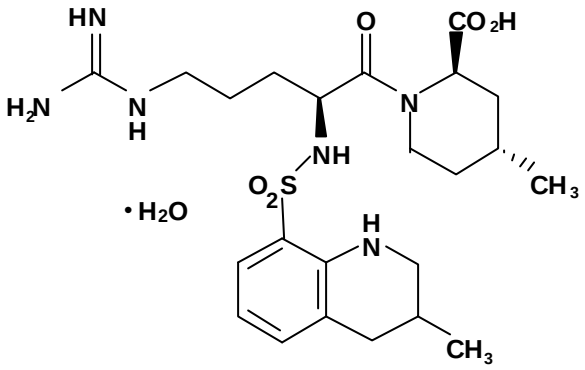
ACOVA™ (argatroban) Injection

DESCRIPTION

Argatroban is a synthetic direct thrombin inhibitor derived from L-arginine. The chemical name for argatroban 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. 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 in a ratio of approximately 65:35.

The molecular formula of argatroban is $C_{23}H_{36}N_6O_5S \bullet H_2O$. Its molecular weight is 526.66. The structural formula is shown below:

Figure 1



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. ACOVA™ (argatroban) Injection is a sterile clear, colorless to pale yellow, slightly viscous solution. ACOVA™ is available in 250 mg (in 2.5 mL) single-use amber vials, with gray flip-top caps. Each mL of sterile, nonpyrogenic solution contains 100 mg argatroban. Inert ingredients: D-sorbitol, dehydrated alcohol.

CLINICAL PHARMACOLOGY

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 effects by inhibiting thrombin-catalyzed or induced reactions, including fibrin formation; activation of coagulation factors V, VIII, and XIII; protein C; and platelet aggregation.

Argatroban is highly selective for thrombin with an inhibitory constant (K_i) of 0.04 μM. At therapeutic concentrations, argatroban has little or no effect on related serine proteases (trypsin, factor Xa, plasmin, and kallikrein).

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

Argatroban does not interact with heparin-induced antibodies. Evaluation of sera from 12 healthy subjects and 8 patients who received multiple doses of argatroban did not reveal antibody formation to argatroban (see **CLINICAL STUDIES**).

Pharmacokinetics

Distribution

Argatroban distributes mainly in the extracellular fluid as evidenced by an apparent steady state volume of distribution of 174 mL/kg (12.18L in a 70 kg adult). Argatroban is 54% bound to human serum proteins, with binding to albumin and α_1-acid glycoprotein being 20% and 34% respectively.

Metabolism

The main route of argatroban metabolism is hydroxylation and aromatization of the 3-methyltetrahydroquinoline ring in the liver. The formation of each of the four known metabolites is catalyzed *in vitro* by the human liver microsomal cytochrome P450 enzymes CYP3A4/5. The primary metabolite (M1) exerts 3 to 5-fold weaker anticoagulant effects than argatroban. Unchanged argatroban is the major component in plasma. The plasma concentrations of M1 range between 0 – 20% of that of the parent drug. The other metabolites (M2 – 4) are found only in very low quantities in the urine and have not been detected in plasma or feces. 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*.

Total body clearance is approximately 5.1 mL/min/kg (0.31 L/hr/kg) for infusion doses up to 40 μg/kg/min. The terminal elimination half-life of argatroban ranges between 39 and 51 minutes.

There is no interconversion of the 21–(R): 21–(S) diastereoisomers. The plasma ratio of these diastereoisomers is unchanged by metabolism or hepatic impairment, remaining constant at 65:35 (±2%).

