HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ARGATROBAN INJECTION safely and effectively. See full prescribing information for ARGATROBAN INJECTION.

ARGATROBAN INJECTION, for intravenous infusion only
Initial U.S. Approval: 2000

INDICATIONS AND USAGE

Argatroban is a direct thrombin inhibitor indicated for:

- For prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT) (1.1)
- As an anticoagulant in adults patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI) (1.3)

DOSAGE AND ADMINISTRATION

- Argatroban injection, USP 50 mg/2.5 mL (1 mg/mL) is ready for intravenous infusion. Dilution is not required. (2.1)

Heparin-Induced Thrombocytopenia
The dose for patients with HIT or HITTS or anticoagulants without heparin impairment is 2 mcg/kg/min administered as a continuous infusion. (2.2)

Percutaneous Coronary Intervention
The dose for patients with HIT undergoing percutaneous coronary intervention is 25 mcg/kg/min and a bolus of 350 mcg/kg, administered via a large bore intravenous line over 3 to 5 minutes. (2.3)

DOSAGE FORMS AND STRENGTHS

- Injection: 50 mg/2.5 mL (1 mg/mL) ready for intravenous infusion single-dose vials. (3)

CONTRAINDICATIONS

- Major bleeding. (4)
- History of hypersensitivity to this product. (4)

WARNINGS AND PRECAUTIONS

- Hemorrhage can occur. Unexplained fall in hematocrit or blood pressure may indicate hemorrhage. (5.1)
- Unexplained significant skin lesions, gangrene, or other severe ischemic events will also have occurred in patients with heparin-induced thrombocytopenia. Avoid use in PCI in patients with clinically significant hepatic impairment. (5.2)

ADVERSE REACTIONS

- HIT patients: The most common (>5%) adverse reactions were dyspnea, thrombosis, fever, diarrhea, sepsis, and cardiac arrest. (6.1)
- PCI patients: The most common (>5%) adverse reactions were chest pain, hypotension, back pain, nausea, vomiting and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Heparin: Allow sufficient time for heparin to effect an unchanged partial thromboplastin time (aPTT) to decrease before initiating Argatroban injection therapy. (7.1)
- Warfarin: Concomitant use results in increased prolongation of PT and INR. (7.2)
- Thrombolytic agents or glycoprotein IIb/IIIa antagonists: Safety and effectiveness of concomitant use with Argatroban have not been studied. (7.3, 7.4)

USE IN SPECIFIC POPULATIONS

- Lactation: Discontinue nursing or stop, taking into account the importance of the drug to the mother. (8.2)
- Pediatric Use: Safety and effectiveness have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 03/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Heparin-Induced Thrombocytopenia

Argatroban injection is indicated for prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT).

1.2 Percutaneous Coronary Intervention

Argatroban injection is indicated as an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI).

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Intravenous Administration

Argatroban injection, USP is supplied as a concentrate (50 mg/2.5 mL, (1 mg/mL).

Argatroban injection USP (50 mg/2.5 mL, (1 mg/mL).

Each 50 mL glass vial contains 50 mg argatroban (1 mg/mL) and, as supplied, is ready for intravenous infusion. Dilution is not required. Argatroban injection is a clear, colorless to pale yellow solution. Minimal yellowing of the solution should be expected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if solution is discolored, cloudy, or precipitate is present. Do not if seals is not intact.

Vial stoppers contained in the vial are made of medical rubber.

2.2 Dosing in Patients with Heparin- Induced Thrombocytopenia

Initial Dosage

Before administering argatroban, discontinue heparin therapy and obtain a baseline activated partial thromboplastin time (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
Recommended Dose and Infusion Rates for 2 mcg/kg/min Dose of Argatroban for Patients With HIT and Without Hepatic Impairment Using Different Concentrations

Body Weight (kg)	Dose (mcg/min)	Infusion Rate (mL/hr)
50	100	6
60	120	7
70	140	8
80	160	10
90	180	11
100	200	12
110	220	13
120	240	14
130	260	16
140	280	17

*with or without thrombosis

a Refreshes may have persisted more than 1 adverse reaction.
b) One patient experienced intracranial hemorrhage 4 days after discontinuation of argatroban and following therapy with oral anticoagulant and thrombolytic.
c) The individual cardiac group consisted of patients with a clinical diagnosis of HIT (with or without thrombosis) that were considered eligible by an independent medical panel.
DIC = disseminated intravascular coagulation
BMA = Bellow Time analysis.

