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APPLICATION NUMBER:

201811Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

BIOPHARMACEUTICS REVIEW

Division Of Biopharmaceutics, Office of Pharmaceutical Quality

Application No.:	NDA 201-811 Resubmission	Reviewer: Angelica Dorantes, Ph.D	
Submission Date:	January 23, 2015		
Division:	ODDP/DHP	Date of Review:	March 9, 2015
Sponsor:	Fresenius Kabi (Formerly APP Pharmaceuticals, Inc.)		
Trade Name:	Argatroban Injection	Type of Submission: 505 (b)(2) NDA –Class 2 Resubmission	
Generic Name:	Argatroban Injection		
Indication:	Argatroban is an anticoagulant indicated for: 1) for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT/HITTS); 2) in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI)		
Formulation/strengths	Injectable IV Solution/ 100 mg/ml (250 mg/2.5 ml vial) - must be diluted 100-fold prior to infusion		
Route of Administration	Intravenous		
Type of Review:	BIOEQUIVALENCE WAIVER REQUEST		

Resubmission:

On January 23, 2015, the Applicant Resubmitted NDA 201-811 for Argatroban (100 mg/ml). This resubmission provides the Applicant's responses to a Complete Response (CR) letter dated February 28, 2014. The CR letter identifies facility inspection deficiencies.

Review: The Biopharmaceutics Review was completed during the second review cycle on April 24, 2012. Approval of the NDA was recommended from the standpoint of Biopharmaceutics. The current fifth resubmission of this NDA does not contain any new biopharmaceutics information for review.

Recommendation:

From the ONDQA-Biopharmaceutics viewpoint, the current resubmission of NDA 201-811 for Argatroban Injection is recommended for approval.

Angelica
Dorantes -S

Digitally signed by Angelica Dorantes -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=130007084
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Date: 2015.03.10 13:18:00 -04'00'

Angelica Dorantes, Ph. D.

Acting Biopharmaceutics Branch Chief
Division of Biopharmaceutics, ONDP, OPQ

CLINICAL PHARMACOLOGY MEMORANDUM

Brand Name	Argatroban injection
INN Name	Argatroban
NDA Number and Type	201,811; 505(b)(2); Class 1 Resubmission
Applicant Name	Fresenius Kabi USA, LLC
Submission Date	1/23/2015
OCP Division	OCPI, Cardiovascular and Renal Products
OND Division	Division of Hematology and Oncology Products
Reviewer	Martina Sahre, PhD
Team Leader	Rajanikanth Madabushi, PhD

The applicant, Fresenius Kabi, LLC, has submitted CMC information to satisfy a complete response requirement. In addition, labeling was updated to reflect a change in the name of the legal entity (new: Fresenius Kabi, from: APP Pharmaceuticals).

The label is consistent with that of the reference listed drug (NDA 20,883).

There are no edits or proposals from the Office of Clinical Pharmacology.

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/s/

MARTINA D SAHRE
02/24/2015

RAJANIKANTH MADABUSHI
02/26/2015

REV-CLINPHARM-02 (Review Noted (NAI))
NDA-201811
ORIG-1
Supporting Document 24
Resubmission/Class 1
Submit Date: 01/23/2015 - FDA Received Date: 01/23/2015

No new clinical pharmacology information was included in the resubmission and the approval recommendation is unchanged.

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/s/

MARTINA D SAHRE
02/26/2015

BIOPHARMACEUTICS REVIEW
Office of New Drug Quality Assessment

Application No.:	NDA 201-811 Resubmission	Reviewer: Angelica Dorantes, Ph.D	
Submission Date:	September 13, 2013		
Division:	ODDP/DHP	Date of Review:	February 4, 2014
Sponsor:	Fresenius Kabi (Formerly APP Pharmaceuticals, Inc.)		
Trade Name:	Argatroban Injection	Type of Submission: 505 (b)(2) NDA –Class 2 Resubmission	
Generic Name:	Argatroban Injection		
Indication:	Argatroban is an anticoagulant indicated for: 1) for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT/HITTS); 2) in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI)		
Formulation/strengths	Injectable IV Solution/ 100 mg/ml (250 mg/2.5 ml vial) - must be diluted 100-fold prior to infusion		
Route of Administration	Intravenous		
Type of Review:	BE WAIVER REQUEST		

Resubmission:

On January September 13, 2013, the Applicant Resubmitted NDA 201-811 for Argatroban (100 mg/ml). This resubmission provides the Applicant's responses to a Complete Response (CR) letter dated April 5, 2013. The CR letter identifies both CMC and facility inspection deficiencies.

The Biopharmaceutics Review was completed during the second review cycle on April 24, 2012, recommending approval of the NDA from the standpoint of Biopharmaceutics. The current fourth resubmission does not contain any new biopharmaceutics information for review.

Recommendation:

From the ONDQA-Biopharmaceutics viewpoint, the current resubmission of NDA 201-811 for Argatroban Injection is recommended for approval.

Angelica Dorantes, Ph. D.

Biopharmaceutics Team Leader
Office of New Drugs Quality Assessment

cc: NDA 201-811/DARRTS, Rik Lostritto

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/s/

ANGELICA DORANTES
02/04/2014

REV-CLINPHARM-02 (Review Noted (NAI))
NDA-201811
ORIG-1
Supporting Document 21
Resubmission/Class 2
Submit Date: 09/13/2013 - FDA Received Date: 09/13/2013

No clinical pharmacology information was included. No action is necessary.

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/s/

YOUNG J MOON
01/30/2014

REV-CLINPHARM-02 (Review Noted (NAI))
NDA-201811
ORIG-1
Supporting Document 17
Resubmission/Class 2
Submit Date: 10/12/2012 - FDA Received Date: 10/12/2012

There is no clinical pharmacology information in this submission. No action is necessary.