Excretion

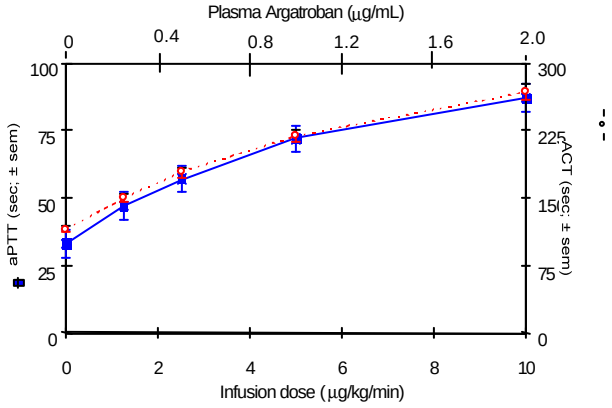
Argatroban is excreted primarily in the feces, presumably through biliary secretion. In a study in which ^{14}C-argatroban (5 μg/kg/min) was infused for 4 hours into healthy subjects, approximately 65% of the radioactivity was recovered in the feces within 6 days of the start of infusion with little or no radioactivity subsequently detected. Approximately 22% of the radioactivity appeared in the urine within 12 hours of the start of infusion. Little or no additional urinary radioactivity was subsequently detected. Average percent recovery of unchanged drug, relative to total dose, was 16% in urine and at least 14% in feces.

Pharmacokinetic/Pharmacodynamic Relationship

When ACOVA™ 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 ACOVA™ infusion, anticoagulant effects are produced as plasma argatroban concentrations begin to rise. Steady-state levels of both drug and anticoagulant effect are typically attained within 1-3 hours and are maintained until the infusion is discontinued or the dosage adjusted. Steady-state plasma argatroban concentrations increase proportionally with dose (for infusion doses up to 40 μg/kg/min in healthy subjects) and are well correlated with steady-state anticoagulant effects. For infusion doses up to 40 μg/kg/min, ACOVA™ 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) in healthy volunteers and cardiac patients. Representative steady-state plasma argatroban concentrations and anticoagulant effects are shown below for ACOVA™ infusion doses up to 10 μg/kg/min (See Figure 2).

Figure 2
Relationship at Steady State between ACOVA™ Dose, Plasma Argatroban Concentration and Anticoagulant Effect



Effect on International Normalized Ratio (INR)

Because argatroban is a direct thrombin inhibitor, co-administration of ACOVA™ 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.

The relationship between INR on co-therapy and warfarin alone is dependent on both the dose of ACOVA™ 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 3 for an ACOVA™ dose of 2 μg/kg/min. Thromboplastins with higher ISI values than shown result in higher INRs on combined therapy of warfarin and ACOVA™. These data are based on results obtained in normal individuals (see **DOSAGE AND ADMINISTRATION, Conversion to Oral Anticoagulant Therapy**).

Figure 3
INR Relationship of Argatroban plus Warfarin Versus Warfarin Alone

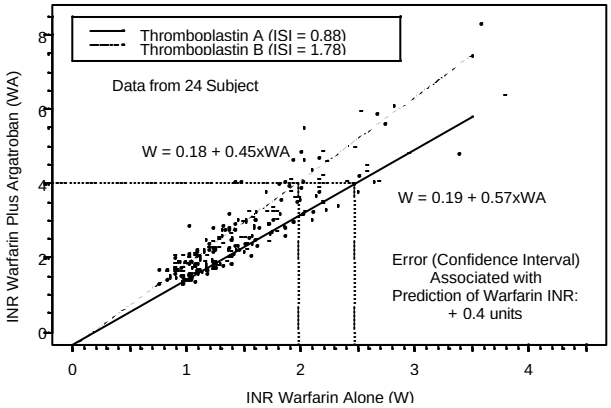


Figure 3 demonstrates the relationship between INR for warfarin alone and INR for warfarin co-administered with argatroban at argatroban doses #2 µg/kg/min. To calculate INR for warfarin alone (INR_W), based on INR for co-therapy of warfarin and argatroban (INR_{WA}), use the equation next to the appropriate curve. Example: At a dose of 2 µg/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). Thus, using an INR_{WA} value of 4.0 obtained on combined therapy: INR_W =0.19 +0.57 (4)=2.47 as the value for INR on warfarin alone. The error (confidence interval) associated with a prediction is $\pm$0.4 units. Thus, for argatroban doses of 1 or 2 µg/kg/min, INR_W can be predicted from INR_{WA}. For argatroban doses greater than 2 µg/kg/min, the error associated with predicting INR_W from INR_{WA} is $\pm$1. Thus, INR_W cannot be reliably predicted from INR_{WA} at doses greater than 2 µg/kg/min.