Table 4 gives a summary of the most frequently observed non-hemorrhagic reactions sorted by decreasing frequency of occurrence (in 2% among argatroban treated HIT/HITTS patients).

Table 4
Non-Hemorrhagic Adverse Reactions in Patients* With HIT

	Argatroban-treated Patients (Study 1 and Study 2) (n = 508) %	Historical Control† (n = 192) %
Dyspnea	6.1	6.8
Angiotensin	7.2	2.6
Fever	6.9	2.1
Diarrhea	6.2	1.6
Sepsis	4.0	12.4
Cardiac arrest	3.8	3.1
Nausea	3.8	3.1
Ventricular tachycardia	3.6	3.1
Pain	3.6	1.1
Urinary tract infection	3.6	5.2
Hypotension	3.4	6.8
Infection	3.7	3.6
Pneumonia	3.3	9.3
Atrial fibrillation	3.0	11.4
Coughing	2.8	1.6
Abnormal renal function	2.8	5.2
Abdominal pain	2.6	1.6
Cardiovascular disorder	2.4	4.1

a) Refreshes may have experienced more than 1 adverse reaction.
b) With or without thrombosis.
c) The individual cardiac group consisted of patients with a clinical diagnosis of HIT (with or without thrombosis) that were considered eligible by an independent medical panel.

Adverse Reactions in Patients with or at Risk for HIT Undergoing PCI

The following safety information is based on 41 patients initially treated with argatroban and 21 patients subsequently re-exposed to argatroban for a total of 110 PCIs with argatroban anticoagulation. Adverse reactions are reported into hemorrhagic (Table 6) and non-hemorrhagic (Table 7) reactions.

Major bleeding was defined as bleeding that was overt and associated with a hemoglobin decrease ≥3 g/dL, that required ≥2 units of blood, or that was intracranial, retroperitoneal, intra-ocular, or intra-pericardial. The rate of major bleeding events in patients treated with argatroban was 2.7%.

Table 5
Major and Minor Hemorrhagic Adverse Reactions in Patients With HIT Undergoing PCI

Major Hemorrhagic Reactions *	
	Argatroban-treated Patients (n = 110)%
Retroperitoneal	0.9
Gastrointestinal	0.9
Intracranial	0.9
Minor Hemorrhagic Reactions * †	
	Argatroban-treated Patients (n = 110)%
Groin (bleeding or hematoma)	15.5
Gastrointestinal (mucosa hemorrhage)	2.4
Genitourinary (includes hematuria)	1.8
Decrease in hemoglobin and/or hematocrit	1.8
CNS (cerebral ischemia)	1.8
Access site	0.6
Hemoptysis	0.6
Other	0.6

a) Refreshes may have experienced more than 1 adverse reaction.
b) Hemorrhagic reactions in the CNS.
c) BMA = Bellow Time analysis.

Table 7 gives an overview of the most frequently observed non-hemorrhagic adverse reactions (>2%), sorted by decreasing frequency of occurrence in argatroban treated PCI patients.

Table 6
Non-hemorrhagic Adverse Reactions in Patients With HIT Undergoing PCI

Coded Term	Argatroban Prophylaxis* (n = 110)%
Myocardial infarction	4 (3.6%)
Angina pectoris	2 (1.8%)
Coronary thrombosis	2 (1.8%)
Myocardial ischemia	2 (1.8%)
Occlusion coronary	2 (1.8%)
Chest pain	1 (0.9%)
Fever	1 (0.9%)
Retroperitoneal hemorrhage	1 (0.9%)
Aortic stenosis	1 (0.9%)
Arterial thrombosis	1 (0.9%)
Gastrointestinal hemorrhage	1 (0.9%)
Gastrointestinal disorder (GERD)	1 (0.9%)
Cerebrovascular disorder	1 (0.9%)
Lung edema	1 (0.9%)
Hypotension	1 (0.9%)

a) Individual reactions may also have been reported elsewhere (see Table 6 and 7).
b) HIT patients underwent 110 procedures. Some patients may have experienced more than 1 reaction.

