

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201811Orig1s000

MEDICAL REVIEW(S)

FILE MEMORANDUM

Memo Date: February 11, 2015
To NDA: 201811
Submission Date: January 23, 2015
FDA Received Date: January 23, 2015
EDR Location: <\\CDSESUB1\evsprod\NDA201811\201811.enx>

From: Hyon-Zu Lee, Pharm.D., Clinical Reviewer; Division of Hematology Products (DHP)
Subject: Argatroban
Via: Virginia Kwitkowski, MS, RN, ACNP-BC, Clinical Team Leader, DHP

ISSUE: N/A

ACTIONS RECOMMENDED: Tentative approval

Summary of Review Findings: No clinical safety or efficacy data were submitted in this NDA application. There were no safety issues from the review of recent literature. The proposed label is acceptable from clinical perspective. For recommendations regarding this NDA, please refer to reviews by other disciplines.

Background:

This is a Class 1 resubmission for a 505(b)(2) application by Fresenius Kabi USA, LLC. This is the fifth cycle for this application. The reference drug product is Pfizer's Argatroban Injection, 250 mg/2.5 mL (NDA 20883). Fresenius' proposed drug product has the same concentration as the listed drug. It differs from the LD in the inactive ingredient in that the proposed drug product replaced dehydrated alcohol and D-sorbitol with propylene glycol as a (b) (4)

DHP issued a complete response letter on February 28, 2014 in the previous cycle due to the Fresenius drug product manufacturing and testing site located in Grand Island, NY which was found unacceptable and received Withhold recommendation by the Office of Compliance.

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/s/

HYON-ZU LEE
02/11/2015

VIRGINIA E KWITKOWSKI
02/11/2015

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA #	201811
Supplement #	
Applicant Name	Fresenius Kabi USA, LLC.
Date of Submission	September 13, 2013
PDUFA Goal Date	March 13, 2014
Proprietary Name / Established (USAN) Name	Argatroban Injection in Sodium Chloride
Dosage Forms / Strength	100 mg/mL concentration
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:	Complete Response

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Virginia Kwitkowski, RNP
Statistical Review	N/A
Pharmacology Toxicology Review	Shwu Luan Lee Ph.D./ Haleh Saber, Ph.D.
CMC Review/OBP Review	Anne Marie Russell, Ph.D./Janice Brown, M.S.
Microbiology Review	J. Metcalfe, Ph.D./ Bryan S. Riley
Clinical Pharmacology Review	Hua Zhang, Ph.D./ Julie Bullock, Pharm.D.
DDMAC	
DSI	N/A
CDTL Review	Janice Brown, M.S.
OSE/DMEPA	
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

This submission for NDA 201811, a 505 b2 application for argatroban, is a response to a Complete Response Letter sent on April 5, 2013. The April 5, 2013 Complete Response letter identified two product quality deficiencies and a facility inspection deficiency that precluded approval.

The Agency filed the resubmission and granted a PDUFA goal date of March 13, 2014.

2. Background

The Reference Listed Drug (RLD) for this submission is Argatroban Injection (NDA 20-883), which is currently marketed by Pfizer.

The following two product quality deficiencies were conveyed in the April 5, 2013 Complete Response Letter.

1. Provide the Analytical Procedure and Validation of Analytical Procedure for the method used in the Identification Test cited in "Table 3.2.S.5-1 Specification for Individual Isomers Argatroban 21-S and 21-R" and demonstrated adequacy of the method to distinguish the individual isomers.
2. Provide drug product stability data for all attributes, utilizing all test methods listed in the specifications.

3. CMC/Device

After the last review cycle, there were two remaining deficiencies in addition to a deficiency regarding the facility inspection. Dr. Russell notes in her primary review that these deficiencies are now resolved except for the facility deficiency. She noted in her review:

The drug product manufacturing site; Grand Island, NY failed inspection. The NDA received an Overall Recommendation of Withhold from the Office of Compliance on

06-DEC-2013.

Therefore until inspectional issues are resolved, this application cannot be approved.

I concur with the CMC review team that the facility issue precludes approval.

4. Nonclinical Pharmacology/Toxicology

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 *in vitro* equivalence data to support bridging between this 505 b2 product and the RLD.

6. Microbiology

No issues that would preclude approval were identified.

7. Clinical/Statistical-Efficacy

No new clinical data was submitted. Previously Dr. Alvandi and Ms. Kwitkowski had 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

None

12. Labeling

All disciplines made recommendations for labeling.