SPECIAL POPULATIONS

Renal Impairment

No dosage 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 Clcr = 95 ± 16 mL/min) and in 18 subjects with mild (mean Clcr = 64 ± 10 mL/min), moderate (mean Clcr = 41 ± 5.8 mL/min), and severe (mean Clcr = 5 ± 7 mL/min) renal impairment. The pharmacokinetics and pharmacodynamics of argatroban at dosages up to 5 μg/kg/min were not significantly affected by renal dysfunction.

Hepatic Impairment

The dosage of argatroban should be decreased in patients with hepatic impairment, (see **DOSAGE AND ADMINISTRATION**). Hepatic impairment is associated with decreased clearance and increased elimination half-life of argatroban (to 1.9 mL/min/kg and 181 minutes, respectively, for patients with a Child-Pugh score >6).

Age, Gender

There are no clinically significant effects of age or gender on the pharmacokinetics or pharmacodynamics (e.g., aPTT) of argatroban.

Drug-Drug Interactions

Digoxin: In 12 healthy volunteers, intravenous infusion of argatroban (2 μg/kg/min) over 5 hours daily for 5 days 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 (a potent inhibitor of CYP3A4/5) at 500 mg four times daily for 7 days had no effect on the pharmacokinetics of argatroban at a dose of 1 μg/kg/min for 5 hours. These data suggest oxidative metabolism by CYP3A4/5 is not an important elimination pathway *in vivo* for argatroban.

CLINICAL STUDIES

Heparin–induced thrombocytopenia (HIT) is a potentially serious, immune–mediated complication of heparin therapy that is strongly associated with subsequent venous and arterial thrombosis. Whereas initial treatment of HIT is to discontinue administration of all heparin, patients may require anticoagulation for prevention and treatment of thromboembolic events.

The conclusion that ACOVA™ is an effective treatment for heparin–induced thrombocytopenia (HIT) and heparin–induced thrombocytopenia and thrombosis syndrome (HITTS) is based upon the data from an historically controlled efficacy and safety study (Study 1) and a follow-on efficacy and safety study (Study 2). These studies were comparable with regard to study design, study objectives, dosing regimens as well as study outline, conduct and monitoring.

In these studies, 568 adult patients were treated with ACOVA™ 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).
Patients with documented unexplained aPTT >200% of control at baseline, documented coagulation disorder or bleeding diathesis unrelated to HITTS, a lumbar puncture within the past 7 days or a history of previous aneurysm, hemorrhagic stroke, or recent thrombotic stroke, within the past 6 months, unrelated to HITTS were excluded from these studies.

The initial dose of argatroban was 2 μg/kg/min not to exceed 10 μg/kg/min. Two hours after the start of the argatroban infusion, an aPTT level was obtained and dose adjustments were made to achieve a steady state aPTT value that was 1.5 to 3.0 times the baseline value, not to exceed 100 seconds. In Study 1, the mean aPTT level for HIT patients was 38 seconds prior to start of argatroban infusion. At first assessment*, during the argatroban infusion, mean aPTT level for HIT patients was 64 seconds. Overall, the mean aPTT level during the argatroban infusion for HIT patients was 62.5 seconds. In Study 1, the mean aPTT level for HITTS patients was 34 seconds prior to start of argatroban infusion. At first assessment*, during the argatroban infusion, mean aPTT level for HITTS patients was 70 seconds. Overall, the mean aPTT level during the argatroban infusion for HITTS patients was 64.5 seconds (see **DOSAGE AND ADMINISTRATION**).
(*First assessment was defined as occurring at least two hours post-infusion start time.)

The primary efficacy analysis was based on a comparison of event rates for a composite endpoint that included death (all causes), amputation (all causes) or new thrombosis during the treatment and follow-up period (study days 0 to 37). Secondary analyses included evaluation of the event rates for the components of the composite endpoint as well as time-to-event analyses.

In Study 1, 304 patients were enrolled having active HIT (129/304, 42%), active HITTS (144/304, 47%) or latent disease (31/304, 10%). Among the 193 historical controls, 139 (72%) had active HIT, 46 (24%) had active HITTS, and 8 (4%) had latent disease. Within each group, those with active HIT and those with latent disease were analyzed together. Positive laboratory confirmation of HIT/HITTS by the heparin-induced platelet aggregation test or serotonin release assay was demonstrated in 174 of 304 (57%) argatroban-treated patients (i.e., in 80 with HIT or latent disease and 94 with HITTS) and in 149 of 193 (77%) historical controls (i.e., in 119 with HIT or latent disease and 30 with HITTS). The test results for the remainder of the patients and controls were either negative or not determined.

