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APPLICATION NUMBER:
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PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 22434
Supporting document/s: Electronic submission (SDN-001)
Applicant's letter date: January 12, 2011
CDER stamp date: January 12, 2011
Product: Argatroban Injection
Indication: Prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia; As an anticoagulant in adult patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention
Applicant: Eagle Pharmaceuticals, Inc.
Review Division: Division of Hematology Products
Reviewer: Shwu-Luan Lee, Ph.D.
Supervisor/Team Leader: Haleh Saber, Ph.D.
Division Director: Ann Farrell, M.D.
Project Manager: Lara Akinsanya

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1 Executive Summary

1.1 Recommendations

Recommending approval.

1.1.1 Approvability

There are no unresolved nonclinical issues.

1.1.2 Additional Non Clinical Recommendations

None

1.1.3 Labeling

The content of the nonclinical sections of the label is similar to that of the reference listed drug (RLD). Changes are made to the label based on the most recent practices and to comply with 21CFR201.56 and 21CFR201.57 on PLR formatting. These changes are reflected in the following sections: 8.1 Pregnancy; 8.3 Nursing Mothers; 12.1 Mechanism of Action; 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility.

1.2 Brief Discussion of Nonclinical Findings

The efficacy and safety evaluation of Argatroban Injection (Eagle) are relied on the FDA finding of safety and effectiveness for the RLD (NDA 20883), as described in the drug's approved labeling.

Two nonclinical studies were submitted to justify the use of lactobionic acid as an excipient in the drug product. Based on the results of nonclinical studies and data available on erythromycin lactobionate (an approved FDA drug), the proposed level of lactobionic acid in the drug product is acceptable.

2 Drug Information

2.1 Drug

2.1.1 CAS Registry Number (Optional)

141396-28-3

2.1.2 Generic Name

Argatroban

2.1.3 Code Name

N/A

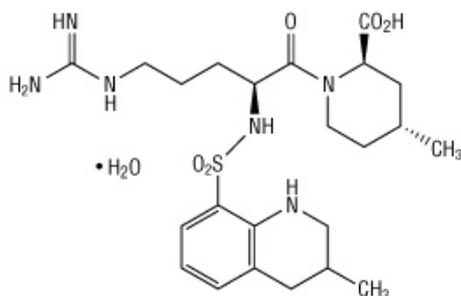
2.1.4 Chemical Name

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

2.1.5 Molecular Formula/Molecular Weight

$C_{23}H_{36}N_6O_5S \cdot H_2O/526.66$

2.1.6 Structure



2.1.7 Pharmacologic class

Direct thrombin inhibitor

2.2 Relevant IND/s, NDA/s, and DMF/s

Reference listed drug: NDA 20883 (Pfizer).

DMF (b) (4)

2.3 Clinical Formulation

2.3.1 Drug Formulation

The composition of Argatroban Injection, 1 mg/mL (50 mg/50 mL) is provided in the table below (from the Applicant).

Ingredient	Quality Standard	Amount per Vial (mg)	Concentration (mg/mL)	Function
Argatroban*	In-House	50	1	Active Ingredient
Lactobionic Acid	EP	100	2	(b) (4)
L-Methionine	USP	100	2	
Sodium Chloride	USP	400	8	
Sodium Hydroxide	NF	(b) (4)	(b) (4)	
Water for Injection	USP	(b) (4)	(b) (4)	
(b) (4)	NF	(b) (4)	(b) (4)	
*Batch quantity of argatroban added is adjusted for assay				

The clinical formulation of RLD is described below:

Ingredients	Amount	Function of ingredients
Argatroban	100 mg/mL	Active pharmaceutical ingredient
D-sorbitol	750 mg/mL	(b) (4)
Dehydrated alcohol	1000 mg/mL	(b) (4)

Qualitative differences between the two formulations include the removal of dehydrated alcohol ((b) (4)) and D-sorbitol from the RLD formulation, and the addition of lactobionic acid and L-methionine to achieve the desired (b) (4)

The information on lactobionic acid is described in the following table:

Ingredient	Amount per unit volume of Argatroban Injection		Maximum IIG levels from FDA Website
	mg/mL	% (w/v)	
Lactobionic Acid	2.0 mg	0.2	Not available

IIG: inactive ingredient grade

See the discussion regarding lactobionic acid under Section 2.3.2.