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/s/

YOUNG J MOON
03/22/2013

REV-CLINPHARM-02 (Review Noted (NAI))
NDA-201811
ORIG-1
Supporting Document 10
Resubmission/Class 2
Submit Date: 01/31/2012 - FDA Received Date: 01/31/2012

NDA 201811 resubmission contained no clinical pharmacology data for review. The labeling will be reviewed prior to labeling meetings.

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/s/

YOUNG J MOON
04/30/2012

BIOPHARMACEUTICS REVIEW
Office of New Drug Quality Assessment

Application No.:	NDA 201-811 Resubmission	Reviewer: Angelica Dorantes, Ph.D	
Submission Date:	January 31, 2012		
Division:	ODDP/DHP	Date of Review:	April 20, 2012
Sponsor:	APP Pharmaceuticals, Inc.		
Trade Name:	Argatroban Injection	Type of Submission: 505 (b)(2) NDA –Class 2 Resubmission	
Generic Name:	Argatroban Injection		
Indication:	Argatroban is an anticoagulant indicated for: 1) for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT/HITTS); 2) in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI)		
Formulation/strengths	Injectable IV Solution/ 100 mg/ml (250 mg/2.5 ml vial) - must be diluted 100-fold prior to infusion		
Route of Administration	Intravenous		
Type of Review:	BIOWAIVER REQUEST		

Background:

On April 12, 2010, APP Pharmaceuticals submitted the Original NDA 201-811 for Argatroban (100 mg/ml) under 505 (b)(2) of the Federal Food, Drug, and Cosmetic Act. However, on February 24, 2011, FDA issued a Complete Response letter due to major deficiencies identified with respect to nonclinical and product quality.

Resubmission:

On January 31, 2012, the Applicant Resubmitted NDA 201-811 for Argatroban (100 mg/ml). This 505 (b)(2) application relies for approval on the FDA’s findings of safety and effectiveness for the Reference Listed Drug. The proposed Argatroban Injection has the same active ingredient, same dosage form (i.e., injectable solution), and route of administration as the Reference Listed Drug (RLD), ARGATROBAN Injection, 100 mg/mol concentrate. The reference product was approved by the FDA under NDA 20-883 on June 30, 2000, for the following indications:

- As an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT/HITTS);
- As an anticoagulant in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI).

The Reference Listed Drug was approved under Encysive Pharmaceuticals, Inc, but is currently marketed by Pfizer.

BIOPHARMACEUTICS:

The Biopharmaceutics review is focused on the evaluation and acceptability of the information supporting the biowaiver request for Argatroban Injection.

Formulation: The formulation of Argatroban Injection proposed by APP Pharmaceuticals is a 100 mg/ml (250 mg/2.5 ml vial) solution and must be diluted 100-fold prior to infusion. The qualitative difference between the RLD and the proposed formulations is that dehydrated alcohol and D-sorbitol were removed from the currently proposed product, and propylene glycol was added as a (b) (4). The sponsor states that the formulation revisions result in an (b) (4).

The composition of the formulation and the function of each component are detailed in the next Table.

Composition of the Formulation for Argatroban Injection Proposed by APP Pharmaceuticals		
Ingredients	Amount	Function
Argatroban	100 mg	Active ingredient
Propylene Glycol, USP	(b) (4)	(b) (4)
(b) (4)		

The comparative description of the proposed formulation and the RLD formulation is given in the table below.

Comparative Formulations of the Proposed Product and Reference product		
Ingredients	APP Pharmaceuticals Argatroban Injection	RLD- Pfizer Argatroban Injection
Argatroban	100 mg/ml	100 mg/ml
Dehydrated Alcohol	NA	(b) (4) mg/ml
D-Sorbitol	NA	(b) (4) mg/ml
Propylene Glycol, USP	(b) (4)	NA
	(b) (4)	NA

The inactive ingredient used in the Argatroban Injection formulation by APP differs from those used in the RLD Argatroban product. Each ml contains 100 mg Argatroban and about 0.92 ml of propylene glycol (92% v/v).

Components Used in the Formulation of Argatroban Injection		
APP's Excipients	Amount per Unit	IIG Levels
Propylene Glycol, USP	92% v/v (954 mg)	82.04%
		(b) (4)

(b) (4)

Note that the use of 92% of propylene glycol (PG) in the Argatroban formulation proposed by APP Pharmaceuticals exceeds the IIG Levels, as well as the FDA's levels for approved intravenous products (i.e., lorazepam contains 0.8 mol PG/mol [80 % v/v]; diazepam contains 0.4 mol PG/mol [40% v/v]). The sponsor justifies the content of PG by maximum daily intake of PG at the maximum human dose of Argatroban of (b) (4) per patient (maximum daily dose of propylene glycol that a 70-kg patient may receive still is within the safe range). The sponsor also refers to a publication (b) (4).

(b) (4) in which the propylene glycol appeared to be safe when given intravenously at up to approximately (b) (4).

Reviewer Comment:

Dr. Shwu-Luan Lee Pharmacology/Toxicology reviewer evaluated the acceptability for using such a high percentage (92%) of propylene glycol exceeding the approved IIG Levels. Dr. Luan concluded that the level of PG in the proposed formulation of Argatroban was acceptable (for details See Dr. Shwu-Luan Lee Pharmacology/Toxicology review dated 2/2/11 in DARRTS).

BIOWAIVER REQUEST:

In this NDA submission, APP Pharmaceuticals is requesting that the Agency waives the CFR's requirement to provide in vivo Bioavailability/bioequivalence (BA/BE) data for their product. To support their BA/BE waiver request, APP Pharmaceuticals provided information showing that the proposed Argatroban Injection will be administered at the same dosage level, for the same duration, and for the same indications as the RLD product, ARGATROBAN Injection from Pfizer.

