

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201743Orig1s000

MEDICAL REVIEW(S)

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Acting Division Director
Subject	Division Director Summary Review
NDA/BLA #	201743
Supplement #	
Applicant Name	Sandoz Canada, Inc.
Date of Submission	April 14, 2010
PDUFA Goal Date	February 14, 2011
Proprietary Name / Established (USAN) Name	Argatroban Injection in Dextrose
Dosage Forms / Strength	1 mg/mL
Proposed Indication(s)	Indicated for prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT), and as an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI).
Action/Recommended Action for NME:	Tentative Approval

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Firoozeh Alvandi, M.D./ Virginia Kwitkowski, RNP
Statistical Review	
Pharmacology Toxicology Review	Shwu Luan Lee Ph.D./ Haleh Saber, Ph.D.
CMC Review/OBP Review	Ravindra Kasliwal, Ph.D./Janice Brown, Ph.D.
Microbiology Review	Stephen Langille, Ph.D.
Clinical Pharmacology Review	Hua Zhang, Ph.D./ Julie Bullock, Pharm.D. Angelica Dorantes, Ph.D./Patrick J. Marroum, Ph.D.
DDMAC	
DSI	N/A
CDTL Review	Sarah Pope Miksinski, Ph.D.
OSE/DMEPA	Yelena Maslov, Pharm. D./ Carol Holquist, R. Ph.
OSE/DDRE	
OSE/DSRCS	
Other	

OND=Office of New Drugs
 DDMAC=Division of Drug Marketing, Advertising and Communication
 OSE= Office of Surveillance and Epidemiology
 DMETS=Division of Medication Errors and Technical Support
 DSI=Division of Scientific Investigations
 DDRE= Division of Drug Risk Evaluation
 DSRCS=Division of Surveillance, Research, and Communication Support
 CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

NDA 201743 is a 505 b2 application for argatroban which was submitted to the Agency on April 14, 2010. The Agency filed the application and granted a standard review with a PDUFA goal date of February 14, 2011.

2. Background

The Reference Listed Drug (RLD) for this submission is Argatroban Injection (NDA 20-883), which is currently marketed by Pfizer. This NDA was approved on June 30, 2000. The RLD has Waxman-Hatch Exclusivity which does not expire until May 5, 2011.

3. CMC/Device

There were no issues identified that preclude approval.

Based on the stability data provided, a 12-month expiration dating period is granted for room temperature storage conditions.

4. Nonclinical Pharmacology/Toxicology

There were no new nonclinical pharmacology/toxicology studies provided in this submission. The pharmacology/toxicology review team reviewed the submission and participated in labeling review. No issues that would preclude approval were identified.

5. Clinical Pharmacology/Biopharmaceutics

No issues that would preclude approval were identified. The only information submitted for review was data to support bridging between this 505 b2 product and the RLD.

6. Clinical Microbiology

This argatroban product is [REDACTED] (b) (4). There are no outstanding microbiology issues related to the manufacturing process and/or overall sterility assurance. No issues that would preclude approval were identified.

7. Clinical/Statistical-Efficacy

No new clinical data was submitted. Dr. Alvandi and Ms. Kwitkowski reviewed the labeling.

8. Safety

No new safety issues have been identified.

9. Advisory Committee Meeting

This product is not a NME.

10. Pediatrics

This product is a 505 b2.

11. Other Relevant Regulatory Issues

The only unresolved relevant regulatory issues is the fact that the Pfizer argatroban product still has patent exclusivity which will not expire until May 5, 2011. Therefore this application may only receive a tentative approval.

12. Labeling

All disciplines made recommendations for labeling which were incorporated.

13. Decision/Action/Risk Benefit Assessment

- - Recommended regulatory action
Tentative Approval
 - Risk Benefit Assessment
N/A

- Recommendation for Post marketing Risk Management Activities
None

- Recommendation for other Post marketing Study Requirements/
Commitments

None

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/s/

ANN T FARRELL
02/09/2011

Cross-Discipline Team Leader Review

Date	07-FEB-2010
From	Sarah Pope Miksinski, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	201743
Supplement#	
Applicant	Sandoz Canada, Inc.
Date of Submission	13-APR-2010
PDUFA Goal Date	14-FEB-2011
Proprietary Name / Established (USAN) names	Argatroban Injection
Dosage forms / Strength	1 mg/mL
Proposed Indication(s)	Indicated for prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT), and as an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI).
Recommended:	Tentative Approval

1. Introduction

NDA 201743 was submitted to the Agency on 13-APR-2010. The Agency filed the application and granted a standard review with a PDUFA goal date of 14-FEB-2011. There were no comments conveyed in the Agency's 10-JUN-2010 filing letter.