Intracranial Bleeding in Other Populations

Increased risks for intracranial bleeding have been observed in investigational studies of argatroban for other uses. In a study of patients with acute myocardial infarction receiving both argatroban and thrombolytic therapy (streptokinase or tissue plasminogen activator), the overall frequency of intracranial bleeding was 1% (8 out of 814 patients). Intracranial hemorrhage was observed in 0.4% (3 out of 814) patients who did not receive concomitant thrombolytic therapy.

The safety and effectiveness of argatroban for cardiac indications other than PCI in patients with HIT have not been established. Intracranial bleeding was also observed in a prospective, placebo-controlled study in acute stroke patients who had onset of acute stroke within 12 hours of study entry. Symptomatic intracranial hemorrhage was observed in 2.1% (2 out of 96) patients treated with argatroban for 96 hours, versus 0% (0 out of 97) patients treated with placebo. Asymptomatic intracranial hemorrhage occurred in 5.4% (5 out of 92) versus 2.1% (2 out of 95) patients, respectively.

Allergic Reactions

One hundred five allergic reactions or suspected allergic reactions were observed in 1,127 individuals who were treated with argatroban in clinical pharmacology studies or for various clinical indications. About 90% (1106/1,127) of these reactions were reported in patients who received argatroban for treatment or prophylaxis, or, intraoperatively or postoperatively, through vascular sheaths or cardiopulmonary bypass circuits in populations other than patients with HIT with or without thrombosis (include (in descending order of frequency):

- Airway reactions (coughing, dyspnea): 19% (n = 21)
- Skin reactions (rash, hives, erythema): 1 % (n = 10)
- General reactions (anaphylaxis): 1 % (n = 10)

Limited data are available on the potential formation of drug-related antibodies. Plasma from 12 healthy volunteers treated with argatroban over 5 days showed no evidence of neutralizing antibodies. No loss of anticoagulant activity was noted with repeated administration of argatroban to more than 40 patients.

7 DRUG INTERACTIONS

7.1 Heparin

Allow sufficient time after cessation of heparin therapy, allow sufficient time for heparin's effect on the aPTT to diminish prior to initiating argatroban therapy.

7.2 Oral Anticoagulant Agents

Pharmacodynamic drug interactions between argatroban and warfarin (2.5 mg single oral dose) have not been demonstrated. However, the concomitant use of argatroban and warfarin for 5 to 9 days initial dose, followed by 3 to 5 mcg/kg/min, prolonged the INR to a greater extent than prolongation of the prothrombin time (PT) and International Normalized Ratio (see *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.2)*).

Drug-Laboratory Test Interactions

No drug-drug interactions have been observed between argatroban and noncontaminating administered heparin or anticoagulant (see *Clinical Pharmacology (12.2)*).

7.4 Thrombolytic Agents

The safety and effectiveness of argatroban with thrombolytic agents have not been established (see *Adverse Reactions (6.1)*).

7.5 Glycoprotein IIb/IIIa Antagonists

The safety and effectiveness of argatroban with glycoprotein IIb/IIIa antagonists have not been established.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Reproductive studies published literature and postmarketing reports do not suggest an association between argatroban and adverse fetal developmental outcomes. There are data from other published studies in pregnant women that describe bleeding and a risk of hemorrhage in the mother and fetus associated with use of anticoagulants (see *Clinical Considerations*). In animal reproductive studies, no adverse fetal developmental effects were observed after administration of subcutaneous doses of argatroban to pregnancy (organogenesis) in rats and rabbits at doses up to 9.3 and 6.6 times, respectively, the maximum recommended human dose (MRHD) (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the general U.S. population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% and 15% of all pregnancies.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Pregnancy carries an increased risk for thromboembolism that is higher for women with underlying thrombotic disease and carries high risk pregnancies. Published literature and postmarketing reports do not suggest an association between argatroban and adverse developmental outcomes. There are data from other published studies in pregnant women that describe bleeding and a risk of hemorrhage in the mother and fetus associated with use of anticoagulants (see Clinical Considerations). In animal reproductive studies, no adverse fetal developmental effects were observed after administration of subcutaneous doses of argatroban to pregnancy (organogenesis) in rats and rabbits at doses up to 9.3 and 6.6 times, respectively, the maximum recommended human dose (MRHD) (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the general U.S. population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% and 15% of all pregnancies.