Also to support the biowaiver request, APP Pharmaceuticals conducted an *in vitro* bridging study to assess the *in vitro* equivalence of the anticoagulant pharmacodynamic (PD) activity between APP's product and the RLD. PD effects were measured by determining the prothrombin time (PT), the activated partial thromboplastin time (aPTT), and the thrombin time (TT) in pooled donor human plasma spiked with clinically relevant concentrations of APP's or Pfizer's Argatroban product. The data from this in vitro bridging study were evaluated by Dr. Lillian Zhang from the Office of Clinical Pharmacology. In her review, Dr. Zhang concluded that the in vitro study bridging the proposed APP Pharmaceuticals Argatroban product and the Argatroban Pfizer's RLD product was acceptable. The results of the data analyses indicate that an acceptable *in vitro* bridge between APP's product and Pfizer's RLD product was established acceptable (*for details refer to Dr. Zhang's review dated 2/16/11 in DARRTS*).

Additionally, the acceptability of the very high percentage (92%) of propylene glycol in the proposed Argatroban formulation was evaluated by Dr. Shwu-Luan Lee, Pharm/Tox reviewer. It was concluded that the proposed level of PG was acceptable.

RECOMMENDATION:

ONDQA-Biopharmaceutics has reviewed the information included in NDA 201-811 for Argatroban Injection 100 mg/ml. Based on the information showing that;

- The in vitro pharmacodynamic activity (aPTT, PT, and TT) of the proposed Argatroban Injection is similar to the activity of the RLD product,
- The difference in the inactive ingredients will not have an impact on the bioavailability of the product,
- The inclusion of a high 92% of propylene glycol in the formulation did not raise a safety concern,
- The proposed product will be administered at the same dosage level for the same duration, and,
- The route of administration, dosage form and indications of the proposed product are the same as the RLD product,

ONDQA-Biophamaceutics is of the opinion that the provided information supports the biowaiver request, therefore, a waiver for the CFR's requirement to provide in vivo BA/BE to support the

approval of the proposed Argatroban Injection, 100 mg/ml (250 mg/2.5 ml vial - must be diluted 100-fold prior to infusion) manufactured by APP Pharmaceuticals is granted.

From the Biopharmaceutics viewpoint, the Resubmission of NDA 201-811 for Argatroban Injection is recommended for approval.

Angelica Dorantes, Ph. D.

Biopharmaceutics Team Leader
Office of New Drugs Quality Assessment

cc: NDA 201-811/DARRTS

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/s/

ANGELICA DORANTES
04/24/2012

Clinical Pharmacology Review

NDA	201-811
Submission Type	Original, 505(b)(2)
Submission Date	2 April 2010, 3 September 2010, 22 November 2010
Brand Name	Argatroban Injection
Generic Name	Argatroban
Indication	An anticoagulant 1) for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT/HITTS); 2) in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI)
Formulation	An intravenous solution containing 100 mg/mL of argatroban (250 mg of argatroban in 2.5 mL), which must be diluted 100-fold prior to infusion
Dosing Regimen	1) HIT/HITTS: 2 µg/kg/min as a continuous infusion then adjusted to steady-state aPTT being 1.5 - 3 times baseline 2) PCI: 25 µg/kg/min and a bolus of 350 µg/kg administered over 3 to 5 minutes then adjusted based on activated clotting time
Sponsor	APP Pharmaceuticals, Inc.
OCP Reviewer	Hua Lillian Zhang, Ph.D.
OCP Team Leader	Julie Bullock, Pharm.D.
OCP Division	Division of Clinical Pharmacology 5
OND Division	Division of Hematology Products

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1 EXECUTIVE SUMMARY

This 505(b)(2) application submitted by APP Pharmaceuticals is for Argatroban Injection, 100 mg/mL in single-dose vials. The APP's Argatroban Injection has the same active ingredient, dose strength, dosage form, and route of administration as the innovator drug approved by the FDA under NDA 20-883 (Encysive Pharmaceuticals, Inc., now Pfizer). The innovator's ARGATROBAN Injection is the reference listed drug (RLD) for this 505(b)(2) application.

In support of a waiver of *in vivo* bioequivalence (BE), the applicant conducted an *in vitro* bridging study to assess *in vitro* equivalence of the anticoagulant pharmacodynamic (PD) activity between APP's product and the RLD. PD effects were measured by determining the prothrombin time (PT), the activated partial thromboplastin time (aPTT), and the thrombin time (TT) in pooled donor human plasma spiked with clinically relevant concentrations of APP's or Pfizer's argatroban product. The results of the data analyses indicate that an acceptable *in vitro* bridge between APP's product and Pfizer's RLD product was established.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 considers this NDA acceptable from a clinical pharmacology perspective.

For labeling recommendations, please refer to Section 3.

1.2 PHASE 4 REQUIREMENT

None.

1.3 SIGNATURES

Lillian Zhang, Ph.D.
Reviewer
Division of Clinical Pharmacology 5

Julie Bullock, Pharm.D.
Team Leader
Division of Clinical Pharmacology 5

Cc: DDOP: CSO - E Ali Ibrahim; MTL - V Kwitkowski; MO - R Alvandi
DCP-5: Reviewers - L Zhang; TL - J Bullock; DDD - B Booth
DD - A Rahman

1.4 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

Argatroban is a synthetic small molecule direct thrombin inhibitor. ARGATROBAN Injection, the RLD for this 505(b)(2) application, was approved by the FDA under NDA 20-883 (Encysive Pharmaceuticals, Inc., now Pfizer) for the following indications:

- as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT/HITTS);
- as an anticoagulant in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI)

The RLD is a sterile solution and available in 250 mg in 2.5 mL (100 mg/mL) single-use vials. The injection solution (100 mg/mL) needs to be diluted in 0.9% Sodium Chloride for Injection, 5% Dextrose for Injection, or Lactated Ringer's for Injection to a final concentration of 1 mg/mL prior to infusion.

