

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**201811Orig1s000**

**PHARMACOLOGY REVIEW(S)**

## Memorandum

**Date:** March 2, 2015

**From:** Shwu-Luan Lee, Ph.D.

**NDA:** 201811 (Argatroban Injection: 100 mg/mL)

**Applicant:** Fresenius Kabi USA, LLC (previously APP Pharmaceuticals, Inc.)

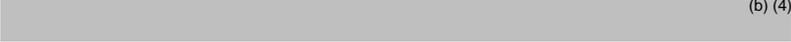
**Subject:** Resubmission date of January 23, 2015 (SDN 024) following Complete Response letter of February 28, 2014

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There is no new pharmacology/toxicology data in this submission. The NDA is recommended for approval from a pharmacology/toxicology perspective.

Changes in labeling:

In order to implement PLLR Guidance<sup>1</sup>, changes are made to Section 8 "Use in Specific Populations". Summary of changes is as follows:

- Removal of Pregnancy Category B
- 8.1 Pregnancy: In addition to the adaptation of PLLR format and statement, information regarding treatment duration in embryo-fetal developmental toxicology studies in rats and rabbits has been added.
-  (b) (4)

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<sup>1</sup> Pregnancy, Lactation and Reproductive Potential: labeling for Human Prescription Drug and Biological Products -- Content and Format Guidance for Industry

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/s/  
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SHWU LUAN LEE  
03/10/2015

PEDRO L DEL VALLE  
03/10/2015

REV-NONCLINICAL-05 (Review Noted (NAI))  
NDA-201811  
ORIG-1  
Supporting Document 21  
Resubmission/Class 2  
Submit Date: 09/13/2013 - FDA Received Date: 09/13/2013

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There are no new pharmacology-toxicology studies submitted to the resubmission. From a pharmacologist-toxicologist's perspective, this NDA is recommended for approval.

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/s/  
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SHWU LUAN LEE  
02/05/2014

REV-NONCLINICAL-05 (Review Noted (NAI))  
NDA-201811  
ORIG-1  
Supporting Document 21  
Resubmission/Class 2  
Submit Date: 09/13/2013 - FDA Received Date: 09/13/2013

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No pharmacology-toxicology issues in this resubmission.

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/s/  
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SHWU LUAN LEE  
01/30/2014

## Memorandum

**Date:** January 11, 2013, 2012

**From:** Shwu-Luan Lee, Ph.D.

**NDA:** 201811 (Argatroban Injection: 100 mg/mL)

**Applicant:** Fresenius Kabi USA, LLC (previously APP Pharmaceuticals, Inc.)

**Subject:** Resubmission date of October 12, 2012 (SDN 017) following Complete Response letter of July 2012

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There is no new pharmacology/toxicology data in this submission. The NDA is recommended for approval from a pharmacology/toxicology perspective.

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/s/  
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SHWU LUAN LEE  
01/11/2013

HALEH SABER  
01/11/2013

## Memorandum

**Date:** June 4, 2012

**From:** Shwu-Luan Lee, Ph.D.

**NDA:** 201811 (Argatroban Injection: 100 mg/mL)

**Applicant:** APP Pharmaceuticals, Inc.

**Subject:** Resubmission date of Jan 31, 2012 (SDN 009) following Complete Response letter of Feb 2011

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### Introduction

APP Pharmaceuticals received a Complete Response (CR) Letter in February 2011 for Argatroban Injection. The following pharmacology/toxicology deficiency was included in the CR letter:

The proposed specification of (b) (4) % for impurity (b) (4) is not acceptable. You should reduce the specification according to ICH Q3B(R2) or adequately justify the proposed level based on nonclinical or clinical data. Alternatively, you may justify this specification based on the level of impurity (b) (4) present in the reference listed drug using adequate analytical method(s). We note your statement regarding impurity (b) (4) being a metabolite of argatroban. You have not provided data to support this claim; therefore, your justification for the proposed level of (b) (4) % is not acceptable.

