deaths

Species/ strains	No. per group	Route	Compound	Dose level (mg/kg)	Observations
				28.9 F: 3.3, 10.4, 27.7	NOEL: < 3.3 mg/kg Dose related increase in aPTT and PT reversible within 24-48 hrs.

IP= Intraperitoneal; IV = Intravenous; PO = Oral; SC = Subcutaneous; NOEL = No-observable-effect-level; NS = Not specified

Long-Term Toxicity Studies

Species/ strains	No. per group	Route	Compound	Dose levels (mg/k)	Duration	Key observations
Rat: Sprague-Dawley	15	IV	Argatroban	C, 3, 9, 27	1X daily / 6 months	Minimal variations in aPTT and PT levels for duration of study Nontoxic dose: 9 mg/kg
Dog: Beagle	4	IV	Argatroban	3, 10, 30	24 hr/day /28 days	No overt toxicity 30 mg/kg/day: No AE dose level
Dog: Beagle	4	IV	Argatroban	1, 3, 9	1X daily/ 6 months	Occasional vomiting after admin. In 3 mg/kg or more groups Non toxic dose: 1 mg/kg
Rat: Sprague-Dawley	8	IV	Argatroban	60/day	24 hr/day /14 days	No adverse systemic effects. Argatroban caused modest irritation at site of catheter implantation.
Dog: Beagle	1-2	IV	Argatroban	60/day	24 hr/day / 13 days	Hepatic Kupffer cell pigmentation attributed to test compound
Dog: Beagle	3	IV	Argatroban	2.5/day	1 injection /day for 1 month	2.5 mg/kg/day considered, systemically a no-effect dose.
Rat: Sprague-Dawley	12	IV	Argatroban	5/day	1X Daily /30 days	Slight perivenous hemorrhage related to antithrombotic action of drug. NOEL: 5 mg/kg/day
Dog: Beagle	4	IV	Argatroban	15, 30, 60	24 hr/day /1 month	No overt toxicity. NOEL: 60 mg/kg/day
Dog: Beagle	3	IV	Argatroban	3, 9, 27	1X daily/ 1 month	No abnormalities in clinical signs or pathology

Species/ strains	No. per group	Route	Compound	Dose levels (mg/k)	Duration	Key observations
						Non toxic dose = 3 mg/kg
Dog: Beagle	4	IV	Argatroban	3, 10, 30	24 hr/day /28 days	No overt toxicity. NOEL = 30 mg/kg/day
Rat: Wistar-slc	10	IV	Argatroban	3, 9, 27	1X daily/ 1 month	Increase in F hematocrit and decrease in F body weight gain at 27 mg/kg/day Non toxic dose = 9 mg/kg
Rat: Sprague-Dawley	10	IV	Argatroban	3, 10, 30	1X daily / 28 days	No deaths or remarkable finding NOEL = 30 mg/kg

AE = Adverse events; IP= Intraperitoneally; IV = Intravenous; PO = Orally; NOEL = No-observable-effect-level

Mutagenicity

Carcinogenesis, Mutagenesis, Impairment of Fertility: *In vitro* assays designed to assess the mutagenic potential of Argatroban in bacteria (Ames, rec-A), effects on DNA synthesis (W1-38 cells), or the ability of Argatroban to induce chromosomal aberrations were conducted both in the presence or absence of metabolic activation. The results indicate that Argatroban does not possess mutagenic potential.

Species/strains	Route	Compound	Concentration (mcg/mL)	Duration	Key observations
CHO cells (Chromosome test)	In vitro	Argatroban	1,3,10,30,100, 300, 1000	16 hrs incubation	No Chromosomal aberrations
Human normal diploid culture cells (UDS test)	In vitro	Argatroban	1,3,10,30,100, 300, 1000	5.5 hrs incubation	No increase in DNA synthesis
B. Subtilis (Rec-Assay)	In vitro	Argatroban	6250, 12500, 25000, 50000	18 hrs incubation	Weak positive response at 12500 mcg /mL or more Possible DNA damaging effect on B.*subtilis.*
S.typhimurium; E. Coli	In vitro	Argatroban	200 mcg/plate 500 mcg /plate 1000 mcg /plate	45 hrs incubation	Argatroban was not mutagenic with or without metabolic activation.
S.typhimurium; E. Coli	In vitro	Argatroban	5, 10, 50, 100, 500, 1000, 5000	48 hrs incubation	Argatroban was not mutagenic with or