Data

Animal Data

Developmental studies performed in rats with argatroban at intravenous doses up to 27 mg/kg/day (9.3 times the maximum recommended human dose, based on body surface area) and in rabbits at intravenous doses up to 19.8 mg/kg/day (13.2 times the maximum recommended human dose, based on body surface area) have revealed no evidence of harm to the fetus.

8.2 Lactation

Risk Summary

There are data on the presence of argatroban in human milk, or the effects on milk production. Argatroban is present in oral milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for argatroban and any potential adverse effects on the breastfed infant from argatroban or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in neonates have not been established in pediatric patients.

Argatroban was studied among 18 neonatal ill pediatric patients who required an alternative to heparin anticoagulation. Most patients were suspected to have HIT or suspected HIT. Argatroban dosage ranged from 0.5 mcg/kg/min to 1.0 mcg/kg/min, n = 16, 8 to 16 years, n = 2, 6 years, n = 1. All patients had serious underlying conditions and received concomitant medications. Two patients had a bleeding event (epistaxis and hematuria). Two patients developed infusion site blood clots. Bleeding was validated in the majority of these 17 patients at 1 mcg/kg/min. Dosing was titrated as needed to achieve and maintain an aPTT of 1.5 to 3 times the baseline value. Most patients required dose reduction. The mean (SD) argatroban clearance was 4.4 (2.4) mL/kg/min, n = 16, 0.1 to 8.1 years. The mean (SD) blood half-life was 1.1 (0.4) hours, n = 16, 0.1 to 8.1 years. Argatroban administration is less patients with Ventricular dysfunction or three other patients. Major bleeding occurred among two patients: one patient experienced an intracranial hemorrhage after 4 days of argatroban therapy in the setting of acute disseminated encephalitis and another patient experienced an intracranial hemorrhage after receiving argatroban for greater than 14 days. The safety and effectiveness of argatroban in neonates with or at risk for thrombosis or suspected HIT in pediatric patients 1 mcg/kg/min was not supported by the pharmacokinetic data (see *Clinical Pharmacology*).

Pediatric Pharmacokinetics (PK) and Pharmacodynamics (PD)

PK parameters of argatroban were characterized in a population PK/PD analysis model with sparse data from 15 seriously ill pediatric patients. Argatroban clearance in these seriously ill pediatric patients (0.16 L/kg/min) was lower than in healthy adult volunteers (0.27 L/kg/min). The PD response (aPTT) was higher than in healthy adult volunteers (related to lower plasma albumin concentration). The PK/PD model predicted that a 1 mcg/kg/min dose (0.5 L/kg) achieved comparable to pediatric patients with normal blood levels.

These PK/PD analyses model based on aPTT prolongation of 1.5 to 3 times the baseline value and assistance of an aPTT < 100 seconds for seriously ill pediatric patients with HIT/HITTS who require an alternative to heparin suggested the following:

- For patients **not receiving renal insufficiency** dialysis initiate at 0.75 mcg/kg/min may have comparable aPTT response as adult patients receiving 2 mcg/kg/min. Titration to achieve a target aPTT response may require more than two hours, increasing the dosage by 0.25 mcg/kg/min could achieve additional aPTT response.
- For patients with **renal insufficiency** requiring dialysis initiate rate of 0.2 mcg/kg/min with increasing dosing by increments of 0.05 mcg/kg/min every three hours until achieve a comparable response in comparison with adult data.

The safety and effectiveness of argatroban with the above dosing have not been adequately assessed in pediatric patients. Monitor aPTT response and adjust argatroban dosage accordingly. Do not exceed a 2 mcg/kg/min dosage. Allow dosage did not take into account multiple factors that could affect the dosage such as current aPTT, target aPTT, and the clinical status of the patient.

8.5 Geriatric Use

Of the total number of subjects (n=578) in clinical studies of argatroban, 30% were 65 and over. In the clinical studies of adult patients with HIT and/or thrombosis, the effectiveness of argatroban was similar in older and younger patients. No trends were observed across age groups for both aPTT and the HITT. The safety analysis did suggest that older patients were more sensitive than younger patients. Dose adjustment in the elderly is not necessary but should be given appropriate consideration in view of their increased risk for adverse reactions.

8.6 Hepatic Impairment

Dose reductions and careful titration are required when administering argatroban to patients with hepatic impairment. Reversal of anticoagulant effect may be prolonged in this population (see *Dosage and Administration (2.4)*, *Adverse Reactions (6.1)*, and *Clinical Pharmacology (12.3)*).