Below is a summary of drug product acceptance criteria and justifications, as proposed by the Applicant (table from the Applicant).

Test	Acceptance Criterion	Justification
Description		(b) (4)
Clarity of Solution		
Identification*		
Osmolality*		
Volume in container*		

Test	Acceptance Criterion	Justification
Particulate Matter		
pH		
Assay (HPLC)		
R:S Isomer Ratio (HPLC)		
Related Substances		
Bacterial Endotoxin		
Sterility		

(b) (4)

Test	Acceptance Criterion	Justification
(b) (4)		

*Release test only

(b) (4)

2.3.2 Comments on Novel Excipients

- Lactobionic acid

Lactobionic acid is a mixture of variable proportions of 4-O-β-D- galactopyranosyl-D-gluconic acid and 4- O-β-D-galactopyranosyl-O-glucon-1,5-lactone, with the following molecular formula and molecular weight:

Molecular formula: C₁₂H₂₂O₁₂ (acid form)/ C₁₂H₂₂O₁₁ (5-lactone),

Molecular weight: 358.3 (acid)/340.3 (lactone).

There is no relevant information on the content of lactobionic acid in the inactive ingredient list of FDA approved drugs. Two studies were submitted in this NDA to support the content (i.e. 2 mg/mL) of lactobionic acid in the clinical formulation. In brief, up to a final argatroban concentration of 0.44 mg /mL, there was no hemolysis noted when Eagle’s argatroban solution was mixed with human blood in an *in vitro* study. In a separate study, a 7-day continuous intravenous infusion study was conducted in dogs. The doses of argatroban vehicle, i.e. lactobionic acid, used in animals were:

2.23 mg/kg (initial bolus dose),

43.2 mg/kg (the second dose given as a 5-hr infusion; this corresponds to 144 µg/kg/min), and

352.08 mg/kg (the last dose given as a 6.8-day infusion; this corresponds to 36 µg/kg/min).

These doses did not induce remarkable changes in mortality, body weights, clinical signs, clinical pathology parameters, or serum levels of heavy metals.

2.3.3 Comments on Impurities

(b) (4)



(b) (4)

- Residual solvents in drug substance:

Solvent	ICH Q3C (R3) Class and Limit	Limit in API
(b) (4)		

2.4 Proposed Clinical Population and Dosing Regimen

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

2.5 Regulatory Background

The Applicant submitted NDA 22434 on January 21, 2011. The Reference Listed Drug is Argatroban Injection (Pfizer, NDA 20883).

3 Studies Submitted

3.1 Studies Reviewed

- Safety pharmacology: *In vitro* study:
Study #1007-849 (b) (4): Hemolytic potential testing of argatroban injection (Module 4)
- Special toxicology study:
Study #1773-001: A 7-day intravenous infusion study to evaluate the effects of argatroban vehicle in dogs with a 7-day recovery period (Module 4)

3.2 Studies Not Reviewed

None:

3.3 Previous Reviews Referenced

NDA 22434, pharmacology/toxicology review by Dr. Ronald Honchel (submission date of September 2008).

4 Pharmacology

4.1 Primary Pharmacology

N/A

4.2 Secondary Pharmacology

N/A

4.3 Safety Pharmacology

- *In vitro* study

Study title: Hemolytic potential testing of argatroban injection (Study #1007-849; (b) (4) (GLP study))

Key findings: No hemolysis was noted in samples of Eagle's argatroban solution or the RLD (up to a final argatroban concentration of 0.44 mg/mL) and their vehicles.

Objective: To assess the hemolytic potential of argatroban injection in human whole blood

Methods:

- Test articles and vehicles:
 - ❖ Argatroban injection (ready-to-use [RTU] solution; Eagle Pharmaceuticals, Lot #V80617; 1 mg/mL; excipients: L-methionine (2 mg/mL), lactobionic acid (2 mg/mL), and sodium chloride (8 mg/mL))
 - ❖ Argatroban injection (RLD; SmithKline Beecham Co., Lot #C460419; 100 mg/mL; excipients: D-sorbitol (750 mg/mL) and dehydrated alcohol (1000 mg/mL)). Upon use, the solution was diluted to a final concentration of 1 mg/mL argatroban using sterile saline for injection (see below).
 - ❖ Vehicle for Eagle argatroban (Vehicle [RTU], Lot #VPL9001): each 100 mL containing L-methionine (2 mg/mL), lactobionic acid (2 mg/mL), and sodium chloride (8 mg/mL).
 - ❖ Vehicle for RLD argatroban injection: 0.9% Sodium Chloride for Injection, USP
- Blood sample: from a fasted human donor
- Hemolytic analysis: 0.15, 0.25 or 0.4 mL of argatroban injection solution (Eagle RTU solution or diluted RLD at 1 mg/mL) and the RTU vehicle were mixed with 0.5 mL of