AAP's argatroban product is also a concentrated solution at a concentration of 100 mg/mL (250 mg of argatroban in 2.5 mL single-use vials). The solution 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 prior to infusion. The difference between the two products is that the inactive ingredients (D-Sorbitol and dehydrated alcohol) of the RLD used to dissolve argatroban, are replaced by propylene glycol in APP's product. See Table 1 for the quantitative comparison between APP's product and Pfizer's RLD product.

The applicant is seeking approval for all the RLD indications.

Table 1. Formulation Comparison Between APP's Argatroban Injection and RLD ARGATROBAN Injection

Ingredients (amount/mL)	Pfizer's Argatroban Injection (RLD)	APP's Argatroban Injection
	250 mg in 2.5 mL amber vial	250 mg in 2.5 mL amber vial
Argatroban	100 mg/mL	100 mg/mL
D-sorbitol	(b) (4) mg/mL	N/A
Dehydrated Alcohol	(b) (4) mg/mL	N/A
Propylene Glycol	N/A	(b) (4)
(b) (4)	N/A	(b) (4)

In support of a waiver of *in vivo* BE, the applicant conducted an *in vitro* "bridge" study (Study No. AA86231) to assess the equivalence of the anticoagulant (PD) activity between APP's Argatroban Injection and the RLD. The PD effects were measured by determining PT, aPTT, and TT in pooled donor human plasma spiked with clinically relevant concentrations of argatroban from either APP or RLD product. Results of the study indicate that equivalence of APP's product *versus* the RLD was demonstrated as for the three observed PD parameters, the 90% confidence intervals (CI₉₀) of the ratios of geometric means between APP's product and the RLD were within the acceptance criteria of 90 – 111% as defined by the applicant.

2 QUESTION BASED REVIEW

Refer to ARGATROBAN Inject original NDA 20-883 (Approval Date: 30-June-2000) and the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette for the Clinical Pharmacology related issues. For brevity only QBR questions related to the current NDA submission are addressed below.

2.1 GENERAL ATTRIBUTITES

2.1.1 What are the proposed dosage and route of administration?

APP's Argatroban Injection is a sterile solution containing 100 mg/mL of argatroban which is intended for intravenous administration.

2.2 GENERAL BIOPHARMACEUTICS

2.5.1 What is the composition of the to-be-marketed formulation?

APP's Argatroban Injection is available in 250 mg (in 2.5 mL) single-use amber vials. Each mL of sterile, nonpyrogenic solution contains 100 mg argatroban. The solution 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 prior to infusion. The composition of the formulation and the function of each component are presented in Table 2.

Table 2. Argatroban Injection 100 mg/mL

Ingredients	Quantity per unit (or per mL)	Function
Argatroban	100 mg	Active ingredient
Propylene Glycol, USP	954 mg	(b) (4)
		(b) (4)

The only difference between the two products is that the inactive ingredients of the RLD, D-Sorbitol and dehydrated alcohol, are replaced by propylene glycol in the APP's product. Refer to Section 1.4 for the quantitative and qualitative comparisons between APP's to-be-marketed product and the RLD. The active ingredient, its strength, dosage form, and route of administration for APP's product are the same as the RLD.

2.5.2 What data support or do not support a waiver of *in vivo* BE data?

In support of the waiver of *in vivo* BE, APP conducted an *in vitro* "bridge" study (Study No. AA86231) to assess the equivalence of the anticoagulant (PD) activity between APP's product (the test product, 100 mg/mL) and the RLD (the reference product, 100 mg/mL).

Briefly, blood samples were collected from 24 healthy subjects (12 males and 12 females) and were pooled for a total of six pools. Each product (100 mg/mL) was first diluted 100-fold with 0.9% Sodium Chloride Inject to 1.0 mg/mL (stock solution), then the stock solution of each product was further diluted using 0.9% Sodium Chloride for Injection to make the spiking solutions at 50, 20, and 2.0 µg/mL. An aliquot of each pooled human plasma (5.4 mL) was spiked with spiking solutions of each product, their placebo solutions, or the sodium chloride vehicle. Seven plasma concentrations of argatroban at 0.3, 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 µg/mL were prepared and tested for PT and aPTT. Concentrations at 0.05, 0.1, 0.2, 0.3 and 0.5 µg/mL of

argatroban were tested for TT. The test placebo and reference placebo at excipient concentrations corresponding to 3.0 µg/mL argatroban were evaluated to confirm that the excipients have no effect on coagulation tests. Concentrations of argatroban in stock and spiking solutions were measured using high performance liquid chromatography (HPLC) with mass spectrometric detection (MS) and concentrations of argatroban in plasma were determined by a validated LC/MS/MS method (see Section 2.3).

Equivalence of APP’s product to the RLD was to be demonstrated if the CI_{90%} of the ratio of their geometric means for PT, aPTT, and TT fell within the acceptance criteria of 90-111%.

Results

In vitro comparison of the anticoagulation effect of APP’s Product to RLD

The applicant generated results are presented in Table 3.

Table 3. Ratios and 90% Confidence Intervals of PD Parameters Between APP’s Product and the RLD

	Ratio (CI₉₀)
PT (sec)	
APP vs. RLD	98.6 (97.6 – 99.7)
aPTT (sec)	
APP vs. RLD	99.9 (99.2 – 100.6)
TT (sec)	
APP vs. RLD	98.8 (96.8 - 100.7)

Results indicate that the CI₉₀ of the ratios of geometric means for the PD parameters between APP’s product and the RLD fell within the acceptance criteria of 90% -111% for equivalence as defined by the applicant.

The applicant’s data analysis was conducted by pooling the data from all the concentrations tested for each PD parameter. As the PD effect comparison at each clinically relevant concentration of argatroban evaluated is not presented by the applicant, the reviewer analyzed the data and reported the PD results between APP’s and the RLD at those concentrations tested (see Table 4). It is confirmed that APP’s product met the predefined criteria for the PD equivalence to the RLD.