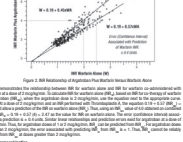
10 OVERDOSAGE

Excessive anticoagulation, with or without bleeding, may be controlled by discontinuing argatroban or by decreasing the argatroban dose. Unlikely that administration of protamine sulfate will reverse the effect of argatroban. Administer within 2 to 4 hours after discontinuation of the drug. Reversal of anticoagulant effect may take longer in patients with hepatic impairment. Monitor the effect of argatroban on the activated partial thromboplastin time (aPTT) and prolong dosing in patients with hepatic impairment. Monitor the effect of argatroban on the activated partial thromboplastin time (aPTT) and prolong dosing in patients with hepatic impairment.

11 DESCRIPTION

Argatroban is a synthetic direct thrombin inhibitor and the chemical name is 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. The synthesis of argatroban is a multiple step process. Argatroban has 4-asymmetric centers and exists in Type 6 and an 2-configuration (predominant Type 6). Argatroban consists of a mixture of 6 and 6 stereoisomers at the 2-asymmetric carbon atoms.

The molecular formula of argatroban is $C_{23}H_{36}N_6O_5S$ and the molecular weight is 526.66 g/mole. The structural formula is shown below:



Argatroban is a white, odorless or pale yellow powder that is freely soluble in glacial acetic acid, slightly soluble in ethanol, methanol, and water, and practically insoluble in ether.

Argatroban Injection, USP 50 mg/2.5 mL (1 mg/mL) is a sterile clear solution for intravenous infusion. Argatroban Injection, USP 50 mg/2.5 mL (1 mg/mL) is available in 50 mg (in 50 mL) single-dose clear vials, with flip-off seals. Each mL of sterile, non-pyrogenic solution contains 1 mg Argatroban, inert ingredients (per USP): Mannitol USP, Sodium Citrate, Citric Acid Dihydrate USP, and Water for Injection USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Argatroban is a direct thrombin inhibitor that reversibly binds to the thrombin active site. Argatroban does not require the co-factor antithrombin III for antithrombotic activity. Argatroban exerts its anticoagulant effect by inhibiting thrombin-catalyzed or -induced reactions, including fibrin formation, activation of coagulation factors V, VIII, and XIII, activation of protein C, and platelet aggregation.

Argatroban inhibits thrombin with an inhibition constant (Ki) of 0.04 μM. At therapeutic concentrations, argatroban has little or no effect on related serine protease (trypsin, factor Xa, plasmin, and kallikrein).

Argatroban is capable of inhibiting the action of both free and clot-associated thrombin.

12.2 Pharmacodynamics

When argatroban is administered by continuous infusion, anticoagulant effects and plasma concentrations of argatroban increase in a linear fashion. Anticoagulant effects and plasma concentrations of argatroban decrease in a linear fashion. Anticoagulant effects, and plasma concentrations of argatroban, are proportional to argatroban administered. Steady-state levels of both drug and anticoagulant effect are typically attained within 1 to 3 hours and are maintained with the infusion for the duration of the infusion. Steady-state levels of anticoagulant effect are typically attained within 1 to 3 hours for infusion doses up to 10 mcg/kg/min in healthy subjects and are well accelerated with steady-state anticoagulant effects. For infusion doses up to 40 mcg/kg/min, argatroban increases in a dose-dependent fashion, the aPTT, the prothrombin time (PT), the activated clotting time (ACT), the thrombin time (TT), the Ecarin clotting time (ECT), the Russell viper venom time (RVVT), and the Hepaptest time. Anticoagulant effects are proportional to infusion doses up to 10 mcg/kg/min (see Figure 1).

Figure 1. Relationship of Steady State Between Argatroban Dose, Plasma Argatroban Concentration and Anticoagulant Effect

Effect on International Normalized Ratio (INR) Because argatroban is a direct thrombin inhibitor, co-administration of argatroban with oral anticoagulants (such as warfarin) results in additive effects on the INR. Because of the additive effect, caution should be exercised when initiating warfarin therapy in patients with argatroban-dependent factor Xa activity.

