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RESEARCH**

APPLICATION NUMBER:

022485Orig1s000

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: 22-485
Supporting document/s: Electronic submission (SDN-001)
Applicant's letter date: March 17, 2010
CDER stamp date: March 17, 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: 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 _i) 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

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)

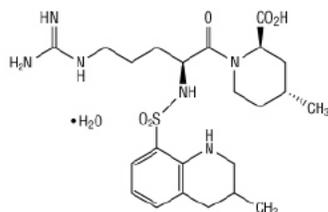
2.1.4 Chemical Name

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

C₂₃H₃₆N₆O₅S•H₂O/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 in Sodium Chloride, 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
Sodium Chloride	9 mg	(b) (4)	USP/BP/ EP	(b) (4)
D-Sorbitol	3 mg	(b) (4)	NF	(b) (4)
Water for Injection	q.s. to 1 mL	(b) (4)	USP/EP	(b) (4)
		(b) (4)	NF/EP	(b) (4)

The amount of individual excipient is within IIG (inactive ingredient grade) limits (data not shown).

The table below is the comparison of drug product formulation between Sandoz product and the RLD (table from the Applicant):

Comparison of the Sandoz Canada Inc. Product and the diluted RLD Product

Ingredients	Sandoz Canada Inc. Argatroban Injection	Argatroban Injection diluted in Sodium Chloride 0.9% ((b) (4) bag)
Argatroban	1 mg/mL	1 mg/mL
Dehydrated Alcohol	Not applicable	4 mg/mL
Sorbitol	3 mg/mL	3 mg/mL
Sodium Chloride	9 mg/mL	9 mg/mL
(b) (4)		
Water for Injection	q.s.1 mL	q.s.1 mL

The drug product in the current NDA is a ready-to-use solution of argatroban in normal saline. In comparison with the RLD, the qualitative difference between the two formulations is the removal of dehydrated alcohol to increase argatroban solubility to create a ready-to-use product. According to the CMC reviewer (Dr. Ravindra K. Kasliwal), there are no concerns regarding stability of API (b) (4) in the drug substance.

The comparative formulation between Sandoz argatroban in NaCl (1 mg/mL) and Argatroban Injection (RLD) is tabulated as following (table from the Applicant). As noted, the impurity levels in the three lots of Sandoz argatroban solution are lower than those in the RLD or less than the ICH Q3B threshold ((b) (4) for each individual impurity).

Physico-Galenical Content and Analytical Tests performed on the RLD and Sandoz Canada Inc. products.

Parameters	Argatroban Injection diluted in Saline	Argatroban Injection in Sodium Chloride (Sandoz Canada Inc.)		
	Lot C305939 Exp. MA 2009	1220804_121	1230804_121	1240804_121
Description	Clear, colourless solution	Clear, colourless solution	Clear, colourless solution	Clear, colourless solution
Viscosity cPs at 25°C	1.0 (20°C)	1.0114	1.0097	1.0085
Density (g/mL) at 25°C	0.9993 (20°C)	1.0046	1.0045	1.0046
pH	6.26	6.0	6.0	5.9
Osmolality (mOsm/kg)	401	301	304	301
Enantiomeric ratio R/S%	64/36	64/36	64/36	64/36
Assay of Argatroban (mg/mL)	0.94	0.99	0.99	0.99

(b) (4)



2.3.2 Comments on Novel Excipients

None

2.3.3 Comments on Impurities/Degradants

The specification of the contents of impurities in the drug product is summarized in the table below: (data excerpted from the Applicant's report)

Test	Method	Specifications	Results		
			1220804_121	1230804_121	1240804_121
Description	Visual	Clear, colorless solution	Conforms	Conforms	Conforms
Identification					
Argatroban	LC-0301	A: Rt conforms to standard	Conforms	Conforms	Conforms
		B: UV spectrum conforms to standard	Conforms	Conforms	Conforms
Sodium Chloride	USP <191>	Positive for chlorides	Conforms	Conforms	Conforms

(b) (4)

Taking into account the maximum daily dose as 560 mg, impurity levels (b) (4) is in line with the ICH Q3B (R2) guidance.

2.4 Proposed Clinical Population and Dosing Regimen

The clinical population is identical to that described in the label of the RLD

- 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 22485 on March 17, 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/

SHWU LUAN LEE
12/20/2010

HALEH SABER
12/20/2010

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22485

Applicant: Sandoz canada

Stamp Date: March 17, 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**

	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.
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.

Shwu-Luan Lee, Ph.D.

5/3/2010

Reviewing Pharmacologist

Date

Team Leader/Supervisor

Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22485	ORIG-1	SANDOZ INC	ARGATROBAN INJECTION 1 MG/ML

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/s/

SHWU LUAN LEE
05/04/2010

HALEH SABER
05/06/2010