			mcg /plate		without metabolic activation.
CHO cells	In vitro	Argatroban	10, 25, 50, 100, 250, 500, 1000, 2500	24 or 48 hrs exposure	Argatroban was not clastogenic.
CHO cells	In vitro	Argatroban	500, 750, 1000, 1500, 2000, 2500, 3000	-	Argatroban was not cytotoxic either in the absence or presence of rat liver S-9 mix.
Mouse	IV	Argatroban	27 mg/kg	24 or 48 hrs	No induction of cytogenic damage to mouse bone marrow cells
Rat hepatocyte (Sprague-Dawley)	In vitro	Argatroban	1.5, 4.74, 15, 47.4, 150, 474, 1500	24 hrs incubation	Induction of Unscheduled DNA Synthesis (UDS)
Rat hepatocyte (Fischer 344)	In vitro	Argatroban	1 mg/mL - 10^{-8} mg/mL	18-20 hrs	Test material precipitated at 1 mg/mL. No induction of DNA repair at # 5 x 10^{-1} mg/mL

IV = Intravenous

Reproduction and Teratology

Overall, in reproductive studies with Argatroban in animals, there were no indications of impaired parental reproductive capacity, embryotoxicity, fetotoxicity, teratogenicity, or effects on weaning, lactation, normal development, or reproductive competence of progeny. The parental "no-effect doses" were 54.9 mg/m^2 in rats and 127.4 mg/m^2 in rabbits; fetal "no-effect doses" were 164.7 mg/m^2 in rats and 127.4 mg/m^2 in rabbits.

Pregnancy in Animals: Reproduction studies performed in rats and rabbits at doses up to two times the recommended dose in man have revealed no evidence of impaired fertility or harm to the fetus due to Argatroban.

Nursing Mothers: Experiments in rats show that Argatroban is detected in milk. It is not known whether this drug is excreted in human milk.

Species/ strains	No. per group	Route	Compound	Dose levels (mg/kg)	Duration	Key observations
Rat: SPF Wistar	28	IV	Argatroban	3, 9, 27	M: daily 60 days prior to mating F: daily 14 days prior to mating to day 7 of gestation	NOEL (toxicity) = 9 mg/kg NOEL (fetal devel.) = 27 mg/kg
Rat: SPF Wistar	40-45	IV	Argatroban	3, 9, 27	F: Daily days 7-17 of gestation	No significant toxic effects on dams or pups.
Rat: SPF Wistar	23	IV	Argatroban	3, 9, 27	Daily day 17 of gestation to day 21 post partum	NOEL (maternal rats) = 9 mg/kg NOEL (maternal reproductive performance and F1 generation development) = 27 mg/kg
Rabbit: NZW	17	IV	Argatroban	0.5, 1.0, 2.0	Daily days 6-18 of gestation	NOEL (maternal rabbits) = 0.5 mg/kg NOEL (fetal rabbits) 1.0 mg/kg No teratogenic effects.

Rabbit: NZW	18	IV	Argatroban	10.8	Daily days 6-18 of gestation	NOEL (maternal rabbits) = 10.8 mg/kg NOEL (fetal rabbits) 10.8 mg/kg No teratogenic effects.

IV = Intravenous; NOEL = No-observable-effect-level

Other Studies

Species/ strains	No. per group	Route	Compound	Dose levels (mg/kg)	Duration	Key observations
Guinea pigs	50 total	ID	Argatroban	2, 10, 50	3X at 2 week intervals	Argatroban not antigenetic in guinea pigs.
Mice	40 total	IP	Argatroban	2, 10, 50	3X at 2 week intervals	Argatroban not antigenetic in mice.
Guinea pigs (Hartley)	10	IP IM	Argatroban	0.3, 6 5	1X every other day X6 3X / week	No Passive Cutaneous Anaphylaxis (PCA) symptoms found against argatroban.
Guinea pigs (Hartley)	10	SC IV	Argatroban + Freunds adjuvant Argatroban	5 mg/mL 10 mg/ kg/2mL	Single Single dose	Results indicate that argatroban may not have any antigenicity.
Rat (CD) Plasma	-	In vitro	Argatroban	0.35 mL	Single dose	Argatroban did not precipitate in rat plasma.
Rabbit (NZW) Blood	-	In vitro	Argatroban	1 mL	-	Argatroban does not cause hemolysis.
Rat (Wistar) Blood	-	In vitro	Argatroban	500 µM	-	Argatroban has weak direct action on erythrocyte membrane.