human blood, while 0.4 mL of sterile saline was mixed with 0.5 mL blood. The final concentrations of argatroban samples were 0.23, 0.33 and 0.44 mg/mL. In addition, 0.4 mL of human plasma or 0.4 mL of 1% saponin was mixed with 0.5 mL of blood to serve as negative control and positive control, respectively.

The mixtures were incubated for 25-30 min at 37 °C. The mixtures were then centrifuged and the supernatants were evaluated by spectrophotometric analysis (at wavelength pairs at 570/600 nm and 660/700 nm) for hemoglobin. Hemolysis was considered present (i.e., as a positive result) if the hemoglobin concentration in supernatant was ≥ 500 mg/dL more than that of the negative control.

Results:

Table below is the summary of the result (table from the Applicant):

Mixture	Hemoglobin ^a (mg/dL)	Test Result	Tube No.
Human blood (0.5 mL) plus:			
Test Article A			
0.15 mL	14	N	1
0.15 mL	12	N	2
0.25 mL	8	N	3
0.25 mL	13	N	4
0.4 mL	6	N	5
0.4 mL	6	N	6
0.4 mL	0	N	7
0.4 mL	1	N	8
Vehicle in Test Article A			
0.15 mL	13	N	9
0.15 mL	24	N	10
0.25 mL	12	N	11
0.25 mL	10	N	12
0.4 mL	12	N	13
0.4 mL	6	N	14
0.4 mL	1	N	15
0.4 mL	0	N	16
Test Article B			
0.15 mL	17	N	17
0.15 mL	18	N	18
0.25 mL	14	N	19
0.25 mL	11	N	20
0.4 mL	6	N	21
0.4 mL	12	N	22
0.4 mL	0	N	23
0.4 mL	0	N	24
Vehicle for Test Article B	9	N	25
Vehicle for Test Article B	8	N	26
Vehicle for Test Article B	1	N	27
Vehicle for Test Article B	0	N	28
Human plasma	12	NA	29
Human plasma	15	NA	30
1% Saponin	7720	P	31
1% Saponin	7658	P	32

N = Negative, no hemolysis.

P = Positive, hemolysis, (hemolysis recorded as a positive test result if the concentration of hemoglobin was greater than or equal to 500 mg/dL more than that of the negative control (human plasma)).

NA = Not applicable.

a Hemoglobin concentration of the mixture supernatants.

No hemolysis was noted in samples of either argatroban solution (up to a final argatroban concentration of 0.44 mg/mL) or their vehicles.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

N/A

5.2 Toxicokinetics

N/A

6 General Toxicology

6.1 Single-Dose Toxicity

N/A

6.2 Repeat-Dose Toxicity

N/A

7 Genetic Toxicology

N/A

7 Carcinogenicity

N/A

9 Reproductive and Developmental Toxicology

9.1 Fertility and early embryonic development

N/A

9.2 Embryonic Fetal Development

N/A

10 Special Toxicology Studies

Study title: A 7-day intravenous infusion study to evaluate the effects of argatroban vehicle in dogs with a 7-day recovery period (Study #1773-001) (GLP study)

Key findings:

Beagle dogs received various doses of argatroban vehicle (representing 2.23, 43.2, and 352.08 mg/kg of lactobionic acid as initial bolus injection, second/mid- dose and the third/concluding dose, respectively) for 7 days. There were no remarkable changes in mortality, body weights, clinical signs, clinical pathology parameters, or serum levels of heavy metals.

Study objective: To evaluate the potential changes in serum levels of iron, zinc and cobalt in Beagle dogs administered intravenous argatroban vehicle. The vehicle contains lactobionic acid which may form salts with various mineral cations.