In this resubmission, APP has identified Impurity (b) (4) via HPLC and LCMS and compared the structure and pharmacokinetic profile of Impurity (b) (4) to that of (b) (4) metabolite of argatroban. The structure of (b) (4) metabolite is described in the review of the reference NDA (# 20883, Pfizer) and in published articles. The Applicant has concluded that Impurity (b) (4) is metabolite (b) (4).

The pharmacology/toxicology review team considers the information to be acceptable. In addition, the Agency has located 2 published articles that further indicate Impurity (b) (4) is a metabolite of argatroban:

(b) (4)

According to the label of the reference drug (NDA 20883), the plasma concentrations of (b) (4) range between (b) (4) % of that of the parent drug.

Conclusion:

The proposed specification of Impurity <sup>(b)</sup><sub>(4)</sub> set at NMT <sup>(b)</sup><sub>(4)</sub> % is acceptable. There are no pending pharmacology/toxicology issues to preclude the approval of this 505(b)(2) NDA.

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/s/  
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SHWU LUAN LEE  
06/04/2012

HALEH SABER  
06/04/2012

**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: 201-811  
Supporting document/s: Electronic submission (SDN-001)  
Applicant's letter date: April 29, 2010  
CDER stamp date: April 30, 2010  
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: APP 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: Ebla Ali Ibrahim

**Disclaimer**

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 201811 are owned by APP Pharmaceuticals, Inc. or are data for which APP Pharmaceuticals, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 201811 that APP Pharmaceuticals, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that APP Pharmaceuticals, Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 201811.

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# 1 Executive Summary

## 1.1 Recommendations

Impurity <sup>(b)</sup><sub>(4)</sub> is above the threshold defined in ICHQ3B (R2).

This application cannot be approved until the impurity issue is adequately addressed.

The following comment will be included in the Complete Response (CR) letter:

Pharmacology-toxicology deficiency:

The proposed specification of <sup>(b)</sup><sub>(4)</sub> % for impurity <sup>(b)</sup><sub>(4)</sub> is not acceptable. You should reduce the specification according to ICH Q3B(R2) or adequately justify the proposed level based on nonclinical or clinical data. Alternatively, you may justify this specification based on the level of impurity <sup>(b)</sup><sub>(4)</sub> present in the reference listed drug using adequate analytical method(s). We note your statement regarding impurity <sup>(b)</sup><sub>(4)</sub> being a metabolite of argatroban. You have not provided data to support this claim; therefore, we cannot accept your justification for the proposed level of <sup>(b)</sup><sub>(4)</sub> %.

### 1.1.1 Approvability

This application cannot be approved until the impurity issue is adequately addressed. See above.

### 1.1.2 Additional Non Clinical Recommendations

None

### 1.1.3 Labeling

The label has not been reviewed. The Agency will issue a Complete Response letter to the Applicant.

## 1.2 Brief Discussion of Nonclinical Findings

The Applicant has not submitted non-clinical studies in this 505(b)(2) NDA. The efficacy and safety evaluation of Argatroban Injection (APP) are relied on the FDA finding of safety or effectiveness for the RLD (NDA 20883), as described in the drug's approved labeling.

## 2 Drug Information

### 2.1 Drug

#### 2.1.1 CAS Registry Number (Optional)

141396-28-3

#### 2.1.2 Generic Name

N/A

#### 2.1.3 Code Name

N/A

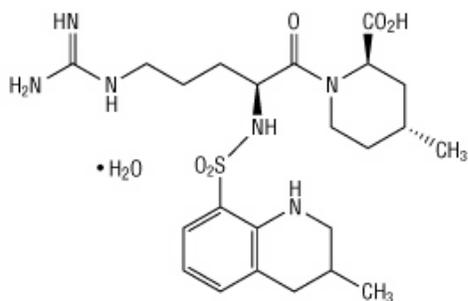
#### 2.1.4 Chemical Name

1-[5-[(aminoiminomethyl)amino]-1-oxo-2-[[[(1,2,3,4-tetrahydro-3-methyl-8-quinoliny)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, 100 mg/mL (250 mg/2.5 mL) is provided in the table below (from the Applicant).