Rabbit (NZ)	3	IM PV	Argatroban	1 mg 0.2 mg	1 or 5 injections 2 injections	Argatroban produced a very slight local reaction when administered by the IM and PV routes.
Rat Erythrocyte	-	In vitro	Argatroban	50 µL, 250 µL	-	Argatroban only produced slight hemolysis in vitro and negligible hemolysis in vivo at low and high micellar concentrations.
Rat Erythrocyte	-	In vitro	Argatroban	1 mg/mL	-	Argatroban produced no hemolysis.
Dog erythrocyte	-	In vitro	Argatroban	1 mg/mL	1/2 dilution 1/10 dilution	Argatroban produced very slight hemolysis at 1/2 dilution: M = 12%; F = 7% and very minor hemolysis at 1/10 dilution: M = 2%; F = 3%

ID = Intradermal; IM = Intramuscular; IP = Intraperitoneal; SC = Subcutaneous; PV=Perivenous

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]ARGATROBAN
(argatroban for injection)
100 mg/mL (250 mg/2.5 mL) Concentrate solution

Read this carefully before you are given **ARGATROBAN**. 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 **ARGATROBAN.**

What is ARGATROBAN used for:
ARGATROBAN is used to prevent blood clots from forming in patients who have received therapy with heparin (another type of blood thinner used to treat blood clots) and developed blood clots as a result of the heparin therapy.

How does ARGATROBAN work?
ARGATROBAN reduces or stops the activity of thrombin, a component in the blood which is necessary for blood clotting.

What are the ingredients in ARGATROBAN?

Medicinal ingredients: argatroban
Non-medicinal ingredients: D-sorbitol, dehydrated alcohol and water for injection.

ARGATROBAN comes in the following dosage forms:
Concentrate, solution for intravenous injection; 250 mg/2.5 mL vial.

Do not use ARGATROBAN if:

- you are hypersensitive or "allergic" to the active ingredient argatroban or to any ingredient in the formulation (see 'What are the ingredients in ARGATROBAN:' section).
- you have active major bleeding or a bleeding disorder.
- you have a rare disease known as hereditary fructose intolerance.

The safety of ARGATROBAN has not been established in children age 18 and younger.

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

- have or have had a bleeding disorder, such as hemophilia (a condition where blood takes a long time to clot) or ulcers (a condition in which sores and possibly bleeding occur in the stomach or intestines);
- have high blood pressure;
- have had or about to have surgery;
- are pregnant or nursing;

- have a liver disease or problems.

Other warnings you should know about:

Check-ups and testing: You will have regular visits with your healthcare professional, before, during and at the end of your treatment. They will do blood tests to check your blood.

Pregnancy and breastfeeding:
- Do not use ARGATROBAN if you are pregnant. It may harm your unborn baby.
- Tell your healthcare professional right away if you become pregnant or think you may be pregnant during your treatment with ARGATROBAN.
- Do not breastfeed while you are given ARGATROBAN.

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 ARGATROBAN:

- Medications used to prevent blood clotting such as ASA, clopidogrel, ticlopidine, prasugrel, ticagrelor
- Medications used to thin the blood such as warfarin, heparin, low molecular weight heparins
- Acetaminophen (a drug taken for pain)

How to use ARGATROBAN:

ARGATROBAN must be administered by a healthcare professional experienced in anti-thrombotic therapy.

Concentrate Solution:
ARGATROBAN is supplied as a concentrate. It should be properly diluted prior to administration. It should not be mixed with other drugs prior to dilution in an infusion.

Usual dose:
ARGATROBAN is a prescription drug and must be used as directed. It is administered as an intravenous injection, which means the injection is made into a vein. ARGATROBAN must NOT be given by any other route.

Overdose:
If you think you, or a person you are caring for, have been given too much ARGATROBAN, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose: n/a

What are possible side effects from using ARGATROBAN?
These are not all the possible side effects you may have when given ARGATROBAN. If you experience any side effects not listed here, tell your healthcare professional.

Along with its intended action, any medication, including ARGATROBAN, may cause side effects. Most adverse events are mild and tend to diminish with continuation of therapy.

The most common side effects are:

- bleeding,
- stomach upset (nausea and vomiting),
- diarrhea,
- low blood pressure,
- difficulty breathing,
- increased heartbeat,
- dizziness,
- fever and
- chest pain**.**

The most serious side effect is unusual bleeding (such as hemorrhage).