Table 4. Comparison of the PD Effect of APP's Product to RLD Based on *In Vitro* Coagulation Parameters

Conc (µg/mL)	Product		Ratio (CI ₉₀)
	APP	RLD	
PT (sec)*			
0.3	12.0 (1.9)	12.1 (2.0)	99.5 (98.2 -100.8)
0.5	13.5 (2.5)	13.6 (2.4)	99.7 (98.1 – 101.3)
1.0	20.4 (3.6)	20.9 (4.4)	98.0 (95.3 – 100.8)
1.5	29.1 (4.2)	29.0 (5.2)	100.1 (97.0 – 103.3)
2.0	36.1 (4.7)	36.3 (4.9)	99.4 (96.3 – 102.7)
2.5	42.3 (4.1)	42.6 (3.9)	99.4 (96.6 – 102.2)
3.0	48.1 (5.4)	47.9 (5.1)	100.4 (96.9 – 104.1)
aPTT (sec)*			
0.3	43.2 (2.9)	43.3 (2.3)	99.9 (98.1 – 101.7)
0.5	49.7 (3.0)	49.6 (2.8)	100.1 (98.2 – 102.1)
1.0	61.0 (2.6)	61.2 (2.6)	99.6 (97.9 – 101.4)
1.5	71.4 (4.0)	71.6 (2.3)	99.7 (97.6 – 101.9)
2.0	80.6 (3.2)	79.9 (2.0)	100.9 (99.1 – 102.7)
2.5	86.5 (2.1)	87.0 (1.5)	99.4 (98.2 – 100.7)
3.0	94.1 (1.9)	94.2 (3.6)	99.9 (98.0 – 101.9)
TT (sec)*			
0.05	25.6 (2.5)	25.8 (3.1)	99.2 (96.6 – 101.9)
0.1	32.4 (2.8)	33.2 (4.5)	97.7 (94.7 – 100.9)
0.2	45.5 (6.2)	45.7 (4.7)	99.7 (96.0 – 103.5)
0.3	59.0 (5.6)	59.4 (6.2)	99.4 (95.3 – 103.8)
0.5	83.1 (5.7)	81.7 (6.6)	101.7 (97.4 – 106.2)

*Geo-mean (CV%)

The effect of excipients on PT, aPTT, & TT for APP versus RLD

The statistical comparisons of plasma argatroban PD parameters for the placebo *versus* the blank are summarized in Table 5. The results indicate that the anticoagulant effects of APP's excipients were equivalent to that of the RLD's excipients and the excipients of each argatroban formulation had no effect on the coagulation tests.

Table 5. Effect of Excipients on PT, aPTT, & TT

	PT (sec)*	Ratio (CI ₉₀) APP/Blank	Ratio (CI ₉₀) RLD/Blank
Blank (plasma only)	10.1 (1.6)		
APP placebo	10.4 (2.0)		
RLD placebo	10.4 (1.8)	102.6 (101.8 -103.4)	102.9 (102.2 – 103.6)
aPTT (sec)*			
Blank (plasma only)	25.8 (2.0)		
APP placebo	26.4 (1.9)		
RLD placebo	26.3 (1.9)	102.4 (101.7 - 103.1)	102.1 (101.7 – 102.5)
TT (sec)*			
Blank (plasma only)	18.6 (2.7)		
APP placebo	18.3 (1.0)		
RLD placebo	18.3 (1.6)	98.5 (97.0 – 100.1)	98.4 (97.2 – 100.0)

*Geo-mean (CV%)

2.3 ANALYTICAL SECTION

2.3.1 How are the active moieties identified and measured in the clinical pharmacology and biopharmaceutics studies?

Argatroban concentrations in stock and spiking solutions and in human plasma were determined by validated LC/MS/MS methods.

The clotting time measurement was conducted based on the principle of light-scattering. Assessment of PT was performed by adding tissue extract and an excess of calcium to citrated plasma to obtain a photo-optical measurement of the time to clot using Sysmex CA-1500 Coagulation Analyzer. Assessment of aPTT was accomplished using Sysmex CA-1500 Coagulation Analyzer to obtain a photo-optical measurement of the time to clot after the addition of calcium chloride. Assessment of TT was accomplished using Sysmex CA-1500 Coagulation Analyzer to obtain a photo-optical measurement time to clot after human thrombin is mixed with the citrated human plasma sample.

2.3.2 What analytical methods are used to assess concentrations?

For argatroban in stock and spiking solutions, an aliquot of dosing solution (0.9% sodium chloride) containing the analyte and internal standard (IS), diltiazem, was extracted using a dilution procedure. The extracted samples were analyzed by an HPLC equipped with an AB/MDS Sciex API 4000 mass spectrometer. Positive ions were monitored in the multiple reaction monitoring (MRM) mode.

For argatroban in plasma, argatroban was extracted using methanol with a dilution procedure. ¹³C₆ Argatroban was used as an IS. The extracted samples were analyzed by an HPCL equipped with an AB/MDS Sciex API 400 mass spectrometer. Positive ions were monitored in the multiple reaction monitoring (MRM) mode. Argatroban was monitored by the m/z 509.2 → m/z 384.3 transition and ¹³C₆-Argatroban was monitored by the m/z 515.2 → m/z 390.3 transition.

2.3.2.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used? What are the lower and upper limits of quantification (LLOQ/ ULOQ)? What are the accuracy, precision and selectivity at these limits? What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)? What is the QC sample plan?

Regarding the LC/MS/MS assay used to measure the concentration of argatroban in stock and spiking solutions, the range of the standard concentration curve is from 1.00 µg/mL to 100 µg/mL. Quantitation was determined using a weighted linear regression analysis (1/concentration²) of peak area ratios of the analyte and IS. Validation summary is presented in Table 6.