Methods:

- Test article and vehicle:
 - ❖ Test article: argatroban vehicle (placebo for argatroban injection); each vial containing L-methionine (2 mg/mL), lactobionic acid (2 mg/mL), and sodium chloride (8 mg/mL) in 100 mL water for injection, USP.
 - ❖ Vehicle: 0.9% Sodium Chloride for Injection, USP
- Test system: Beagle dogs (6.5-7.5 months; 8.2-11.35 kg)
- A polyurethane central venous catheter was attached to a vascular access port and was implanted into the right femoral vein of the animal. The dogs were randomized to either the test article group or the vehicle group (n=5/sex/group). The agent (argatroban vehicle or 0.9% sterile saline) was infused continuously for 7 days. The details of loading dose (initial dose, infused for 5 minutes), second/mid- dose (infused for 5 hours) and concluding dose (infused for 163 hours, i.e., 6 days and 19 hours) are described in the following table (table from the Applicant):

Infusion (7-Day Continuous)									
Test and Control Articles	Initial Dose			Mid-Dose			Concluding Dose		
	Dose Rate	Dose Volume	Duration	Dose Rate	Duration	Dose Rate	Duration		
	(mL/kg/min)	(μ L/kg)	Min	(mL/kg/hr)	(μ L/kg/min)	Hr	(mL/kg/hr)	(μ L/kg/min)	Hr
0.9 % Saline									
Argatroban Vehicle	0.234	1170	5	4.32	72	5	1.08	18	163

Hr – hours; Min - minutes

Dose volumes of argatroban vehicle during initial, second, and last/concluding doses were 1.17, 21.6 (4.32 mL/kg/hr x 5 hr), and 176.04 mL/kg (1.08 mL/kg/hr x 163 hr), respectively. Considering the 2 mg/mL concentration of lactobionic acid, the doses of lactobionic acid in initial, second, and last/concluding doses was 2.23 mg/kg (bolus), 43.2 mg/kg (given in 5 hrs), and 352.08 mg/kg (in 6.8 days), respectively.

Reviewer's note: The dose rate indicated in the table, i.e., 0.234 mL/kg/min, 72 μ L/kg/min and 18 μ L/kg/min is referred to argatroban vehicle, not to lactobionic acid.

- Justification of dosage of argatroban vehicle in the study:
Justification is based on the clinical protocol for a patient with ACT < 300 seconds undergoing PCI, where the intravenous argatroban is given as: the initial bolus dose of 650 μ g/kg, followed by 40 μ g/kg/min for 2.5 hours (total of 6 mg/kg), then 10 μ g/kg/min for 6 days (total of 86.4 mg/kg). These argatroban doses will correspond to the following lactobionic doses:
 - 1300 μ g/kg (initial bolus dose),
 - 12 mg/kg (the second dose given as a 2.5-hr infusion; 80 μ g/kg/min), and
 - 173 mg/kg (the last/concluding dose given as a 6-day infusion; 20 μ g/kg/min)

The conversion of human equivalent dose (HED) to canine equivalent dose is based on a ratio of 1: 1.85. Thus, based on the above doses in humans, the canine equivalent dose for initial, second and concluding doses of argatroban would be (in total): 1.2 mg/kg, 11.1 mg/kg, and 159.84 mg/kg, respectively. This will correspond to the following lactobionic doses in dogs:

- 2.4 mg/kg (initial bolus dose),
- 22 mg/kg (the second dose given a 2.5-hr of infusion; 148 μ g/kg/min), and
- 320 mg/kg (the last dose given as a 6 day infusion; 37 μ g/kg/min).

Doses and rate of infusion used in the present study are:

- 2.23 mg/kg (initial bolus dose),
- 43.2 mg/kg (the second dose given as a 5-hr infusion; this corresponds to 144 μ g/kg/min), and
- 352.08 mg/kg (the last dose given as a 6.8-day infusion; this corresponds to 36 μ g/kg/min).

Reviewer's note:

The human dose/schedule used to justify the dose/schedule in dogs could not be located in the drug label; however, the Applicant submitted justifications for the clinical protocol referenced in the current study. The justification is acceptable (see Appendix for the summary table).

Observations and Results

- Clinical signs: At least twice daily for mortality, moribundity and gross abnormality during pretest and dosing period. Detailed examinations were conducted daily starting Day -1.
- Body weight: Pre-test period: on Day -1
Dosing period: Weekly.
- Food consumption: Daily starting on Day -1.
- Ophthalmoscopy test: Not conducted.
- Hematology: On Days -7, and -1, 5 hours after the start of infusion (SOI) on Day 1, within 2 minutes prior to the end of infusion (EOI) on Day 8 and

on Days 9 and 10 (i.e., 24 hr and 72 hr after EOI), and during the recovery period on Day 15.