APP Product Ingredients	Function of Ingredients
Argatroban	Active Pharmaceutical Ingredient
Propylene Glycol	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)

A summary of excipients and their inactive ingredient grade (IIG) limits is described in the following table:

APP's Excipients	Amount per Unit	IIG Levels
Propylene Glycol	(b) (4) % v/v	82.04%
(b) (4)	(b) (4)	(b) (4)

As noted the amount of propylene glycol (v/v) (b) (4) IIG (inactive ingredient grade) limits. See the discussion regarding the content of propylene glycol under Section 2.3.2.

Comparison of drug product to the RLD (table from the Applicant); "APP" refers to APP Argatroban Injection.

RLD		APP		Function of Ingredients
Ingredients	Amount	Ingredients	Amount	
Argatroban	100 mg/mL	Argatroban	100 mg/mL	Active Pharmaceutical Ingredient
D-sorbitol	(b) (4)	N/A	N/A	(b) (4)
Dehydrated Alcohol	(b) (4)	N/A	N/A	(b) (4)
N/A	N/A	Propylene Glycol	(b) (4)	(b) (4)
N/A	N/A	(b) (4)	(b) (4)	(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 replacement of propylene glycol to achieve the (b) (4) of argatroban at the concentration of 100 mg/mL.

The impurity specification of the drug product (DP) is provided in the Appendix.

### 2.3.2 Comments on Novel Excipients

There are no novel excipients. Below is a discussion on the level of propylene glycol.

The content of the excipient, propylene glycol (PG) is 92% v/v (i.e., 954 mg or 0.92 mL/mL of DP). This exceeds levels in FDA approved intravenous products (e.g., lorazepam contains 0.8 mL PG/mL [80 % v/v]; diazepam contains 0.4 mL PG/mL [40% v/v]).

The Applicant justifies the content of PG by maximum daily intake of PG at the maximum human dose of argatroban of (b) (4) per patient. The derivation of maximum daily dose (mL) of PG is as follows:

The maximum daily dose of propylene glycol from Argatroban Injection is (b) (4) or approximately (b) (4) mL Argatroban Injection, based on the concentration of argatroban at 100 mg/mL and PG content at 0.92 mL/mL of DP.

(b) (4)

(b) (4)

The Applicant refers to a clinical research where patients (n=21) in medical ICU received IV benzodiazepine delivered in propylene glycol (such as lorazepam or diazepam) versus patients (n=23) receiving benzodiazepine delivered in an alternative solvent (such as midazolam) (b) (4). According to this article, propylene glycol appeared to be safe when given intravenously at up to approximately (b) (4).

The Applicant also compares the maximum infusion rate per minute of PG of argatroban with lorazepam. The IV infusion of argatroban would give a maximum (b) (4) mL/min of PG at the recommended infusion dose of (b) (4) mcg/kg/min, as compared to the infusion dose at 0.8 mL/min of PG in lorazepam (2 mg/min).

The proposed level of PG is acceptable.

### 2.3.3 Comments on Impurities/Degradants of Concern

The impurity levels in three lots of finished drug product, assessed under accelerated and room temperature conditions, are summarized in the table below. The Applicant also compared the impurity profile of APP Pharmaceuticals' product with that of the Pfizer argatroban (RLD) under accelerated condition as well as under room temperature. See Appendix for more information.

- Accelerated condition: summary of assessment in 6 months (Table from the Applicant)

Impurity	Proposed Acceptance Criteria	Justification	Argatroban Injection Accelerated (40° ± 2°C/75 ± 5% RH)		
			Lot # S780004	Lot # S780013	Lot # S780014
Known Impurity (b) (4)	NMT (b) (4) %	APP stability data and API specification	(b) (4)	(b) (4)	(b) (4)
Any Other Impurity	NMT (b) (4) %	ICH Q3B identification threshold	(b) (4)	(b) (4)	(b) (4)
Total Impurities	NMT (b) (4) %	APP stability data and API specification	(b) (4)	(b) (4)	(b) (4)

Reviewer’s note: The third column of the table “Justification” indicates the Applicant’s justification.