The following table contains a list of side effects that may occur with ARGATROBAN.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Stomach pain, nausea or diarrhea		X	
COMMON			
Any unusual bleeding		X	
Difficulty Breathing		X	
Chest pain		X	
Dizziness		X	
Fever		X	
Rapid heartbeat		X	
Pain		X	
Infection		X	
UNKNOWN			
Allergic reaction (symptoms like itching, swelling of the face, lips, tongue and throat, difficulty breathing)			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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

Keep out of reach and sight of children.

Store the vials in the original cartons at room temperature (15 – 25°C, 59 – 77°F). Do not freeze. Store in carton until use. PROTECT FROM LIGHT.
Discard prepared solution if haziness, particulate matter, precipitate, discoloration or leakage is found upon inspection.

If you want more information about ARGATROBAN:

- 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: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html ; the manufacturer's website www.sandoz.ca or by calling 1-800-361-3062.

This leaflet was prepared by Sandoz Canada Inc.

Last revised: JUN 28, 2024

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]ARGATROBAN
(argatroban injection)
1 mg/ mL (50 mg/ 50 mL) Ready to Use Solution

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ARGATROBAN reduces or stops the activity of thrombin, a component in the blood which is necessary for blood clotting.

What are the ingredients in ARGATROBAN?

Medicinal ingredients: argatroban

Non-medicinal ingredients: Sodium chloride, Sorbitol, and water for injection.

ARGATROBAN comes in the following dosage forms:

Ready to Use pre-diluted solution for intravenous injection, 50 mg/ 50 mL vial.

Do not use ARGATROBAN if:

- you are hypersensitive or "allergic" to the active ingredient argatroban or to any ingredient in the formulation (see 'What are the ingredients in ARGATROBAN:' section).
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- Tell your healthcare professional right away if you become pregnant or think you may be pregnant during your treatment with ARGATROBAN.
- Do not breastfeed while you are given ARGATROBAN.

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 ARGATROBAN:

- Medications used to prevent blood clotting such as ASA, clopidogrel, ticlopidine, prasugrel, ticagrelor
- Medications used to thin the blood such as warfarin, heparin, low molecular weight heparins
- Acetaminophen (a drug taken for pain)

How to use ARGATROBAN:

ARGATROBAN must be administered by a healthcare professional experienced in anti-thrombotic therapy.

Ready To Use Formulation

ARGATROBAN is supplied as a ready to use formulation. It should not be mixed with other drugs in an infusion. The vial can be inverted for use with medical infusion set.

Usual dose:

ARGATROBAN is a prescription drug and must be used as directed. It is administered as an intravenous injection, which means the injection is made into a vein. ARGATROBAN must NOT be administered by any other route.

Overdose:

If you think you, or a person you are caring for, have been given too much ARGATROBAN, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose: n/a

What are possible side effects from using ARGATROBAN?

These are not all the possible side effects you may have when given ARGATROBAN. If you experience any side effects not listed here, tell your healthcare professional.

Along with its intended action, any medication, including ARGATROBAN, may cause side effects. Most adverse events are mild and tend to diminish with continuation of therapy.

The most common side effects are:

- bleeding,
- stomach upset (nausea and vomiting),
- diarrhea,
- low blood pressure,
- difficulty breathing,
- increased heartbeat, dizziness,
- fever and
- chest pain**.**

The most serious side effect is unusual bleeding (such as hemorrhage).

The following table contains a list of side effects that may occur with ARGATROBAN.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Stomach pain, nausea or diarrhea		X	
COMMON			
Any unusual bleeding		X	
Difficulty Breathing		X	
Chest pain		X	
Dizziness		X	
Fever		X	
Rapid heartbeat		X	
Pain		X	
Infection		X	
UNKNOWN			
Allergic reaction (symptoms like itching, swelling of the face, lips, tongue and throat, difficulty breathing)			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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

Keep out of reach and sight of children.

Store the vials in the original cartons at room temperature (15 – 30°C). Store in carton until use. Do not refrigerate or freeze. PROTECT FROM LIGHT. Discard unused portion of the solution.
Discard prepared solution if haziness, particulate matter, precipitate, discoloration or leakage is found upon inspection.

If you want more information about ARGATROBAN:

- 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: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html ; the manufacturer's website www.sandoz.ca or by calling Sandoz Canada 1-800-361-3062.

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