A categorical analysis showed a significant improvement in the composite outcome in patients with HIT and HITTS treated with ACOVA™ versus those in the historical control group (see Table 1). The components of the composite endpoint are shown in Table 2.

Table 1
Efficacy Results of Study 1:
Composite Endpoint†

	HIT		HITTS		HIT/HITTS	
Parameter, N (%)	Control n=147	Argatroban n=160	Control n=46	Argatroban n=144	Control n=193	Argatroban n=304
Composite Endpoint	57 (38.8)	41(25.6)	26 (56.5)	63 (43.8)	83 (43.0)	104 (34.2)

† Death (all causes), amputation (all causes) or new thrombosis within 37-day study period.

Table 2
Efficacy Results of Study 1:
Components of the Composite Endpoint, Ranked by Severity†

	HIT		HITTS		HIT/HITTS	
Parameter, N (%)	Control n = 147	Argatroban n = 160	Control n = 46	Argatroban n = 144	Control n = 193	Argatroban n = 304
Death	32 (21.8)	27 (16.9)	13 (28.3)	26 (18.1)	45 (23.3)	53 (17.4)
Amputation	3 (2.0)	3 (1.9)	4 (8.7)	16 (11.1)	7 (3.6)	19 (6.2)
New Thrombosis	22 (15.0)	11 (6.9)	9 (19.6)	21 (14.6)	31 (16.1)	32 (10.5)

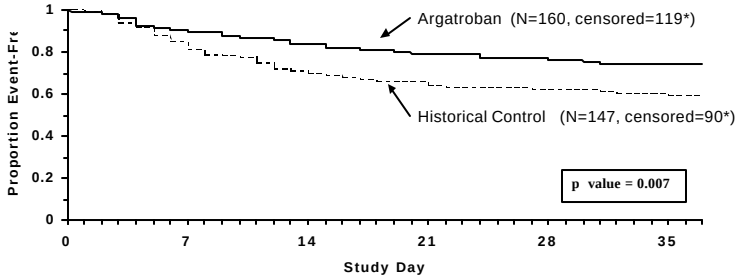
† Reported as the most severe outcome among the components of composite endpoint (severity ranking: death > amputation > new thrombosis); patients may have had multiple outcomes.

Time-to-event analyses showed significant improvements in the time-to-first event in patients with HIT or HITTS treated with ACOVA™ versus those in the historical control group. The between-group differences in the proportion of patients who remained free of death, amputation or new thrombosis were statistically significant in favor of argatroban by these analyses (p=0.007 in patients with HIT and p=0.018 in patients with HITTS, as calculated by the log-rank test).

A time-to-event analysis for the composite endpoint is shown in Figure 4 for patients with HIT and Figure 5 for patients with HITTS.

Study 1

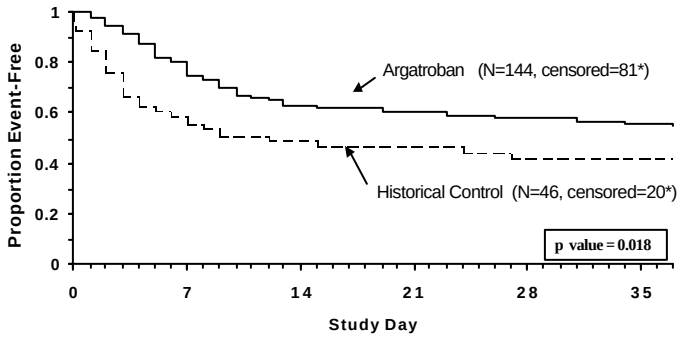
Figure 4
Time to First Event for the Composite Efficacy Endpoint: HIT Patients



*censored indicates no clinical endpoint (defined as death, amputation or new thrombosis) was observed during the follow-up period (maximum period of follow-up was 37 days).