13. Decision/Action/Risk Benefit Assessment

- - Recommended regulatory action
Complete Response letter will include a statement that the inspection of the Grand Isle Facility revealed problems that preclude 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
02/28/2014

Cross-Discipline Team Leader Review

Date	See Electronic Date Stamp
From	Janice Brown M.S.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 201811 (4 th review cycle)
Applicant	Fresenius Kabi USA, LLC
Date of Submission	September 13, 2013 (received September 13, 2013) Original NDA submitted on 02-Apr-2010 (received 05-Apr-2010)
PDUFA Goal Date	March 13, 2014
Proprietary Name / Established (USAN) names	Argatroban Injection
Dosage forms / Strength	Injection, solution, concentrate/250 mg/2.5 mL vial (100 mg/mL)
Proposed Indication(s)	<ol style="list-style-type: none"> 1. Indicated for prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT). 2. As an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI).
Recommended:	Complete Response

1. Introduction

Argatroban is a small molecule, synthetic direct thrombin inhibitor derived from L-arginine and approved for intravenous administration for treatment and prevention of thrombosis in patients with heparin-induced thrombocytopenia (HIT) and for anticoagulation in patients with HIT who are undergoing percutaneous coronary interventions (PCI). The current application for Argatroban Injection 250 mg/2.5 mL vial (100 mg/mL) aqueous solution was submitted as a 505(b)(2) NDA. The product must be diluted to a final concentration of 1 mg/mL in 0.9% sodium chloride injection, 5% dextrose injection, or Lactated Ringer's injection prior to intravenous infusion. The innovator product (NDA 20-883, Argatroban Injection, 250 mg/2.5 mL) is also a concentrated solution which must be diluted prior to use. The inactive ingredient used in the Argatroban Injection formulation by Fresenius Kabi differs from those used in the listed drug (LD) Argatroban product. The qualitative difference between the LD and the proposed formulation is that dehydrated alcohol and D-sorbitol was replaced with propylene glycol as a (b) (4).

2. Background

This NDA was originally submitted on April 2, 2010 (received on April 5, 2010). This is the fourth review cycle for this application. See the Cross-Discipline Team Leader (CDTL) reviews dated February 16, 2011, July 20, 2012, and March 21, 2013 for details of the regulatory history prior to this NDA resubmission and reviews for a summary and details of the application review history prior to this cycle. On April 5, 2013 the Division issued a Complete Response letter to the sponsor citing unresolved chemistry, manufacturing and controls (CMC) deficiencies and manufacturing facility issues that remained to be resolved before the product can be approved.

The sponsor submitted a response to the CR letter on September 13, 2013 (received on September 13, 2013).

3. CMC

CMC: The applicant has satisfactorily addressed the product quality deficiencies in the April 5, 2013 Complete Response letter. The NDA received an Overall Recommendation of Withhold from the Office of Compliance on February 4, 2014. The Fresenius Kabi drug product manufacturing and testing site located in Grand Island, NY was found unacceptable. As a result of the Withhold recommendation from the Office of Compliance, CMC is recommending a Complete Response action for this NDA. The deficiency for the manufacturing facility can be found under item 13 in this review.

Microbiology - The microbiology reviewer (John Metcalfe, Ph.D.) previously recommended approval of this NDA in his review dated February 25, 2013. The reviewer filed an updated

memo dated January 31, 2014 indicating that there is no new product quality microbiology information in the resubmission and recommended approval of the NDA.

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer (Shwu-Luan Lee, Ph.D.) previously recommended approval of the NDA in her review dated June 4, 2012. Since there was no pharmacology-toxicology information in the resubmission, the reviewer indicated that there was no action necessary and the NDA is recommended for approval in her review dated February 5, 2014.

5. Clinical Pharmacology/Biopharmaceutics

The biopharmaceutics reviewer (Angelica Dorantes, Ph.D.) previously recommended approval of the NDA in her review dated April 24, 2012 in the second review cycle. The reviewer filed an updated memo dated February 4, 2014 indicating that there is no new biopharmaceutics information in the resubmission and recommended approval of the NDA.

The clinical pharmacology reviewer (Hua Lillian Zhang, Ph.D.) previously recommended approval of the NDA in her review dated February 9, 2011. Since there was no clinical pharmacology information in the resubmission, the reviewer (Young-Jin Moon, Ph.D.) indicated that there was no action necessary in her review dated January 20, 2014.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

No new efficacy information is included in the resubmission. There are no outstanding clinical or statistical issues that would preclude approval of the NDA.

8. Safety

The clinical review of the resubmission was completed by Adam George, Pharm.D. on January 31, 2014. The applicant submitted a safety update consisting of four published articles. The clinical reviewer found that referenced articles provided by the applicant were not pertinent to the proposed product in this application since they do not discuss the formulation of Argatroban injection proposed in this NDA. The clinical reviewer did not identify any deficiencies and recommends an approval of the NDA.