This CDTL memo serves to highlight the critical approvability issues discussed in all review disciplines and recommends a "Tentative Approval" action for this application. All individual discipline reviews may be found in DARRTS. Final and acceptable container labels were provided on 12-JAN-2011. Final Package Insert (PI) labeling was received on 27-JAN-2011 and was confirmed as final and acceptable for all disciplines.

2. Background

The Reference Listed Drug (RLD) for this submission is Argatroban Injection (NDA 20-883), which is currently marketed by Pfizer. The qualitative difference between the RLD and the proposed formulations is that dehydrated alcohol was removed from the currently proposed product, in order to create a ready to use formulation. The RLD drug is not a ready to use formulation and must be diluted prior to administration. The other ingredients and their amounts in the diluted RLD formulation and the currently proposed formulation are the same. The Chemistry Review contains (page 20) a detailed comparison of the RLD and currently proposed formulations.

Dosing Regimen and Administration

For HIT/HITTS, the recommended initial dose of Argatroban Injection for adult patients without hepatic impairment is 2 mcg/kg/min, administered as a continuous infusion. For Percutaneous Coronary Interventions (PCI) in HIT/HITTS patients, an infusion of Argatroban should be started at 25 mcg/kg/min and a bolus of 350 mcg/kg administered via a large bore intravenous (IV) line over 3 to 5 minutes. Subsequent dosing adjustments are made in both regimens as clinically indicated.

3. CMC

NDA 201743 was initially submitted on 13-APR-2010 as a 505(b)(2) application. The NDA included a full dossier of CMC information, along with proposed container/carton and PI labeling. Chemistry Review #1 (13-JAN-2011) recommends approval of this NDA and identified no outstanding CMC issues for the NDA.

- General product quality considerations
There are no outstanding product quality issues for this NDA. During the review, the CMC reviewer confirmed the acceptability of all cross-referenced Drug Master Files (DMFs) to support this proposed formulation. The CMC reviewer also confirmed all standard and required aspects of product quality (see the 13-JAN-2011 review for details).

NDA 201743 included a request for a biowaiver. This request was evaluated in a 31-JAN-2011 review (Dr. A. Dorantes) which grants the Applicant's request.

The Applicant's NDA submission included up to 18 months of real time (25°C/60% RH) (b)(4) stability data for three registration batches of the drug product. All studies were conducted on both upright and inverted configurations. The reviewer conducted linear regression using the provided stability data, and subsequently noted concern regarding the potential for Impurity (b)(4) levels to exceed the Applicant's proposed specification (NMT (b)(4)) at the (b)(4) month timepoint. Therefore, a deficiency was issued to the Applicant on 03-JAN-2011. In a 12-JAN-2011 response, the Applicant amended the proposed expiration dating period to 12 months, when stored in the original container at room temperature, protected from light, and including a "Do Not Freeze" statement. The Applicant's approved expiration dating period should be captured in the action letter, as there were negotiations during the review clock.

- Facilities review/inspection
An Establishment Evaluation Request (EER) was submitted to the Office of Compliance, and an overall acceptable recommendation was issued for the application on 09-SEP-2010.
- Microbiology

Argatroban Injection is a (b)(4) product. The microbiology reviewer (Dr. S. Langille) recommends approval of this NDA in his review dated 20-JAN-2011. There are no outstanding microbiology issues related to the manufacturing process and/or overall sterility assurance.

- Other notable issues (resolved or outstanding)
None

4. Nonclinical Pharmacology/Toxicology

There were no new nonclinical pharmacology/toxicology studies provided in this submission. The final Pharmacology/Toxicology memo was finalized in DARRTS on 24-JAN-2011 and captures a recommendation of approval for the NDA (see review by Dr. S. Lee). The finalized memo also references the CMC review and confirms (page 10) that acceptance criteria for all impurities in the drug substance and drug product are proposed at levels at or below the ICH qualification (Q3B, R2) threshold. This review also captures related revisions to the PI.