Study 1

Figure 5
Time to First Event for the Composite Efficacy Endpoint: HITTS Patients



*censored indicates no clinical endpoint (defined as death, amputation or new thrombosis) was observed during the follow-up period (maximum period of follow-up was 37 days).

In Study 2, 264 patients were enrolled, having either HIT (125/264, 47.3%) or HITTS (139/264, 52.7%), and then treated with argatroban. Categorical analysis demonstrated significant improvement in the composite efficacy outcome for argatroban-treated patients, versus the same historical control group from Study 1, among patients having HIT (25.6% vs. 38.8%), patients having HITTS (41.0% vs. 56.5%), and patients having either HIT or HITTS (33.7% vs. 43.0%). Time-to-event analyses showed significant improvements in the time-to-first event in patients with HIT or HITTS treated with argatroban versus those in the historical control group. The between-group differences in the proportion of patients who remained free of death, amputation or new thrombosis were statistically significant in favor of argatroban.

Anticoagulant Effect: In Study 1, the mean (±SE) dose of argatroban administered was 2.0 ±0.1 µg/kg/min in the HIT arm and 1.9 ±0.1 µg/kg/min in the HITTS arm. Seventy-six percent of patients with HIT and 81% of patients with HITTS achieved a target aPTT at least 1.5 fold greater than the baseline aPTT at the first assessment occurring on average at 4.6 hours (HIT) and 3.9 hours (HITTS) following initiation of argatroban therapy.

No enhancement of aPTT response was observed in subjects receiving repeated administration of argatroban.

Platelet Count Recovery*:* In Study 1, the majority of patients, 53% of those with HIT and 58% of those with HITTS had a recovery of platelet count by day 3. Platelet Count Recovery was defined as an increase in platelet count to > 100,000/µL or to at least 1.5 fold greater than the baseline count (platelet count at study initiation) by day 3 of the study.

Additional Information

Cardiac Therapy: ACOVA™ has been administered in combination with aspirin to HIT patients undergoing coronary interventions including PTCA, coronary stent placement or atherectomy (n = 118). The safety and effectiveness of ACOVA™ for cardiac indications have not been established.

Reexposure and Lack of Antibody Formation: Plasma from 12 healthy volunteers treated with argatroban over six days showed no evidence of neutralizing antibodies. Repeated administration of argatroban to more than 40 patients was tolerated with no loss of anticoagulant activity. No change in the dose is required.

INDICATIONS AND USAGE

ACOVA™ is indicated as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia.

CONTRAINDICATIONS

ACOVA™ is contraindicated in patients with overt major bleeding, or in patients hypersensitive to this product or any of its components (see **WARNINGS**).

WARNINGS

ACOVA™ is intended for intravenous administration. All parenteral anticoagulants should be discontinued before administration of ACOVA™.

Hemorrhage

Hemorrhage can occur at any site in the body in patients receiving ACOVA™. An unexplained fall in hematocrit, fall in blood pressure, or any other unexplained symptom should lead to consideration of a hemorrhagic event. ACOVA™ 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 congenital or acquired bleeding disorders and gastrointestinal lesions such as ulcerations.

PRECAUTIONS

Hepatic Impairment

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. Also, upon cessation of ACOVA™ infusion in the hepatically-impaired patient, full reversal of anticoagulant effects may require longer than 4 hours due to decreased clearance and increased elimination half-life of argatroban (see **DOSAGE AND ADMINISTRATION**).

Laboratory Tests

Anticoagulation effects associated with ACOVA™ infusion at doses up to 40 μg/kg/min are well correlated with the activated partial thromboplastin time (aPTT). Although other global clot-based tests including prothrombin time (PT), the International Normalized Ratio (INR), the activated clotting time (ACT) and thrombin time (TT) are affected by argatroban; the therapeutic ranges for these tests have not been identified for ACOVA™ therapy. Plasma argatroban concentrations also correlate well with anticoagulant effects (see **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 ACOVA™ and warfarin therapy are described in a subsequent section (see **DOSAGE AND ADMINISTRATION**).

Drug Interactions

Heparin: Since heparin is contraindicated in patients with heparin-induced thrombocytopenia, the co-administration of argatroban and heparin is unlikely for this indication. However, if argatroban is to be initiated after cessation of heparin therapy, allow sufficient time for heparin's effect on the aPTT to decrease prior to initiation of ACOVA™ therapy.