9. Advisory Committee Meeting

There was no Advisory Committee meeting held for this application.

10. Pediatrics

There is no new information in the resubmission that would require another Pediatric and Maternal Health Staff (PMHS) review.

11. Other Relevant Regulatory Issues

Manufacturing Facilities: On February 4, 2014 the Office of Compliance issued an overall withhold recommendation for this application.

12. Labeling

The proposed labeling for the Fresenius Kabi argatroban is essentially the same in content as that of the innovator LD product, except for the Description and How Supplied sections of the labeling. The formatting of the applicant's proposed labeling has been constructed to comply with the requirements of the Physician's Labeling Rule (PLR).

The exact wording of the labeling in the PLR format has been reviewed and comments from all disciplines were conveyed to the applicant. Since a Complete Response action is planned, the proposed labeling was not reviewed in this cycle.

13. Recommendations/Risk Benefit Assessment

The CMC deficiencies have been resolved. No pharmacology/toxicology or clinical pharmacology issues have been found to preclude approval. Clinical review finds the application adequate and recommends approval. CMC did not recommend approval of the NDA due to the withhold recommendation from the Office of Compliance for the facility used to manufacture the Argatroban drug product.

- Recommended Regulatory Action

A "Complete Response" action is recommended for this NDA based on the withhold recommendation from the Office of Compliance.

- Risk Benefit Assessment

Due to the withhold recommendation from the OC, this product is currently unsuitable for commercial production and marketing.

- Recommendation for Postmarketing Risk Management Activities:

None

- Recommendation for other Postmarketing Study Commitments:

None identified

- Recommended Comments to Applicant

Insert the following language into the action letter:

During a recent inspection of the Fresenius Kabi, Grand Island, NY facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

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/s/

JANICE T BROWN
02/05/2014

HASMUKH B PATEL
02/05/2014
Signed for Dr. Ramesh Sood.

File Memorandum

NDA: 201811

Applicant: Fresenius Kabi USA, LLC.

Product: Argatroban Injection 100 mg/mL (2.5mL in (b) (4) vial)

Resubmission date: September 13, 2013

Clinical reviewer: Adam George, PharmD.

Clinical team leader: Virginia Kwitkowski, M.S., R.N., A.C.N.P.-B.C.

Regarding: Class 2 resubmission of 505(b)(2) NDA

Application background

The Applicant has submitted a Class 2 resubmission for a 505(b)(2) for an argatroban formulation that differs from the listed drug (LD) in its inert ingredient. The inert ingredient in the Applicant's proposed argatroban is 954 mg propylene glycol (the inert ingredients in the LD are (b) (4) mg D-sorbitol, (b) (4) mg dehydrated alcohol). The formulation proposed in the 505(b)(2) application has not been approved by the Agency and the Applicant has not conducted clinical trials with this formulation. The Applicant stated in the cover letter for this resubmission that no changes have been made to the labeling that was submitted for the last review cycle.

On April 5, 2013 the Agency issued the Applicant a Complete Response letter for their 505(b)(2) application for Argatroban Injection 250 mg/2.5mL vial (100 mg/mL). The reason for the complete response was that the Applicant needed to address the following product quality issues:

1. The Applicant needs to provide the analytic procedure and validation of analytical procedure in the identification test for the individual isomers of 21-R and 21-S argatroban
2. The Applicant needs to provide drug product stability data for all attributes, utilizing all test methods listed in the specifications

In the Complete Response letter the Agency also requested that the Applicant provide a safety update as described by 21 CFR 314.50(d)(5)(vi)(b).

In the September 13th class 2 resubmission, the Applicant provided a safety update which consists of 4 published articles. The table below provides a brief description of each article.

