CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022485Orig1s000

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 # **Supplement #**	22485
Applicant Name	Sandoz Canada, Inc.
Date of Submission	March 16, 2010
PDUFA Goal Date	January 17, 2011
Proprietary Name / **Established (USAN) Name**	Argatroban Injection in Sodium Chloride
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.
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 22485 is a 505 b2 application for argatroban which was submitted to the Agency on March 16, 2010. The Agency filed the application and granted a standard review with a PDUFA goal date of January 17, 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. Both the primary reviewer and the CDTL noted that the product should not be kept in the freezer as argatroban may precipitate out from solution.

From the CMC CDTL memo:

Based on the stability data provided, a 24-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 (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 not a NME.

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
01/13/2011

Cross-Discipline Team Leader Review

Date	27-DEC-2010
From	Sarah Pope Miksinski, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	22485
Applicant	Sandoz Canada, Inc.
Date of Submission	16-MAR-2010
PDUFA Goal Date	17-JAN-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 22485 was submitted to the Agency on 16-MAR-2010. The Agency filed the application and granted a standard review with a PDUFA goal date of 17-JAN-2011. There were no comments conveyed in the Agency's 11-MAY-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 27-DEC-2010. Final Package Insert (PI) labeling was also received on 27-DEC-2010 but needs to be confirmed as final and acceptable for all disciplines prior to issuing the action letter.

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 22485 was initially submitted on 16-MAR-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 (21-DEC-2010) recommends approval of this NDA and identified no outstanding CMC issues for the NDA, with the exception of a final container/carton labeling recommendation and pending PI labeling.

- 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 21-DEC-2010 for details).

  NDA 22485 included a request for a biowaiver. This request was evaluated in a 23-DEC-2010 review (Dr. A. Dorantes) which grants the Applicant's request.

  The Applicant's NDA submission, including the 29-JUL-2010 amendment, included 24 months of real time (25^{o}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. Based on the stability data provided, a 24-month expiration dating period is granted for room temperature storage conditions.

- 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 21-DEC-2010. 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 20-DEC-2010 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 11) 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 14-DEC-2010. 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 approval of this NDA in a 13-DEC-2010 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 12-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 in combination with previous CMC container/carton deficiencies on 15-DEC-2010. The Applicant submitted revised container/carton labels on 17-DEC-2010, which incorporated all issued recommendations. Overlapping container/carton labeling comments are covered in the 21-DEC-2010 CMC review.

Subsequent to the Applicant's 17-DEC-2010 submission, internal discussions between the CMC and DMEPA reviewers resulted in the development of an individual further recommendation for container/carton labeling. Initially, the DMEPA reviewer had recommended that the statement "Do Not Freeze" be removed entirely from the container/carton labels; however, the chemistry review team views this statement as critical to the quality of an injectable product. A summary of the chemist's assessment of the "Do Not Freeze" statement is located in the 21-DEC-2010 chemistry review.

On 21-DEC-2010, the DMEPA and CMC reviewers agreed that the statement "Do Not Freeze" should be replaced in the container/carton labels, provided that it was not placed on the principal display panel. This final recommendation was issued to the Applicant on 21-DEC-2010, and acceptable updated container/carton labels were provided by the Applicant on 27-DEC-2010.

Issues not resolved at the time of CDTL memo completion:
All disciplines were involved with in labeling discussions and review. A proposed and final PI was submitted by the Applicant on 27-DEC-2010. This PI should be confirmed as acceptable by all disciplines, prior to issuing the action letter.

Carton and immediate container labels:
See above section titled "DMEPA comments." Overlapping container/carton labeling comments are also covered in the 21-DEC-2010 CMC review.