Aspirin/Acetaminophen: Pharmacokinetic or pharmacodynamic drug-drug interactions have not been demonstrated between argatroban and concomitantly administered aspirin (162.5 mg orally given 26 and 2 hours prior to initiation of argatroban 1μg/kg/min over 4 hours) or acetaminophen (100 mg orally given 12, 6 and 0 hours prior to, and 6 and 12 hours subsequent to, initiation of argatroban 1.5 μg/kg/min over 18 hours).

***Oral anticoagulant agents*:** Pharmacokinetic drug-drug interactions between argatroban and warfarin (7.5 mg single oral dose) have not been demonstrated. However, the concomitant use of argatroban and warfarin (5-7.5 mg initial oral dose followed by 2.5-6 mg/day orally for 6-10 days) results in prolongation of the prothrombin time (PT) and International Normalized Ratio (INR). (see **CLINICAL PHARMACOLOGY** and **DOSAGE**

AND ADMINISTRATION).

***Thrombolytic agents*:** The safety and effectiveness of ACOVA™ with thrombolytic agents have not been established (see **ADVERSE REACTIONS: Intracranial Bleeding**).

Co-administration: Concomitant use of argatroban with antiplatelet agents, thrombolytics, and other anticoagulants may increase the risk of bleeding (see **WARNINGS**). Drug-drug interactions have not been observed between argatroban and digoxin or erythromycin (see **CLINICAL PHARMACOLOGY**, **Drug-Drug Interactions**).

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate the carcinogenic potential of argatroban.

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 WI-38 human fetal lung cell unscheduled DNA synthesis (UDS) tests, or the mouse micronucleus test.

Argatroban at intravenous doses up to 27 mg/kg/day (0.3 times the recommended maximum human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy. Teratogenic Effects. Pregnancy Category B

Teratology studies have been performed in rats with intravenous doses up to 27 mg/kg/day (0.3 times the recommended maximum human dose based on body surface area) and rabbits at intravenous doses up to 10.8 mg/kg/day (0.2 times the recommended maximum human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to argatroban. There are however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Experiments in rats show that argatroban is detected in milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from argatroban, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Geriatric Use

In the clinical studies of adult patients with HIT or HITTS, the effectiveness of argatroban was not affected by age.

Pediatric Use

The safety and effectiveness of ACOVA™ in patients below the age of 18 years have not been established.

ADVERSE REACTIONS

Adverse Events Reported in HIT/HITTS Patients

The following safety information is based on all 568 patients treated with ACOVA™ in Study 1 and Study 2. The safety profile of the patients from these studies is compared with that of 193 historical controls in which the adverse events were collected retrospectively. The adverse events reported in this section include all events regardless of relationship to treatment. Adverse events are separated into hemorrhagic and non-hemorrhagic events.

Major bleeding was defined as bleeding that was overt and associated with a hemoglobin decrease $\geq$ 2 g/dL, that led to a transfusion of $\geq$ 2 units, or that was intracranial, retroperitoneal, or into a major prosthetic joint. Minor bleeding was overt bleeding that did not meet the criteria for major bleeding.

Table 3 gives an overview of the most frequently observed hemorrhagic events, presented separately by major and minor bleeding, sorted by decreasing occurrence among argatroban-treated patients.

Table 3
Major and Minor Hemorrhagic Adverse Events

Major Hemorrhagic Events*		
	Study 1 & Study 2 (All argatroban-treated patients) (n=568) %	Historical Control (n=193) %

Gastrointestinal	2.3	1.6
Genitourinary and hematuria	0.9	0.5
Decrease hemoglobin/ hematocrit	0.7	0
Multisystem hemorrhage and DIC	0.5	1
Limb and BKA stump	0.5	0
Intracranial hemorrhage	0	0.5

Minor Hemorrhagic Events*		
	Study 1 & Study 2 (All argatroban-treated patients) (n=568) %	Historical Control (n=193) %
Gastrointestinal	14.4	18.1
Genitourinary and hematuria	11.6	0.8
Decrease in hemoglobin and hematocrit	10.4	0
Groin	5.4	3.1
Hemoptysis	2.9	0.8
Brachial	2.4	0.8

*Patients may have experienced more than one event.
DIC = disseminated intravascular coagulation;
BKA = below the knee amputation.