Identification of Literature Source	Dose of Argatroban / Number of Patients (N)	Summary of Study Design	Primary Safety Results
Cruz-Gonzalez / 2012 / (1)	Variable dosing regimens were reviewed in this patient population. The number of patients was not reported.	These authors reviewed potential use of argatroban for the treatment of acute coronary syndrome and presented the pharmacokinetic data currently available in this patient population. The authors also presented an overview of the safety and tolerability of the drug from a postmarketing perspective.	<ul style="list-style-type: none"> Available postmarketing data demonstrated that argatroban used in its approved indications is well tolerated. The most significant postmarketing adverse events for argatroban were hemorrhagic complications, but they were infrequently reported. The most common reported adverse events were mild gastrointestinal disturbances. Allergic reactions were reported mainly in patients who concomitantly received thrombolytic therapy for myocardial infarction and also received contrast media.
Yarbrough / 2012 / (2)	The initial dosage was 0.2 mcg/kg/min to achieve an aPTT of between 60 and 85 sec. (N=1)	Case report of a 58 year old male with deep venous thrombosis initially treated with heparin that developed HIT with concomitant Child-Pugh Class C liver disease.	<ul style="list-style-type: none"> Despite the dose reduction at the start of therapy, the aPTT measured 6 hours following the initiation of argatroban was supratherapeutic, at 101 seconds. Argatroban was stopped but the aPTT remained supratherapeutic for greater than 24 hours. After 24 hours, reintroduction of argatroban infusions first at 0.1 and then 0.05 mcg/kg/min were required to achieve the target aPTT. The patient stabilized and was eventually switched to oral warfarin.
Identification of Literature Source	Dose of Argatroban / Number of Patients (N)	Summary of Study Design	Primary Safety Results
Pasala / 2013 / (3)	Argatroban was started at 2 mcg/kg/min and incrementally increased to 20 mcg/kg/min to achieve therapeutic aPTT. High-dose argatroban (> 10 mcg/kg/min) was required for 9 days. (N=1)	Case report of a 10 year old boy with congenital dilated cardiomyopathy who was receiving support from a ventricular assist device complicated by a thrombus in the right ventricular assist device. He was treated with heparin but experienced HIT that was successfully treated with high-dose argatroban infusion to attain therapeutic aPTT.	<ul style="list-style-type: none"> The hospital course was complicated by persistent ventricular fibrillation and development of a thrombus in the right ventricular assist device. The assist device required replacement and after 59 days of cardiac support he underwent a successful orthotopic heart transplant. The hospital course after transplant was uncomplicated and he was eventually discharged home.
Ferguson / 2013 / (4)	Argatroban was infused at 5 mcg/kg/min (N=1)	Case report of a 46-year-old Caucasian man with type 2 diabetes mellitus, hypertension and coronary artery disease who underwent a 4-vessel coronary artery by-pass graft after a myocardial infarction.	<ul style="list-style-type: none"> The hospital course was complicated by sepsis, kidney failure for which the patient required hemodialysis and extra corporeal perfusion support. Multiple thrombi developed in his extra corporeal circuit (ECC) despite heparin therapy. Argatroban was initiated, the clots resolved, and the ECC thereafter remained patent. The patient stabilized from sepsis, acute kidney injury, and was eventually discharged to hospice.

Reviewer comment: The articles provided by the Applicant are not pertinent to the product in this application because they do not discuss the formulation of argatroban proposed in this 505(b)(2) application.

Conclusion: CMC is recommending a complete response because of inspection issues with the manufacturing facility. Due to the fact that a complete response is planned, labeling was not reviewed during this cycle. There were no deficiencies identified in the review of the clinical portion of this NDA.

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/s/

ADAM N GEORGE
01/31/2014

VIRGINIA E KWITKOWSKI
01/31/2014

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA #	201811
Supplement #	
Applicant Name	Fresenius Kabi USA, LLC.
Date of Submission	October 12, 2012
PDUFA Goal Date	April 12, 2013
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:	Complete Response

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Firoozeh Alvandi, M.D./ Virginia Kwitkowski, RNP
Statistical Review	N/A
Pharmacology Toxicology Review	Shwu Luan Lee Ph.D./ Haleh Saber, Ph.D.
CMC Review/OBP Review	Anne Marie Russell, Ph.D./Janice Brown, M.S.
Microbiology Review	J. Metcalfe, Ph.D./ Bryan S. Riley
Clinical Pharmacology Review	Hua Zhang, Ph.D./ Julie Bullock, Pharm.D.
DDMAC	
DSI	N/A
CDTL Review	Janice Brown, M.S.
OSE/DMEPA	
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

This submission for NDA 201811, a 505 b2 application for argatroban, is a response to a Complete Response Letter sent on July 23, 2012. The July 23, 2012 Complete Response letter identified nine product quality deficiencies and a facility inspection deficiency that precluded approval.

The Agency filed the resubmission and granted a PDUFA goal date of April 12, 2013.

2. Background

The Reference Listed Drug (RLD) for this submission is Argatroban Injection (NDA 20-883), which is currently marketed by Pfizer.

3. CMC/Device

The CMC CDTL review noted that some minor issues were still unresolved:

The remaining minor outstanding issues include the need for additional drug product stability data, submission of an analytical procedure, and method validation data.