5. Clinical Pharmacology

There were no clinical pharmacology data submitted to this NDA, with the exception of a bridging study conducted to support the bioequivalence of the currently proposed product to the RLD. The clinical pharmacology reviewer (Dr. H. Zhang) provided an assessment of this study and subsequently recommends approval of this NDA in her review dated 25-JAN-2011. This review also captures related revisions to the PI.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

There are no new clinical data provided in the current submission. The clinical reviewer (Dr. F. Alvandi) recommends tentative approval of this NDA in a 26-JAN-2011 memorandum. This review also captures related revisions to the PI.

8. Safety

No new clinical data were provided for this submission.

9. Advisory Committee Meeting

Not applicable

10. Pediatrics, Geriatrics, and Special Populations

A 27-JUL-2010 review by Tammie Howard, R.N., MSN, identifies several suggested revisions to the “Pregnancy and Nursing Mothers” section of the PI. These revisions were discussed and incorporated, as appropriate, during the review and labeling negotiations.

11. Other Relevant Regulatory Issues

- Application Integrity Policy (AIP): This was not raised during the pre-approval inspections for this NDA.
- Exclusivity or patent issues of concern: Given a 3-year Waxman-Hatch (WH) Exclusivity granted to the innovator (Pfizer), approval of this Applicant’s NDA 22485 will be tentative until the date of expiration of the WH Exclusivity (05-MAY-2011).
- Financial disclosures: Not applicable
- Other GCP issues: None
- DSI audits: Not applicable
- Other discipline consults: None
- Any other outstanding regulatory issues: None

12. Labeling

General:

All disciplines participated in internal labeling meetings held throughout the review clock. Specific labeling recommendations are captured in each discipline-specific review.

Proprietary name:

There was no proprietary name proposed for this product.

DMEPA comments:

In a review dated 13-DEC-2010, DMEPA identified several specific deficiencies in the proposed container/carton labeling. These deficiencies were subsequently conveyed to the firm. The Applicant submitted revised container/carton labels on 12-JAN-2011, which incorporated all issued recommendations.

Of particular note is the Agency (DMEPA) recommendation to remove the “Do Not Freeze” statement from all container/carton labeling. This issue was discussed internally as part of the labeling review for NDA 22-485, and specific discussion points are captured in the 27-DEC-2010 CDTL memo for NDA 22-485. These specific details are not re-captured here, but the Agency’s ultimate agreement that the “Do Not Freeze” statement should be replaced in the labeling was similarly implemented in the current case (NDA 201743).

Issues not resolved at the time of CDTL memo completion:

All disciplines were involved with in labeling discussions and review. A proposed, final and acceptable PI was submitted by the Applicant on 27-JAN-2011. This PI has been confirmed as acceptable by all disciplines.

Carton and immediate container labels:

See above section titled “DMEPA comments.” See also the 27-DEC-2010 CDTL memo for NDA 22-485.

Patient labeling/Medication guide:

This is not required for this product.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**
This reviewer recommends tentative approval of this NDA based on the absence of any outstanding review issues for all disciplines. The approval must be tentative at this time, due to the unexpired WH exclusivity of the innovator (Argatroban Injection, Pfizer, NDA 20-883).
- **Risk Benefit Assessment**
The review of this NDA is based primarily on chemistry, manufacturing and controls data. The NDA is recommended for approval from all remaining disciplines, and there are no outstanding issues from any disciplines, which would preclude the drug’s approval (pending the outstanding WH exclusivity of the innovator).
- **Recommendation for Postmarketing Risk Management Activities**
This does not apply to this NDA.
- **Recommendation for other Postmarketing Study Commitments**
None
- **Recommended Comments to Applicant**
In order to capture the negotiation and confirmation of expiration dating period, the following language should be inserted into the action letter: “The tentatively approved expiration dating period is twelve (12) months for the drug product, when stored between 20°C and 25°C (See USP Controlled Room Temperature) in the original container. Protect from Light. Do Not Freeze.”

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/s/

SARAH P MIKSINSKI
02/07/2011

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/s/

EBLA ALI IBRAHIM
01/31/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			X	
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (<i>e.g.</i> , QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?			X	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _Yes_

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

Firoozeh Alvandi, MD	06/07/2010
Reviewing Medical Officer	Date
Robert Kane, MD	
Clinical Team Leader	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/

FIROOZEH ALVANDI
06/07/2010

ROBERT C KANE
06/08/2010