- Room temperature (25° ± 2°C, 60 ± 5% RH): summary of assessment in 18 months

Impurity	Proposed acceptance criteria	Applicant’s Justification*	Lot #S780004	Lot #S780013	Lot #S780014
Known impurity (b) (4)	NMT (b) (4) %	APP stability data and API specification	(b) (4)	(b) (4)	(b) (4)
Any other impurity	NMT (b) (4) %	ICH Q3B identification threshold	(b) (4)	(b) (4)	(b) (4)
Total impurity	NMT (b) (4) %	APP stability data and API specification	(b) (4)	(b) (4)	(b) (4)

\* Table is adapted from Applicant (data at 18 months), See Appendix>

As the maximum daily dose of Argatroban Injection is to be (b) (4) based on ICHQ3B (R2), the limit of any single impurity is up to (b) (4) %. Thus, the content of Impurity (b) (4) is not acceptable.

- Impurity (b) (4):  
According to the Applicant, impurity (b) (4) (see structure and chemical name below) is a (b) (4) of the API. Thus, the Applicant proposes much higher specification for impurity (b) (4) than specified in ICHQ3B (R2), i.e., NMT (b) (4).

Impurity (b) (4):

Adequate data have not been provided to support that Impurity (b) (4) is a metabolite of argatroban.

## 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 201811 on April 30, 2010. The Reference Listed Drug is Argatroban Injection (Pfizer, NDA 20883).

## 3 Studies Submitted

### 3.1 Studies Reviewed

No studies are included in this submission.

### 3.2 Studies Not Reviewed

No studies are included in this submission.

### 3.3 Previous Reviews Referenced

None.

## **4 Pharmacology**

### **4.1 Primary Pharmacology**

N/A

### **4.2 Secondary Pharmacology**

N/A

### **4.3 Safety Pharmacology**

N/A

## **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

N/A

## 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. No new nonclinical data have been submitted for review; therefore, no additional safety assessment is done for this NDA.

The specification proposed for Impurity (b) (4) at (b) (4) % is above the threshold defined in ICHQ3B (R2). This specification should be reduced or should be adequately justified. The Applicant stated that Impurity (b) (4) is a metabolite of argatroban; adequate data have not been provided to support this claim. The Applicant may provide more information or may reduce the level of Impurity (b) (4).

### **Communications to the Applicant: the communication will be part of the "complete response (CR) letter"**

Pharmacology-toxicology deficiency:

The proposed specification of (b) (4) % for impurity (b) (4) is not acceptable. You should reduce the specification according to ICH Q3B(R2) or adequately justify the proposed level based on nonclinical or clinical data. Alternatively, you may justify this specification based the level of impurity (b) (4) present in the reference listed drug using adequate analytical method(s). We note your statement regarding impurity (b) (4) being a metabolite of argatroban. You have not provided data to support this claim; therefore, we cannot accept your justification for the proposed level of (b) (4) %.

## 12 Appendix/Attachments

### Applicant's proposal: Specification, acceptance criteria and stability of drug product:

#### Specification and acceptance criteria:

The finished product specification based on data from 3 lots of APP Pharmaceuticals' Argatroban Injection (100 mg/mL) is tabulated as follows (table from the Applicant):

Test	Acceptance Criteria	Test Method <sup>1</sup>	Results		
			Lot # S780004	Lot # S780013	Lot # S780014
Description	Liquid in an amber glass vial	Visual Inspection	Liquid in an amber glass vial	Liquid in an amber glass vial	Liquid in an amber glass vial
Visual Inspection: A. Clarity B. Particulate Matter  C. Visual Color	A. Clear B. Essentially free of visible particulates  C. Colorless to slightly yellow	A. USP <1> B. USP <1>  C. 99-08-03-6008	A. Clear B. Essentially free of visible particulates  C. Slightly yellow	A. Clear B. Essentially free of visible particulates  C. Slightly yellow	A. Clear B. Essentially free of visible particulates  C. Slightly yellow
Instrumental Color: (b) (4)	NMT (b) (4)	99-08-00-6016	(b) (4)		
Volume Check <sup>2</sup>	NLT (b) (4) mL	USP <1>	(b) (4)		
Container/Closure Integrity <sup>3</sup>	The (b) (4) concentration in each test sample is NMT (b) (4)	10-08-03-6458 (Specific) 10-08-00-6015 (General)	Meets specification	N/A	N/A