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 and provided that the 27-DEC-2010 PI is determined to be acceptable 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
  None

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/s/

SARAH P MIKSINSKI
12/27/2010

Division of Hematology Products
Clinical Team Leader
Memorandum to File

NDA: 22, 485
Product: Argatroban Injection, 1 mg/mL (125 mL) in Sodium Chloride
Sponsor: Sandoz, Inc.
Submission Date: 03/16/10
PDUFA Date: 01/16/10
Date of Review: 12/14/10
Supporting Document Number: 1

Review Team
CDTL: Sarah Pope Miksinski (CMC)
Clinical: Firoozeh Alvandi, MD (DHP)
Regulatory Project Manager: Ebla Ali Ibrahim (DHP)
Pharmacology Toxicology: Shwu Luan Lee
Clinical Pharmacology: Hua Zhang
Chemistry, Manufacturing, and Controls: Ravindra Kasliwal

Executive Summary: The Sponsor submitted a New Drug Application for Argatroban Injection, 1 mg/mL (125 mL) in Sodium Chloride under Section 505 (b)(2) of the Federal Food Drug, and Cosmetic Act and 21 CFR 314.54. This application refers to the Sandoz pre-IND file 101,957 for Argatroban Injection. The application also refers to the approved Reference Listed Drug from Pfizer, Argatroban 100 mg/mL under NDA 20-883.

Product: Argatroban is an anticoagulant that is a small molecule direct thrombin inhibitor. It 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 aggregration.

Differences between RLD and Proposed Product:
The RLD Argatroban contains dehydrated alcohol. The alcohol is needed to maintain a concentrated solution, such as 100mg/mL, as in the RLD. Sandoz proposes that a ready-to-use product reduces the manipulation of the product required by health care professionals. In addition, the alcohol excipient is not compatible with equipment commonly used in manufacturing injectable products because it can extract plasticizers (like DHP) from plastic and PVC equipment, intravenous bags, and tubing. DHP is a phthalate which may lead to adverse health effects. Avoidance of reconstitution and removal of denatured alcohol from the formulation may be an improvement to the product.

Status of Reference Listed Drug:
The Pfizer Argatroban product marketing exclusivity expires on May 5, 2011. This includes a 3-year Waxman-Hatch (WH) Exclusivity granted to the innovator (Encysive, now Pfizer) for the addition of pediatric safety data to the product labeling.

Proposed Indications:

- Argatroban is indicated as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia.
- Argatroban is indicated as an anticoagulant in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI).

Waiver Requests
Sandoz requested and was granted an e-CTD waiver on 10/06/08.
The Sponsor has submitted, with this NDA, an *in vivo* bioequivalence waiver request.
The Sponsor has completed *in vitro* equivalence testing, which is submitted in the NDA.

The application did not contain clinical data or summaries for review. The Sponsor references the approved RLD for Agratroban from Pfizer. The Sandoz Argatroban product differs from the RLD due to absence of alcohol and that the product requires no reconstitution prior to use.

Product Labeling
Labeling was submitted in the original application in non-PLR format. PLR format is now required for new drug applications. The Sponsor was requested to resubmit product labeling in PLR format. Sandoz submitted the proposed labeling in PLR format on 04/01/10.

It was the recommendation of the clinical team, with consultation from the Pediatric and Maternal Health consultant, that pediatric dosing and safety information be retained in the proposed labeling.

Regulatory Recommendation:
I concur with the recommendation of the primary clinical reviewer, Firoozeh Alvandi, MD. Recommend tentative approval of the Sandoz Argatroban product until the expiration of Pfizer's marketing exclusivity on May 5, 2011.

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/s/

VIRGINIA E KWITKOWSKI
12/14/2010

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 022485 **Applicant: Sandoz Canada** **Stamp Date: 3-16-2010**

Drug Name: Argatroban 1mg/mL (125 mL) in Sodium Chloride **NDA/BLA Type: NDA 505 (b)(2)**

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Non eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?		X		
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?		X		Hyperlinks are nonfunctional
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?		X		PLR labeling requested
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?			X	
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			RLD Argatroban by (Encysive) Pfizer - 505(b)(2)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:			X	

File name: Clinical Filing Checklist for NDA 22485

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 arythmogenic potential of the product (*e.g.*, 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 (*e.g.*, 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	4/29/2010
Reviewing Medical Officer	Date
Robert Kane, MD	4/30/2010
Clinical Team Leader	Date

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

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/s/

FIROOZEH ALVANDI
05/03/2010

ROBERT C KANE
05/03/2010