The relationship between INR (or co-therapy and warfarin doses is dependent on both the dose of argatroban and the thromboplastin reagent used. The relationship is influenced by the International Sensitivity Index (IS) of the thromboplastin. Data for 2 commonly utilized thromboplastins with ISI values of 0.88 (Ironclad, Beckman and Coulter) and 1.0 (Thromborel S, Dade Behring) are shown in Figure 2. Patients with liver disease and patients with higher ISI values tend to exhibit a higher INR on combined therapy of warfarin and argatroban. These data are based on results obtained in normal individuals (see *Drug Interactions (7.2)*, *Dosage and Administration (2.5)*, *Warnings and Precautions (5.3)*).

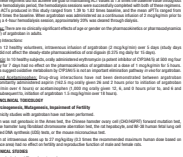


Figure 2. INR Relationship of Argatroban Plus Warfarin Versus Warfarin Alone

Figure 2 demonstrates the relationship between INR for warfarin alone and INR for warfarin co-administered with argatroban. The relationship between INR and plasma argatroban concentration is independent of the dose of argatroban, and of the argatroban dosing regimen. For argatroban, use the equation next to the argatroban curve. Example: At a dose of 2 mcg/kg/min (and an INR performed with Thromborel S, the equation 0.18 + 0.0 7 (INR) $_{Ir}$ = Plasma argatroban concentration (PAC) predicts a PAC of 0.18 + 0.0 7 (2.0) = 0.32 mcg/mL. Alternatively, the equation INR $_{Ir}$ = 0.18 + (0.0 7 x 2.0 7 or the value for INR on warfarin alone. The error (confidence interval) associated with a prediction is ± 0.5 units. Similar linear relationships and precision errors exist for argatroban at a dose of 10 mcg/kg/min. The slope of the line relating INR to plasma argatroban is 0.21 for Thromborel S and 0.26 for Ironclad (greater than 2 standard deviations from zero). The INR, from INR $_{Ir}$ = 1, Thus, INR $_{Ir}$ can be reliably predicted from INR $_{Ir}$ at doses greater than 2 mcg/kg/min.

12.3 Pharmacokinetics

Distribution

Argatroban distributes mainly in the extracellular fluid as evidenced by an apparent steady-state volume of distribution of 174 mL/kg (32.1 L in a 70 kg subject). Argatroban binds to human serum proteins, with binding to albumin and α1-acid glycoprotein 54% and 22% of the total, respectively.

Metabolism

The main route of argatroban metabolism is hydroxylation and aromatization of the 3-methylpiperidinyl-piperazine ring in the liver. The formation of each of the 4 known metabolites is catalyzed in vitro by the human liver microsomal cytochrome P450 isoenzyme, CYP3A4/5. The 4 metabolites are: M1, M2, M3, and M4. Metabolites M3 and M4 are stereoisomers. Their ingestion. Anticoagulant ingestion in the major component in plasma. Plasma concentrations of M1 range between 0% and 30% of that of the parent drug. The other metabolites (M3 to M4) are found only in very low quantities in human plasma. Metabolites M1 and M3 are active thrombin inhibitors, but are less potent than argatroban (4-potent 0.04 Ki inhibitors) as argatroban (prolongation, as, suggest that CYP3A4 is a major metabolic pathway and an important elimination pathway in vivo.

Total body clearance (approximately 5 L/h) in Argatroban 20.31 L/kg/hr for chronic dosage up to 48 mcg/kg/min. The terminal elimination half-life of argatroban ranges between 39 and 51 minutes.

There is no interaction between of the 2-R-(+)- and 2-S-(-)- diastereomeres. The plasma ratio of these diastereomers is unchanged by metabolism or hepatic impairment, remaining constant at 66.35 (n. 2%).

Excretion

Argatroban is excreted primarily in the feces, presumably through biliary secretion. In a study in which radiolabeled argatroban was given to healthy subjects, 65% of the administered radioactivity was recovered in the feces and 18% was recovered in the urine. Only a small fraction of argatroban is excreted unchanged in the urine. Approximately 22% of the radioactivity appeared in the urine within 13 hours of the start of infusion. Little or no radioactivity was detected in the urine after 24 hours. Average percent recovery of unchanged drug, relative to total dose, was 14% in urine and 4% in feces.