Clinical chemistry: See "hematology". Serum levels of total cobalt, zinc and iron concentrations were analyzed in addition to the conventional items for clinical chemistry analysis.

Urinalysis: Urine samples (12 hour collection) were collected on Day -1, 11 and 15.

Gross pathology: Not conducted.

Organ weights: Not conducted.

Histopathology: Not conducted.

Toxicokinetics: Not conducted.

Results:

- Mortality: no mortality.
- Clinical signs: not remarkable
- Body weights; not remarkable
- Food consumption: not remarkable
- Clinical pathology: not remarkable in hematology, clinical chemistry and urinalysis findings
- Serum metal levels:
Changes from the baseline of serum levels of Fe²⁺, Zn²⁺ and Co²⁺, in argatroban vehicle or saline-infused animals on Days 9, 11 and 15 are summarized in the table below (Table from the Applicant):

Serum Levels of Iron, Zinc, and Cobalt (Change from Baseline)

Parameter (ng/mL)	Day 9 ^a		Day 11 ^b		Day 15	
	Argatroban Vehicle Mean CFB (LCB)	Control Mean CFB	Argatroban Vehicle Mean CFB (LCB)	Control Mean CFB	Argatroban Vehicle Mean CFB (LCB)	Control Mean CFB
Iron	333.70 (59.75)	427.85	-178.70 (-355.86)*	51.45	418.20 (225.59)	370.45
Zinc	51.40 (-157.57)	-27.85	48.40 (-15.15)	35.15	93.70 (0.67)	70.25
Cobalt	0.0855 (-0.1390)	0.306	-0.0335 (-0.3323)	0.065	-0.2215 (-0.5820)	-0.013

^a 24 hours after EOI on Day 8
^b 72 hours after EOI on Day 8
* p=0.0411 indicating that the Argatroban Vehicle group had an average reduction in serum iron level that was significantly different from the serum iron level of the Saline (control) group on Day 11.
LCB: 1-sided 95% lower confidence bound; CFB = Change from baseline.
Bold text indicating the direction of Argatroban Vehicle group CFB was opposite to the CFB direction of the Saline (control) group.

EOI: end of infusion

While there were changes in the serum levels of zinc, iron and cobalt, the changes were seen in both argatroban vehicle and the saline control groups. High variability was observed within groups and in individual animals. Furthermore, the high variability during treatment and recovery periods suggest that effects are independent of the

treatment. There were no physiologically meaningful differences in serum metal levels between these two dose groups. On Day 11, statistically significant reduction in serum iron level was observed. This finding did not have supportive findings in clinical signs or clinical pathology parameters.

11 Integrated Summary and Safety Evaluation

This submission is a 505(b)(2) NDA. The efficacy and safety evaluation of argatroban in the present submission is based on the FDA finding of safety or effectiveness for the RLD (NDA 20883), as described in the drug's approved labeling.

Lactobionic acid, an excipient used in the drug formulation, is a weak acid with a pH range of 1 to 2. There are limited toxicological studies of lactobionic acid (Acros Organics Material Safety Data Sheet: http://www.chemblink.com/MSDS/MSDSFiles/96-82-2_Acros%20Organics.pdf). It is not listed as a carcinogen by ACGIH, IARC, NTP, or CA Prop 65. Lactobionic acid is also used in the cosmetics industry as an antioxidant, and in the pharmaceutical industry as a salt form; for example, one of the approved formulations for the antibiotic erythromycin is erythromycin lactobionate which is administered intravenously.

Based on nonclinical studies conducted and the information available on erythromycin lactobionate, the proposed level of lactobionic acid in the drug product is acceptable.