Table 6. Validation Summary

Analyte	Argatroban
Internal standard (IS)	Diltiazem
Method description	Dilution procedure with analysis/detection by LC-MS/MS
Limit of quantization (µg/mL)	1.00
Standard curve concentrations (µg/mL)	1.00, 2.00, 5.00, 10.0, 20.0, 50.0, 80.0, and 100
QC concentrations (µg/mL)	3.00, 20.0, and 75.0
QC intra-assay precision range (% CV)	0.9 to 7.4
QC intra-assay accuracy range (% bias)	-19.5 (LLOQ) to 4.0
QC inter-assay precision range (% CV)	4.7 to 11.6
QC inter-assay accuracy range (% bias)	-8.3 to -4.0
Bench-top stability (hours)	29 hours @ ambient temperature under white light
Processed stability (hours)	132 hours @ 5°C
Freeze-thaw stability (freeze-thaw cycles)	3 freeze-thaw cycles
Long-term storage stability (days)	81 days @ -80°C
Dilution integrity	up to 1000 µg/mL diluted 25 fold

This assay appears to be validated in a manner consistent with the guidance “Bioanalytical Method Validation”.

With respect to the LC/MS/MS assay used to determine the concentration of argatroban in plasma, the range of the standard concentration curve is from 0.025 µg/mL to 5.00 µg/mL. The calibration curve was established by a weighted linear regression analysis ($1/\text{concentration}^2$) of peak area ratios of the analyte and IS. Validation summary is presented in Table 7.

Table 7. Validation Summary

Analyte	Argatroban
Internal standard (IS)	¹³ C ₆ -Argatroban
Method description	Dilution procedure with analysis/detection by LC-MS/MS
Limit of quantization (µg/mL)	0.025
Average recovery of Argatroban (%) (Low , Med, High QC)	97%, 91%, 94%
Average Recovery of IS (% Mean)	89%
Standard curve concentrations (µg/mL)	0.025, 0.050, 0.100, 0.200, 0.500, 1.00, 2.00, 4.00, 5.00
QC concentrations (µg/mL)	0.075, 0.375, 3.75
QC intra-assay precision range (% CV)	0.6 to 6.7
QC intra-assay accuracy range (% bias)	1.3 to 13.6
QC inter-assay precision range (% CV)	1.7 to 5.9
QC inter-assay accuracy range (% bias)	2.7 to 10.8
Bench-top stability (hours)	26 hours @ ambient temperature
Processed stability (hours)	125 hours @ 5°C
Freeze-thaw stability (freeze-thaw cycles)	3 freeze-thaw cycles
Long-term storage stability (days)	53 days @ -80°C
Dilution integrity	up to 50.0 µg/mL diluted 25 fold

The assay seems to be validated in a manner consistent with the “Bioanalytical Method Validation” guidance.

Regarding the coagulation assays, the accuracy, precision, and stability of the quality control samples are summarized in Table 8.

Table 8. Validation Parameters for Coagulation Assays

	PT	aPTT	TT
Accuracy (% of the nominal concentrations range)			
Intra-Assay	100.0 – 101.7	99.3 – 101.1	100.0 – 100.02
Inter-Assay	100.8 – 101.7	99.9 – 100.4	100.0 – 100.01
Precision range (% CV)			
Intra-Assay	0.0 – 0.5	0.4 – 0.8	2.5 – 5.7
Inter-Assay	0.6 – 1.1	0.7 – 1.6	2.8 – 3.7
Refrigerator stability (@ 2 - 8° C)	24 hours	24 hours	71 hours
Bench-top stability (ambient temperature)	3 hours	3 hours	5 hours
Freeze-thaw stability (freeze-thaw cycles)	4	4	4
Long-term storage stability (@ - 20° C)	46 days	46 days	6 days

3 DETAILED LABELING RECOMMENDATIONS

Only relevant Clinical Pharmacology sections of the applicant’s proposed PLR format package insert is reproduced. The contents added by the agency are in Red and strikethroughs in Blue indicate content taken out by the agency.

PRESCRIBING INFORMATION
HIGHLIGHTS OF PRESCRIBING INFORMATION

ARGATROBAN

-----WARNINGS AND PRECAUTIONS-----

(b) (4)

- Use in hepatic impairment: Adjust starting dose and titrate carefully in patients with HIT who have moderate or severe hepatic impairment. Avoid use in PCI in patients with clinically significant hepatic impairment (5.2).

-----DRUG INTERACTIONS-----

(b) (4)

- Heparin: Allow sufficient time for heparin’s effect on 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 established (7.4, 7.5).

-----USE IN SPECIFIC POPULATIONS-----

(b) (4)

- Pediatric use: Safety and effectiveness have not been established; if used initial infusion doses are lower than in adult patients (2.4, 8.4, 12.3).

FULL PRESCRIBING INFORMATION
2 DOSAGE AND ADMINISTRATION
2.3 Dosing with Hepatic Impairment

(b) (4)

(b) (4)

(b) (4)

For adult patients with HIT and moderate or severe hepatic impairment (based on Child-Pugh classification), an initial dose of 0.5 mcg/kg/min is recommended, based on the approximately 4-fold decrease in argatroban clearance relative to those with normal hepatic function. Monitor the aPTT closely, and adjust the dosage as clinically indicated.

Monitoring Therapy: Achievement of steady state aPTT levels may take longer and require more dose adjustments in patients with hepatic impairment compared to patients with normal hepatic function.

For patients with hepatic impairment undergoing PCI and who have HIT or are at risk for HIT, carefully titrate argatroban until the desired level of anticoagulation is achieved. Use of Argatroban in PCI patients with clinically significant hepatic disease or AST/ALT levels ≥ 3 times the upper limit of normal should be avoided [see *Warnings and Precautions (5.2)*].

(b) (4)

5 WARNINGS AND PRECAUTIONS

5.2 Use in Hepatic Impairment

(b) (4) when administering argatroban to patients with hepatic impairment (b) (4) with a lower dose and carefully (b) (4) 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 hepatic impairment compared to patients with normal hepatic function [see (b) (4) Use in Specific Populations (b) (4)].~~ Also (b) (4) upon cessation of argatroban 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** *Dosage and Administration (2.3) and Clinical Pharmacology (12.3)*]. (b) (4)

7 DRUG INTERACTIONS

7.1 Heparin

(b) (4) 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 argatroban therapy.

