

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**201743Orig1s000**

**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: 201-743  
Supporting document/s: SDN-001  
Applicant's letter date: April 13, 2010  
CDER stamp date: April 14, 2010  
Product: Argatroban Injection  
Indication: Prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia  
Applicant: Sandoz Inc. Canada  
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

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# 1 Executive Summary

## 1.1 Recommendations

There are no pharmacology/toxicology issues which preclude the approval of Argatroban Injection for the intended indication.

### 1.1.1 Approvability

Recommend approval.

### 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.

The following presents the FDA proposed language for the nonclinical sections of the label.

8.1 Pregnancy	Pregnancy Category B There are no adequate and well-controlled studies of argatroban use in pregnant women. Developmental studies performed in rats with argatroban at intravenous doses up to 27 mg/kg/day (0.3 times the maximum recommended human dose, based on body surface area) and in rabbits at intravenous doses up to 10.8 mg/kg/day (0.2 times the maximum recommended human dose, based on body surface area) have revealed no evidence of impaired fertility or harm to the fetus. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
8.3 Nursing Mothers	It is not known whether argatroban is excreted in human milk. Argatroban is detected in rat milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from argatroban, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
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.

	Argatroban inhibits thrombin with an inhibition constant (K <sub>i</sub> ) of 0.04 μM. At therapeutic concentrations, argatroban has little or no effect on related serine proteases (trypsin, factor Xa, plasmin and kallikerein). Argatroban is capable of inhibiting the action of both free and clot-associated thrombin.
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	Carcinogenicity studies with argatroban have not been performed. Argatroban was not genotoxic in the Ames test, the Chinese hamster ovary cell (CHO/HGPRT) forward mutation test, the Chinese hamster lung fibroblast chromosome aberration test, the rat hepatocyte, and WI-38 human fetal lung cell unscheduled DNA synthesis (UDS) tests, or the mouse micronucleus test. Argatroban at intravenous doses up to 27 mg/kg/day (0.3 times the recommended maximum human dose based on body surface area) had no effect on fertility and reproductive function of male and female rats.

## 1.2 Brief Discussion of Nonclinical Findings

## 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 (Sandoz) 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

1006435 (Sandoz)

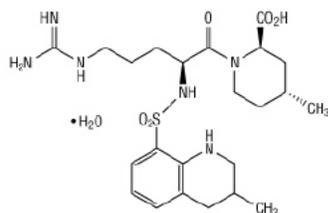
### 2.1.4 Chemical Name

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<sub>23</sub>H<sub>36</sub>N<sub>6</sub>O<sub>5</sub>S•H<sub>2</sub>O/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; previously Encysive).

DMF (b) (4)

## 2.3 Clinical Formulation

### 2.3.1 Drug Formulation

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

Ingredients	Quantity per unit	Percentage	Standards	Function
Argatroban	1 mg	(b) (4)	USP	Active ingredient
Dextrose anhydrous	50 mg	(b) (4)	USP/NF	(b) (4)
Sorbitol	3 mg		NF	
Water for Injection	q.s. to 1 mL		USP/EP	
			NF/EP	

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

Excipients	%	IIG Levels
Dextrose anhydrous	5.0% (50 mg)	5.00%
Sorbitol	0.3% (3 mg)	7.14%
Water for Injection*	q.s. 1 mL	N/AP
		(b) (4) N/AP

The amount of individual excipient is within IIG (inactive ingredient grade) limits.

The comparison of drug product to the RLD (diluted 100 times in 5% dextrose) is provided in the following table:

Ingredients	Sandoz Argatroban Injection in Dextrose, 1 mg/mL	Encysive Argatroban Injection, prior to dilution	Encysive Argatroban Injection, diluted in Dextrose*
Argatroban	1 mg	100 mg	1 mg
Dextrose anhydrous	50 mg	N/A	50 mg
Dehydrated Alcohol**	N/A	(b) (4)	4 mg
Sorbitol	(b) (4)	(b) (4)	3 mg
Water for Injection	q.s. 1 mL	q.s. 1 mL	q.s. 1 mL
	(b) (4)	N/A	N/A

The drug product in the current NDA (Sandoz) is a ready-to-use product of argatroban in dextrose. In comparison with the RLD, the qualitative difference between the two formulations is the removal of dehydrated alcohol and addition of dextrose. The argatroban concentration in Sandoz product is 1 mg/mL. According to the CMC reviewer, there are no concerns regarding the stability of argatroban (b) (4) in the drug product.

Below is a tabulated summary of quality parameters for the drug product, including impurities for 3 lots of Argatroban Injection (1 mg/mL; table from the Applicant):

Test	Method	Specifications	Results		
			1250804_121	1260804_121	1270804_121
Description	Visual	Clear, colorless solution	Conforms	Conforms	Conforms
Identification of:					
Argatroban	LC-0301	A: Rt conforms to standard	Conforms	Conforms	Conforms
		B: UV spectrum conforms to standard	Conforms	Conforms	Conforms

(b) (4)

**2.3.2 Comments on Novel Excipients**

None

**2.3.3 Comments on Impurities/Degradants of Concern**

The proposed specification (b) (4) for each impurity) is in line with ICH Q3B(R2) guidance, taking into consideration the maximum daily dose of 560 mg argatroban.

**2.4 Proposed Clinical Population and Dosing Regimen**

- For prophylaxis or treatment of thrombosis in adult 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 201743 on April 13, 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 specifications proposed for impurities in the drug product (i.e., (b) (4) are acceptable; they are in line with ICH Q3B (R2).

There are no nonclinical issues to be addressed.

## **12 Appendix/Attachments**

None

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/s/  
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SHWU LUAN LEE  
01/20/2011

HALEH SABER  
01/24/2011

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

NDA/BLA Number: 201,743    Applicant: Sandoz

Stamp Date: April 14, 2010

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		Only three published literatures were included as reference. No original pharmacology/toxicology data 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).			The need for additional studies is a review issue and will depend on the impurity profile.
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?			See comment in #1.
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?			See comment in #1.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			Not applied.

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

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
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?			Using RLD package insert.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			Pending on CMC review
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.

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Reviewing Pharmacologist

Date

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Team Leader/Supervisor

Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201743	ORIG-1	SANDOZ INC	ARGATROBAN INJECTION 1 MG/ML

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/s/

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06/07/2010

HALEH SABER  
06/07/2010