Table 4 gives an overview of the most frequently observed non-hemorrhagic events sorted by decreasing frequency of occurrence (≥2%) among argatroban-treated patients.

Table 4
Non-hemorrhagic Adverse Events*

	Study 1 & Study 2 (All argatroban-treated patients) (n=568) %	Historical Control (n=193) %
Dyspnea	8.1	8.8
Hypotension	7.2	2.6

Fever	6.9	2.1
Diarrhea	6.2	1.6
Sepsis	6.0	12.4
Cardiac arrest	5.8	3.1
Nausea	4.8	0.5
Ventricular tachycardia	4.8	3.1
Pain	4.6	3.1
Urinary tract infection	4.6	5.2
Vomiting	4.2	0
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	4.7
Abdominal pain	2.6	1.6
Cerebrovascular disorder	2.3	4.1

*Patients may have experienced more than one event.

Adverse Events Reported in Other Populations

The following safety information is based on a total of 1127 individuals who were treated with ACOVA™ in clinical pharmacology studies (n=211) or for other clinical indications (n=916).

Intracranial Bleeding. In the HIT/HITTS population, intracranial bleeding was not observed. Intracranial bleeding only occurred in patients with acute myocardial infarction who were started on both ACOVA™ and thrombolytic therapy with streptokinase. The overall frequency of this potentially life-threatening complication among patients receiving both ACOVA™ and thrombolytic therapy (streptokinase or tissue plasminogen activator) was 1% (8 out of 810 patients). Intracranial bleeding was not observed in 317 subjects or patients who did not receive concomitant thrombolysis (see **WARNINGS**).

Allergic Reactions. 156 allergic reactions or suspected allergic reactions were observed in 1,127 individuals who were treated with ACOVA™ in clinical pharmacology studies or for other clinical indications. About 95% (148/156) of these reactions occurred in patients who concomitantly received thrombolytic therapy (e.g., streptokinase) for acute myocardial infarction and/or contrast media for coronary angiography.

Allergic reactions or suspected allergic reactions in populations other than HIT patients include (in descending order of frequency*):

- Airway reactions (coughing, dyspnea): 10% or more
- Skin reactions (rash, bullous eruption): 1 to <10%
- General Reactions (vasodilation): 1 to 10%

* The CIOMS (Council for International Organization of Medical Sciences) III standard categories are used for classification of frequencies.

OVERDOSAGE

Symptoms/Treatment

Excessive anticoagulation, with or without bleeding, may be controlled by discontinuing ACOVA™ or by decreasing the ACOVA™ infusion dosage (see **WARNINGS**). In clinical studies at therapeutic levels, anticoagulation parameters generally return to baseline within 2 to 4 hours after discontinuation of the drug. Reversal of anticoagulant effect may take longer in patients with hepatic impairment.

No specific antidote to argatroban is available; if life-threatening bleeding occurs and excessive plasma levels of argatroban are suspected, ACOVA™ should be discontinued immediately, aPTT and other coagulation tests should be determined. Symptomatic and supportive therapy should be provided to the patient (see **WARNINGS**).

Single intravenous doses of argatroban at 200, 124, 150, and 200 mg/kg were lethal to mice, rats, rabbits, and dogs, respectively. The symptoms of acute toxicity were loss of righting reflex, tremors, clonic convulsions, paralysis of hind limbs, and coma.

DOSAGE AND ADMINISTRATION

ACOVAÔ, as supplied, is a concentrated drug (100 mg/mL) which must be diluted 100-fold prior to infusion. ACOVAÔ should not be mixed with other drugs prior to dilution in a suitable intravenous fluid.

Preparation for Intravenous Administration

ACOVA™ should be diluted in 0.9% Sodium Chloride Injection, 5% Dextrose Injection, or Lactated Ringer's Injection to a final concentration of 1 mg/mL. Each 2.5 mL vial should be diluted 100-fold by mixing with 250 mL of diluent. Use 250 mg (2.5 mL) per 250 mL of diluent or 500 mg (5 mL) per 500 mL of diluent. 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. The pH of the intravenous solution prepared as recommended is 3.2-7.5.