12 Appendix/Attachments

The Applicant’s justification for the human dose and schedule used to design the 7-day toxicology study in dogs

(b) (4) Study 1773-001 Dosing Regimen	Human Dose		Schedule	
	ARGATROBAN INJECTION label	Rationale	ARGATROBAN INJECTION label	Rationale
‘Initial dose’	Section 2.2 Dosing in Patients Undergoing Percutaneous Coronary Intervention Initial Dosage (350 mcg/kg) Dosage Adjustment (up to two additional bolus doses of 150 mcg/kg each)	650 mcg/kg (maximum cumulative bolus dose possible)	Initial Dosage: over 3 to 5 min First additional bolus dose: 5 to 10 min after initial dose Second additional bolus dose: 5 to 10 min after first additional bolus dose Cumulative administration duration of 13 to 25 min	Used 5 min duration as worst case administration scenario
‘Mid-Dose’	Section 2.2 Dosing in Patients Undergoing Percutaneous Coronary Intervention Continuous infusion initiated at 25 mcg/kg/min, may be increased to 30 mcg/kg/min after 5 to 10 min, and may be further increased to a maximum of 40 mcg/kg/min	40 mcg/kg/min (maximum infusion rate)	Duration of PCI not specified	Selected 5 hour duration based on the reported average time of infusion therapy (2.5 hr) and administration based on limit of repeated intravenous infusion dose volume and rate for dog (based on 4 hr daily infusion) ¹
‘Concluding Dose’	Section 2.1 Dosing in Patients with Heparin-Induced Thrombocytopenia Dosing initiated at 2 mcg/kg/min and may be increased to 10 mcg/kg/min	10 mcg/kg/min (maximum infusion rate)	Not specified	Total study duration of 6 days selected based on FDA comment that “the treatment of HIT typically involves continuous infusion of argatroban for 5 or more days” ² and administration based on limit of repeated intravenous infusion dose volume and rate for dog (based on 24 hr daily infusion) ¹

¹ Diehl KH, Hull R, Morton D, Pfister R, Rabemampianina Y, Smith D, Vidal JM, van de Vorstenbosch C (2001) A Good Practice Guide to the Administration of Substances and Removal of Blood, Including Routes and Volumes. J. Appl. Toxicol. (21)15–23

² July 24, 2008: FDA Response to Specific Questions regarding our Type B meeting

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/s/

SHWU LUAN LEE
06/22/2011

HALEH SABER
06/22/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 22-434
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: September 26, 2008
PRODUCT: Argatroban Injection RTU
INTENDED CLINICAL POPULATION: Patients with Heparin-Induced
Thrombocytopenia
SPONSOR: Eagle Pharmaceuticals, Inc.
DOCUMENTS REVIEWED: Module 1/volume 1, Module 2/volume 1, and
Module 4/volume 1
REVIEW DIVISION: Division of Medical Imaging and Hematological
Drug Products (HFD-160)
PHARM/TOX REVIEWER: Ronald Honchel, Ph.D.
PHARM/TOX SUPERVISOR: Adebayo Lanionu, Ph.D.
DIVISION DIRECTOR: R. Dwaine Rieves, M.D.
PROJECT MANAGER: Ebla Ali Ibrahim

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

The Sponsor failed to provide adequate information in regards to impurities and degradation products. Therefore, from a preclinical standpoint, we cannot recommend approval at this time.

B. Recommendation for nonclinical studies

None at this time. However, the Sponsor did not provide adequate information in regards to impurities and degradation products. Nonclinical studies could potentially be required to qualify impurities or degradation products if qualification thresholds are exceeded as described in ICH Guidance Q3A and Q3B.

C. Recommendations on labeling

None

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

The sponsor relies on the Agency's previous findings of safety and efficacy for this 505(b)(2) application. The safety of Argatroban was established in preclinical toxicity studies conducted by the innovator. In acute toxicity studies, the minimal single intravenous bolus dose of Argatroban that induced lethality in mice, rats, and rabbits was 200, 124, and 150 mg/kg, respectively. Argatroban was negative in various genotoxic assays. Argatroban did not affect fertility or reproductive performance, and was not fetotoxic or teratogenic.

B. Pharmacologic activity

Argatroban is a direct thrombin inhibitor that produces an anticoagulant effect via the reversible binding of Argatroban to the thrombin active site.

C. Nonclinical safety issues relevant to clinical use

None.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-434

Review number: 01

Sequence number/date/type of submission: 000/September 26, 2008/Original

Information to sponsor: Yes () No (X)

Sponsor and/or agent: Eagle Pharmaceuticals, Inc.,

Manufacturer for drug substance: (b) (4)

Reviewer name: Ronald Honchel, Ph.D.