7.2 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 to 7.5 mg initial oral dose, followed by 2.5 to 6 mg/day orally for 6 to 10 days) results in prolongation of the prothrombin time (PT) and International Normalized Ratio (INR) [see *Dosage and Administration (2.5) and Clinical Pharmacology (12.2)*].

7 (b) (4) 3 Aspirin/Acetaminophen

(b) (4)

No drug-drug interactions have been demonstrated between argatroban and concomitantly administered aspirin or acetaminophen [see *Clinical Pharmacology (12.3)*].

(b) (4)

7.4 Thrombolytic Agents

The safety and effectiveness of argatroban with thrombolytic agents have not been established [see (b) (4) *Adverse Reactions (6.3)*].

7.5 Glycoprotein IIb/IIIa Antagonists

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

(b) (4)

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of argatroban, including the appropriate anticoagulation goals and duration of therapy, have not been established among pediatric patients.

Argatroban was studied among 18 seriously ill pediatric patients who required an alternative to heparin anticoagulation. Most patients were diagnosed with HIT or suspected HIT. Age ranges of patients were <6 months, n = 8; six months to <8 years, n = 6; 8 to 16 years, n = 4. All patients had serious underlying conditions and were receiving multiple concomitant medications. Thirteen patients received argatroban solely as a continuous infusion (no bolus dose). Dosing was initiated in the majority of these 13 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 multiple dose adjustments to maintain anticoagulation parameters within the desired range. During the 30-day study period, thrombotic events occurred during argatroban administration to two patients and following argatroban discontinuation in 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 sepsis and thrombocytopenia. Another patient completed 14 days of argatroban treatment in the study, but experienced an intracranial hemorrhage while receiving argatroban following completion of the study treatment period.

When argatroban is used among seriously ill pediatric patients with HIT/HITTS who require an alternative to heparin and who have normal hepatic function, initiate a continuous infusion of argatroban at a dose of 0.75 mcg/kg/min. Initiate the infusion at a dose of 0.2 mcg/kg/min among seriously ill pediatric patients with impaired hepatic function [see *Clinical Pharmacology (12.3)*]. Check the aPTT two hours after the initiation of the argatroban infusion and adjust the dose to achieve the target aPTT. These dose recommendations are based upon a goal of aPTT prolongation of 1.5 to 3 times the baseline value and avoidance of an aPTT >100 seconds. Increments of 0.1 to 0.25 mcg/kg/min for pediatric patients with normal hepatic function and increments of 0.05 mcg/kg/min or lower for pediatric patients with impaired hepatic function may be considered but dose selection must take into account multiple factors including the current argatroban dose, the current aPTT, target aPTT, and the clinical status of the patient. These dose recommendations are based upon a goal of aPTT prolongation of 1.5 to 3 times the baseline value and avoidance of an aPTT >100 seconds.

8.5 Geriatric Use

(b) (4)

Of the total number of subjects (1340) in clinical studies of argatroban, 35% were 65 and over. In the clinical studies of adult patients with HIT (with or without thrombosis), the effectiveness of argatroban was not

affected by age. No trends were observed across age groups for both aPTT and the ACT. The safety analysis did suggest that older patients tended to have an increased incidence of events compared to younger patients; however, older patients had increased underlying conditions, which may predispose them to events. The studies were not sized appropriately to detect differences in safety between age groups.

8.6 Hepatic Impairment

Dose reduction and careful titration are required when administering argatroban to patients with hepatic impairment. Reversal of anticoagulation effect may be prolonged in this population [see *Dosage and Administration* (2.3), *Warning and Precautions* (5.2), *Clinical Pharmacology* (12.3)].

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 effects 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.

(b) (4) 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.

(b) (4)

12.3 Pharmacokinetics

Distribution

~~Argatroban distributes mainly in the extra-cellular fluid as evidenced by an apparent steady state volume of distribution of 174 mL/kg (12.18 L 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 4 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% and 20% of that of the parent drug. The other metabolites (M2 to M4) 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/kg/min (0.31 L/kg/hr) for infusion doses up to 40 mg/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 (\pm 2%).~~

Excretion

~~Argatroban is excreted primarily in the feces, presumably through biliary secretion. In a study in which ^{14}C -argatroban (5 mg/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.~~

(b) (4) -12.2 Pharmacodynamics

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 within 1 to 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 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), the 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 argatroban infusion doses up to 10 mcg/kg/min (see [Figure 1](#)).

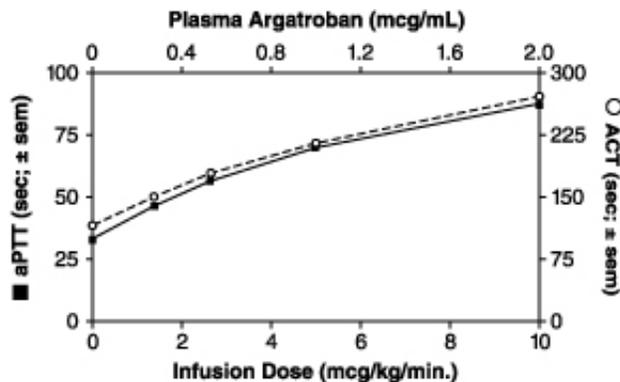


Figure 1. Relationship at Steady State Between Argatroban Dose, Plasma Argatroban Concentration and Anticoagulant Effect

(b) (4) *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.