Test	Acceptance Criteria	Test Method <sup>1</sup>	Results		
			Lot # S780004	Lot # S780013	Lot # S780014
Identification <sup>2</sup> A. UV spectra using photodiode array detector  B. HPLC	A. The extracted spectra collected between 200 nm and 350 nm at the apex of the argatroban peak in the <i>Standard Preparation</i> and <i>Finished Product Assay Preparation</i> exhibit maxima at the same wavelength ( $\pm 2$ nm).  B. The chromatogram of the <i>Finished Product Sample Preparation</i> exhibits a major peak for (r)-argatroban and (s)-argatroban, for which the retention times correspond to those exhibited in the chromatogram of the <i>Standard</i> (b) (4)	A. 10-08-03-6457>  B. 10-08-03-6457	A. Meets specification  B. Meets specification	A. Meets specification  B. Meets specification	A. Meets specification  B. Meets specification
Argatroban Assay (Label Claim: 100 mg/mL)	(b) (4) % of Label Claim	10-08-03-6457	(b) (4)		
Impurities: A. Known Impurity (b) (4) B. Any Other Impurity C. Total Impurities	A. NMT (b) (4) B. NMT (b) (4) C. NMT (b) (4)	10-08-03-6457	(b) (4)		

Test	Acceptance Criteria	Test Method <sup>1</sup>	Results		
			Lot # S780004	Lot # S780013	Lot # S780014
Other Requirements Test <sup>2</sup>	Meets requirements	USP <1>	Meets the requirements	Meets the requirements	Meets the requirements
Particulate Matter (Microscopic Particle Count Test)	$\geq$ (b) (4) $\mu$ m: NMT (b) (4) particles/container	USP <788>	(b) (4)		
	$\geq$ (b) (4) $\mu$ m: NMT (b) (4) particles/container				
Bacterial Endotoxins	NMT (b) (4) U/mg	USP <85>	(b) (4)		
Sterility <sup>2</sup>	Sterile	USP <71>	Sterile	Sterile	Sterile

Stability of drug product:

Below is a tabulated summary (table from the Applicant):

Test	Acceptance Criteria	Accelerated (40°C/75% RH) 0, 1, 2, 3, 6 months	Room Temperature (25°C/60% RH) 0, 3, 6, 9, 12, 18 months
		Description	Liquid in an amber glass vial
Visual Inspection A. Clarity B. Particulate Matter C. Visual Color	A. Clarity B. Essentially free of visible particulates C. Colorless to slightly yellow	All comply	All comply
Instrumental Color (b) (4)	NMT (b) (4)	Upward trend; all values are $\leq$ (b) (4)	Slight upward trend; all values are $\leq$ (b) (4)
Argatroban Assay Label Claim: 100 mg/mL	(b) (4) %	No trend; all values vary between (b) (4) %	No trend; all values vary between (b) (4) %
Impurities: A. Known Impurity (b) (4) B. Any Other Impurity C. Total Impurities	A. NMT (b) (4) % B. NMT (b) (4) % C. NMT (b) (4) %	A. Upward trend; all values are $\leq$ (b) (4) % B. Slight upward trend; all values are $\leq$ (b) (4) % C. Upward trend; all values are $\leq$ (b) (4) %	A. Upward trend; all values are $\leq$ (b) (4) % B. Slight upward trend; all values are $\leq$ (b) (4) % C. Upward trend; all values are $\leq$ (b) (4) %
Particulate Matter (Microscopic Particle Count Test)	$\geq$ (b) (4) $\mu$ m: NMT (b) (4) particles/container $\geq$ (b) (4) $\mu$ m: NMT (b) (4) particles/container	All comply	All comply

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/s/  
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SHWU LUAN LEE  
02/02/2011

HALEH SABER  
02/02/2011