Initial Dosage for Patients with Heparin-Induced Thrombocytopenia

Before administering ACOVA™, discontinue heparin therapy and obtain a baseline aPTT. The recommended initial dose of ACOVA™ for adult patients without hepatic impairment is 2 µg/kg/min, administered as a continuous infusion (see Table 5).

Table 5
Standard Infusion Rates for 2 µg/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 and Adjusting Therapy

Monitoring therapy: In general, therapy with ACOVA™ is monitored using the aPTT. Tests of anticoagulant effects (including the aPTT) typically attain steady-state levels within 1 – 3 hours following initiation of ACOVA™. Dose adjustment may be required to attain the target aPTT. Check the aPTT two hours after initiation of therapy to confirm that the aPTT is within the desired therapeutic range.

Dosage adjustment: After the initial dose of ACOVA™, the dose can be adjusted as clinically indicated (not to exceed 10 μg/kg/min), until the steady-state aPTT is 1.5 to 3 times the initial baseline value (not to exceed 100 seconds)(see **CLINICAL STUDIES** for mean values of aPTT obtained after initial doses of ACOVA™).

Hepatically Impaired Patients

For patients with heparin-induced thrombocytopenia with hepatic impairment, the initial dose of ACOVA™ should be reduced. For patients with moderate hepatic impairment, an initial dose of 0.5 μg/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 (see **PRECAUTIONS**).

Renally Impaired Patients

No dosage adjustment is necessary in patients with renal impairment (see **PRECAUTIONS**).

CONVERSION TO ORAL ANTICOAGULANT THERAPY

Initiating Oral Anticoagulant Therapy

Once the decision is made to initiate oral anticoagulant therapy, recognize the potential for combined effects on INR with co-administration of argatroban and warfarin. A loading dose of warfarin should not be used. Initiate therapy using the expected daily dose of warfarin.

Co-Administration of Warfarin and ACOVA™ at Doses Up to 2 µg/kg/min

Use of ACOVA™ with warfarin results in prolongation of INR beyond that produced by warfarin alone. The previously established relationship between INR and bleeding risk is altered. The INR value on warfarin alone (INR_W) can be calculated from the INR value on combination argatroban and warfarin therapy (see **CLINICAL PHARMACOLOGY, Figure 3)**. INR should be measured daily while ACOVA™ and warfarin are co-administered. In general, with doses of ACOVA™ up to 2 µg/kg/min, ACOVA™ can be discontinued when the INR is >4 on combined therapy. After ACOVA™ 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 ACOVA™ and repeat the procedure daily until the desired therapeutic range on warfarin alone is reached. The relationship between INR obtained on combined therapy and INR obtained on warfarin alone is dependent on both the dose of ACOVA™ and the thromboplastin reagent used.

The combination of argatroban and warfarin does not cause further reduction in the vitamin K dependent factor Xa activity than that which is seen with warfarin alone.

Co-Administration of Warfarin and ACOVA™ at Doses Greater than 2 µg/kg/min

For doses greater than 2 µg/kg/min, the relationship of INR on warfarin alone to the INR on warfarin plus ACOVA™ is less predictable. In this case, in order to predict the INR on warfarin alone, temporarily reduce the dose of ACOVA™ to a dose of 2 µg/kg/min. Repeat the INR on ACOVA™ and warfarin 4 to 6 hours after reduction of the ACOVA™ dose and follow the process outlined above for administering ACOVA™ at doses up to 2 µg/kg/min.

STABILITY/COMPATIBILITY

ACOVA™ is a clear, colorless to pale yellow, slightly viscous solution. If the solution is cloudy, or if an insoluble precipitate is noted, the vial should be discarded.

Solutions prepared as recommended are stable at 25°C (77°F) with excursions permitted to 15 - 30°C (59 - 86°F) 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.

HOW SUPPLIED

ACOVA™ (argatroban) Injection is supplied in 2.5 mL solution in single-use vials at the concentration of 100 mg/mL. Each vial contains 250 mg of argatroban.

NDC 0007-4407-01 (Package of 1)
NDC 0007-4407-10 (Package of 10)

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