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 2 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 *Dosage and Administration (2.5)*

(b) (4)

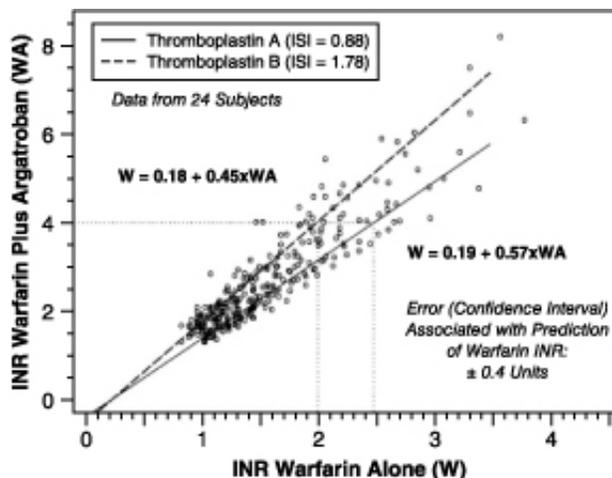


Figure 2. INR Relationship of Argatroban Plus Warfarin Versus Warfarin Alone

Figure 2 demonstrates the relationship between INR for warfarin alone and INR for warfarin co-administered with argatroban at a dose of 2 mcg/kg/min. To calculate INR for warfarin alone (INR_W), based on INR for co-therapy of warfarin and argatroban (INR_{WA}), when the argatroban dose is 2 mcg/kg/min, 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). 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 ± 0.4 units. Similar linear relationships and prediction errors exist for argatroban at a dose of 1 mcg/kg/min. Thus, for argatroban doses of 1 or 2 mcg/kg/min, INR_W can be predicted from INR_{WA} . For argatroban doses greater than 2 mcg/kg/min, the error associated with predicting INR_W from INR_{WA} is ± 1 . Thus, INR_W cannot be reliably predicted from INR_{WA} at doses greater than 2 mcg/kg/min.

12.3 Pharmacokinetics

Distribution

Argatroban distributes mainly in the extra cellular fluid as evidenced by an apparent steady-state volume of distribution of 174 mL/kg (12.18 L 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 4 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% and 20% of that of the parent drug. The other metabolites (M2 to M4) 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/kg/min (0.31 L/kg/hr) for infusion doses up to 40 mcg/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 ($\pm 2\%$).

Excretion

Argatroban is excreted primarily in the feces, presumably through biliary secretion. In a study in which ^{14}C -argatroban (5 mcg/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.

(b) (4) **Special Populations** (b) (4)

Hepatic Impairment: The dosage of argatroban should be decreased in patients with hepatic impairment [see (b) (4) **Dosage and**

Administration (2.3) and Warnings and Precautions (5.2)]. Patients with hepatic impairment were not studied in percutaneous coronary intervention (PCI) trials. At a dose of 2.5 mcg/kg/min, hepatic impairment is associated with decreased clearance and increased elimination half-life of argatroban (to 1.9 mL/kg/min and 181 minutes, respectively, for patients with a Child-Pugh score >6).

(b) (4)

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 $Cl_{cr} = 95 \pm 16$ mL/min) and in 18 subjects with mild (mean $Cl_{cr} = 64 \pm 10$ mL/min), moderate (mean $Cl_{cr} = 41 \pm 5.8$ mL/min), and severe (mean $Cl_{cr} = 5 \pm 7$ mL/min) renal impairment. The pharmacokinetics and pharmacodynamics of argatroban at dosages up to 5 mcg/kg/min were not significantly affected by renal dysfunction.

Use of argatroban was evaluated in a study of 12 patients with stable end-stage renal disease undergoing chronic intermittent hemodialysis. Argatroban was administered at a rate of 2 to 3 mcg/kg/min (begun at least 4 hours prior to dialysis) or as a bolus dose of 250 mcg/kg at the start of dialysis followed by a continuous infusion of 2 mcg/kg/min. Although these regimens did not achieve the goal of maintaining ACT values at 1.8 times the baseline value throughout most of the hemodialysis period, the hemodialysis sessions were successfully completed with both of these regimens. The mean ACTs produced in this study ranged from 1.39 to 1.82 times baseline, and the mean aPTTs ranged from 1.96 to 3.4 times baseline. When argatroban was administered as a continuous infusion of 2 mcg/kg/min prior to and during a 4-hour hemodialysis session, approximately 20% was cleared through dialysis.

(b) (4)

~~The dosage of argatroban should be decreased in patients with hepatic impairment. Patients with hepatic impairment were not studied in percutaneous coronary intervention (PCI) trials. At a dose of 2.5 mcg/kg/min, hepatic impairment is associated with decreased clearance and increased elimination half life of argatroban (to 1.9 mL/kg/min and 181 minutes, respectively, for patients with a Child Pugh score >6).~~

(b) (4)

(b) (4)

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

Pediatric: Argatroban clearance is decreased in seriously ill pediatric patients. Pharmacokinetic parameters of argatroban were characterized in a population pharmacokinetic/pharmacodynamic analysis with sparse data from 15 seriously ill pediatric patients. Clearance in pediatric patients (0.16 L/hr/kg) was 50% lower compared to healthy adults (0.31 L/hr/kg). Four pediatric patients with elevated bilirubin (secondary to cardiac complications or hepatic impairment) had, on average, 80% lower clearance (0.03 L/hr/kg) when compared to pediatric patients with normal bilirubin levels. [See *Use in Specific Populations* (b) (4) (8.4).]

Drug-Drug Interactions

Digoxin

In 12 healthy volunteers, intravenous infusion of argatroban (2 mcg/kg/min) over 5 days (study days 11 to 15) 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 mcg/kg/min for 5 hours. These data suggest oxidative metabolism by CYP3A4/5 is not an important elimination pathway *in vivo* for argatroban.

Aspirin and Acetaminophen

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 1 mcg/kg/min over 4 hours) or acetaminophen (1,000 mg orally given 12, 6, and 0 hours prior to, and 6 and 12 hours subsequent to, initiation of argatroban 1.5 mcg/kg/min over 18 hours).

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/s/

HUA ZHANG
02/16/2011

JULIE M BULLOCK
02/16/2011