Special Populations

Renal Impairment: The dosage of argatroban should be decreased in patients with hepatic impairment (see *Dosage and Administration (2.4)*, *Warnings and Precautions (5.2)*. Patients with hepatic impairment were not included in pericardial-venous cannulas (intravenous (IV) Hole. At a dose of 2 mcg/kg/min, hepatic impairment is associated with decreased clearance and increased elimination half-life of argatroban (1.9-fold, 39 and 101 minutes, respectively, for patients with cirrhosis versus healthy subjects.

Hepatic Impairment: Dose adjustment is necessary in patients with renal dysfunction. The effect of renal disease on the pharmacokinetics of argatroban was studied in 6 subjects with normal renal function (mean Ccr = 104 mL/min) and in 19 subjects with end-stage (mean Ccr = 4.4 ± 10 mL/min). Compared with Ccr = 0.1 ± 0.4 mL/min), and mean (mean Ccr = 3.7 ± 10 mL/min) renal impairment. The pharmacokinetics and pharmacodynamics of argatroban were not altered by renal impairment. Total clearance of argatroban was unaffected in a study of 12 patients with stable renal failure undergoing chronic intermittent hemodialysis. Argatroban was administered at a rate of 2 to 3 mcg/kg/min dogan at least 6 hours prior to dialysis or as a bolus dose of 100 mcg/kg. After the start of dialysis followed by a continuous infusion of 1 mcg/kg/min. Although these regimens did not achieve the goal of maintaining APC values of 1.5 times the baseline value throughout the dialysis procedure, the APC was increased to 1.5 times the baseline value in 10 of the 12 patients during the dialysis procedure. The mean APC during the dialysis procedure was 1.9 times the baseline value. Hemodialysis, and the mean aPTT ranged from 1.96 to 3.4 times the baseline. When argatroban was administered as a continuous infusion at 2 mcg/kg/min prior to and during a 4-hour hemodialysis session, approximately 30% was cleared through dialysis.

Sex, Gender: There are no clinically significant effects of age or gender on the pharmacokinetics or pharmacodynamics of argatroban (see *Dosage and Administration*).

Drug-Drug Interactions

Heparin: In 12 healthy volunteers, intravenous infusion of argatroban (2 mcg/kg/min) over 5 days (study days 1 through 5) prolonged the aPTT and the plasma concentrations of argatroban (0.375 mg/kg) for 10 days.

Erythromycin: In healthy subjects, orally administered erythromycin (a potent inhibitor of CYP3A4/5) at 500 mg four times daily for 7 days had no effect on the pharmacokinetics of argatroban (a substrate of CYP3A4/5 and its inhibitors). These data suggested cytochrome by CYP3A4/5 is not important elimination pathway in vivo for argatroban.

Warfarin: Administration of warfarin (2.5 mg single oral dose) and argatroban (2 mcg/kg/min) for 5 days prolonged the prothrombin time (PT) and the International Normalized Ratio (INR) to a greater extent than prolongation of the PT and INR by warfarin alone (see *Drug Interactions (7.2)*).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenic studies with argatroban have not been performed.

Argatroban was not genotoxic in the Ames test, the Chinese hamster ovary cell (CHO-HGPRT) forward mutation test, the Chinese hamster lung fibroblast chromosome aberration test, the rat hepatocyte, and NK-3B human fetal lung cell unscheduled DNA synthesis (UDS) test, or the mouse micronucleus test.

Argatroban at intravenous doses up to 27 mg/kg/day (9.3 times the recommended maximum human dose based on body surface area) had no effect on fertility and reproduction function of male and female rats.

14 CLINICAL STUDIES

14.1 Heparin-Induced Thrombocytopenia

The safety and efficacy of argatroban were evaluated in a historically controlled efficacy and safety study (Study 1) and a follow-up efficacy and safety study (Study 2). These studies were comparable with regard to study design, study population, and study endpoints. Study 1 was a multinational, multicenter, open-label, parallel-group, historically treated with argatroban (n = 508) and 192 patients treated with other treatments for HIT/HITTS (heparin-induced thrombocytopenia/thrombosis, without thrombosis (HIT) or with thrombosis (HITS) (heparin-induced thrombocytopenia and thrombosis syndrome) and were made on non-conjugated heparin. Between the ages of 18 and 90 years. All HITTS and patients 90 years and older. Study 1 was a multinational, multicenter, open-label, parallel-group, historically treated with argatroban (n = 508) and 192 patients treated with other treatments for HIT/HITTS (heparin-induced thrombocytopenia/