Division name: Division of Medical Imaging and Hematological Drug Products

HFD #: 160

Review completion date: December 22, 2009

Drug:

Trade name: Argatroban

Generic name: N/A

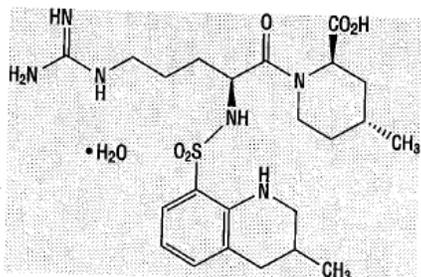
Code name: N/A

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

CAS registry number: 74863-84-6

Molecular formula/molecular weight: $C_{23}H_{36}N_6O_5S \cdot H_2O$ /526.66

Structure:



Relevant INDs/NDAs/DMFs: NDA 20-883 (Argatroban; Texas Biotechnology Corporation, Houston, TX)

Drug class: Thrombin Inhibitor

Intended clinical population: Argatroban Injection is intended for the prophylaxis and/or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT) with or without thrombosis. Argatroban injection is also being proposed as an

anticoagulant in patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI).

Clinical formulation: Argatroban Injection RTU is a sterile solution (b) (4) of drug substance (1 mg/mL), Lactobionic Acid (2 mg/mL), L-methionine (2 mg/mL), sodium chloride, sodium hydroxide (for pH adjustment) and water.

Route of administration: Intravenous.

Data reliance: There were no preclinical studies submitted in this application. The sponsor relies on the Agency's previous finding of safety and efficacy for intravenously administered Argatroban as described in approved drug labeling (the sponsor referenced NDA 20-883).

Studies reviewed within this submission: There were no preclinical studies submitted for this 505(b)(2) application.

Studies not reviewed within this submission: None

2.6.2 PHARMACOLOGY

Pharmacology data was not submitted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

N/A

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

Pharmacokinetic/toxicokinetic data was not submitted.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

N/A

2.6.6 TOXICOLOGY

Toxicology study reports were not submitted.

2.6.7 TOXICOLOGY TABULATED SUMMARY

N/A

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Argatroban is a synthetic direct thrombin inhibitor derived from L-arginine that produces its anticoagulant effect by reversibly binding to the thrombin active site. There were no preclinical studies submitted with this 505(b)(2) application. The sponsor relies on the Agency’s previous findings of safety and efficacy for Argatroban originally approved under NDA 20-883 (ACOVA™ (Argatroban) Injection, Encysive Pharmaceuticals, Inc., approved under Texas Biotechnology Corporation).

The safety of Argatroban was established in preclinical toxicity studies conducted by the innovator. In acute toxicity studies, the minimal single intravenous bolus dose of Argatroban that induced lethality in mice, rats, and rabbits was 200, 124, and 150 mg/kg, respectively.

Argatroban was negative in the Ames test, the Chinese hamster ovary cell forward mutation test, the Chinese hamster lung fibroblast chromosome aberration test, the rat hepatocyte unscheduled DNA synthesis test, the WI-38 human fetal lung cell unscheduled DNA synthesis test, and the mouse micronucleus test.

Fertility and reproductive performance were not affected in studies in rats administered intravenous doses of up to 27 mg/kg/day Argatroban. Argatroban was not fetotoxic or teratogenic at intravenous doses of up to 27 mg/kg/day in rats and 10.8 mg/kg/day in rabbits.

The indications, route of administration, and dosing of premixed Argatroban Injection proposed in this submission (NDA 22-434) are identical to that approved in NDA 20-883. ACOVA™ had to be diluted 100-fold prior to use to obtain an Argatroban concentration of 1 mg/mL. Argatroban Injection RTU is formulated at an Argatroban concentration of 1 mg/mL (does not require dilution). Although there is no difference in the final Argatroban concentration, there are differences in the final formulation for Argatroban Injection RTU and 1:100 diluted ACOVA™ (identified as Argatroban Injection in the Sponsor’s Table below).

Argatroban Injection	Argatroban Injection RTU	Function
D-Sorbitol		(b) (4)
Dehydrated Alcohol		
	Lactobionic Acid	
	L-Methionine, USP	
	Sodium Chloride, NF	
	Sodium Hydroxide, NF	
	Water for Injection, USP	pH Adjustment (b) (4)

Sodium chloride and sodium hydroxide are listed on FDA’s Inactive Ingredient List and are used at standard concentrations for intravenous injection and pH adjustment, respectively. L-Methionine and lactobionic acid are also listed on FDA’s Inactive Ingredient List. The current recommended daily intake for methionine in patients

receiving total parental nutrition is 26 mg/kg, but this amount can be increased by 4-fold in malnourished patients and patients with metabolic stress (van de Poll et al., *J Nutr* 136:1694S-1700S, 2006; cited by the sponsor). Additionally, methionine was well tolerated in nitroglycerin-tolerant volunteers administered approximately 70 mg/kg methionine (Levy et al., *J Am Coll Cardiol* 17:474-9, 1991; cited by the sponsor) and acetaminophen poisoning patients administered 400 mg/kg methionine (Prescott et al., *Lancet* 7977:109-13, 1976; cited by the sponsor). Based on the approved labeling for Argatroban, the highest daily dose will be 5.76 mg/kg/day methionine and the highest bolus dose will be 3.5 mg/kg methionine. These methionine dose levels are well below the current recommended daily dose level and doses that have been safely used in the treatment of nitroglycerin-tolerant patients and acetaminophen poisoned patients. Lactobionic acid is a component of the approved drug Erythromycin Lactobionate (2:1 erythromycin to lactobionic acid on a weight basis). At the highest approved dose (4 g erythromycin/day) patients are administered 40 mg/kg/day lactobionic acid (assuming a 50 kg body weight). Based on the approved labeling for Argatroban, the highest daily dose will be 5.76 mg/kg/day lactobionic acid and the highest bolus dose will be 3.5 mg/kg lactobionic acid. These lactobionic dose levels are well below the lactobionic dose levels current approved for Erythromycin Lactobionate. From a preclinical standpoint, there are no preclinical issues with the inactive ingredients used in Argatroban Injection RTU.

There were a number of CMC issues with this application. The FDA Chemist's (Mark Sassaman, Ph.D.) NDA Review of this submission (review date November 20, 2009) stated that "in its current form, NDA 22434 cannot be approved". Pertinent to nonclinical, the FDA Chemist concluded that the analytical methodology employed by the Sponsor "is not capable of detecting potential impurities and degradants". As a result, we were unable to make a determination whether any impurity or degradation product exceeded qualification threshold since impurities and degradation products were neither properly identified nor properly quantitated as required by ICH Guidance Q3A and Q3B, respectively.

Overall, the preclinical studies conducted with Argatroban by the innovator under NDA 20-883 support the safety of Argatroban Injection at the proposed doses. Additionally, the formulation should be safe in regards to inactive ingredients. However, we were unable to make a determination whether any impurity or degradation required qualification as per ICH Guidance Q3A and Q3B, respectively, since impurities and degradation products were neither properly identified nor properly quantitated by the Sponsor. Therefore, nonclinical studies could potentially be required to qualify impurities or degradation products if qualification thresholds are exceeded as described in ICH Guidance Q3A and Q3B.

Recommendations:

1. The Sponsor failed to provide adequate information in regards to impurities and degradation products. Therefore, from a preclinical standpoint, we cannot recommend approval at this time.
2. Nonclinical studies could potentially be required to qualify impurities or degradation products if qualification thresholds are exceeded as described in ICH Guidance Q3A and Q3B.

Suggested labeling: None

APPENDIX/ATTACHMENTS

NONE.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22434	ORIG-1	EAGLE PHARMACEUTICA LS INC	ARGATROBAN INJECTION

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RONALD HONCHEL
12/22/2009

ADEBAYO A LANIYONU
12/22/2009

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22434

Applicant: Eagle

Stamp Date: January 12, 2011

Drug Name: Argatroban

NDA/BLA Type: 505(b)2

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	x		Pharmacology/toxicology data including two studies (7-day toxicology study of argatroban vehicle in dogs, and hemolytic assessment of argatroban injection) were submitted.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	x		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	x		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	x		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	x		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	x		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?		x	The two no-clinical studies (one for safety assessment of argatroban vehicle, the other for hemolytic assessment of argatroban injection) were not GLP compliant. However, this is acceptable as the studies are not considered pivotal.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x		

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	x		Using RLD package insert as the template.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			Pending CMC review. A request for the justification of proposed specification limit of impurity (b)(4) will be sent to the Applicant.
11	Has the applicant addressed any abuse potential issues in the submission?			Not applied
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applied

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Shwu-Luan Lee, Ph.D.
Reviewing Pharmacologist

4/8/2011
Date

Team Leader/Supervisor

Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHWU LUAN LEE
04/13/2011

HALEH SABER
04/13/2011