The following text is from the CMC CDTL memo who requests that the following text be placed in the complete response letter:

- 1. During a recent inspection of the APP Pharmaceuticals, LLC., Grand Island, NY facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.*
- 2. Provide the Analytical Procedure and Validation of Analytical Procedure for the method used in the Identification Test cited in "Table 3.2.S.5-1 Specification for Individual Isomers Argatroban 21-S and 21-R" and demonstrated adequacy of the method to distinguish the individual isomers.*
- 3. Provide drug product stability data for all attributes, utilizing all test methods listed in the specifications.*

- *Facilities review/inspection*

The Office of Compliance has issued a “Withhold” recommendation on 1/18/2013. Therefore until inspectional issues are resolved, this application cannot be approved.

I concur with the CDTL that these issues preclude approval.

4. Nonclinical Pharmacology/Toxicology

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 *in vitro* equivalence data to support bridging between this 505 b2 product and the RLD.

6. Microbiology

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

None

12. Labeling

All disciplines made recommendations for labeling.

13. Decision/Action/Risk Benefit Assessment

- - Recommended regulatory action
Complete Response letter will include deficiencies from CMC including lack of a facility for inspection
 - 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
03/26/2013

Cross-Discipline Team Leader Review

Date	Electronic Date Stamp
From	Janice Brown M.S.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 201811 (3 rd review cycle)
Applicant	Fresenius Kabi USA, LLC
Date of Submission	October 12, 2012 (received October 12, 2012)
PDUFA Goal Date	April 12, 2013
Proprietary Name / Established (USAN) names	Argatroban Injection (b) (4)
Dosage forms / Strength	Injection, (b) (4) /250 mg/2.5 mL vial (100 mg/mL)
Proposed Indication(s)	<ol style="list-style-type: none"> 1. Indicated for prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT). 2. As an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI).
Recommended:	Complete Response

1. Introduction

Argatroban is a small molecule, synthetic direct thrombin inhibitor derived from L-arginine and approved for intravenous administration for treatment and prevention of thrombosis in patients with heparin-induced thrombocytopenia (HIT) and for anticoagulation in patients with HIT who are undergoing percutaneous coronary interventions (PCI). The current application for Argatroban Injection 250 mg/2.5 mL vial (100 mg/mL) aqueous solution was submitted as a 505(b)(2) NDA. The product must be diluted to a final concentration of 1 mg/mL in 0.9% sodium chloride injection, 5% dextrose injection, or Lactated Ringer's injection prior to intravenous infusion. The innovator product (Argatroban Injection, 250 mg/2.5 mL, (NDA 20-883) is also a concentrated solution which must be diluted prior to use. The inactive ingredient used in the Argatroban Injection formulation by APP differs from those used in the RLD Argatroban product. The qualitative difference between the RLD and the proposed formulations is that dehydrated alcohol and D-sorbitol were removed from the applicant's drug product, and propylene glycol was added as a (b) (4).

2. Background

This NDA was originally submitted on April 2, 2010 (received on April 5, 2010). This is the third review cycle for this application. See the Cross-Discipline Team Leader (CDTL) reviews dated February 16, 2011 and July 31, 2012 for details of the regulatory history prior to this NDA resubmission and reviews for a summary and details of the application review history prior to this cycle. On July 23, 2012 the Division issued a Complete Response letter to the sponsor citing unresolved chemistry, manufacturing and controls (CMC) deficiencies and manufacturing facility issues that remained to be resolved before the product can be approved.

The sponsor submitted a response to the CR letter on October 12, 2012.

3. CMC

CMC: While some of the deficiencies in the Complete Response letter were satisfactorily addressed, the applicant did not provide acceptable responses to all the deficiencies. The remaining minor outstanding issues include the need for additional drug product stability data, submission of an analytical procedure, and method validation data. The complete list of CMC deficiencies is not duplicated here and can be found under item 13 in this review.

Microbiology - Argatroban Injection is an (b) (4) drug product. The Microbiology review (John Metcalfe, Ph.D., final signature February 25, 2013) stated, "NDA 201811 is recommended for approval from the standpoint of product quality microbiology." There are no outstanding microbiology issues related to the sterility assurance of the Argatroban injection product and the review recommended approval.

Biopharmaceutics – There is no new biopharmaceutics information in the resubmission. The Biopharmaceutics Review (Angelica Dorantes, Ph.D., final signature April 24, 2012) stated, “From the Biopharmaceutics viewpoint, the resubmission of NDA 201-811 for Argatroban Injection is recommended for approval.” There are no outstanding biopharmaceutics issues related to the Argatroban injection product and the review recommended approval.

4. Nonclinical Pharmacology/Toxicology

There is no new pharmacology/toxicology data in this resubmission. The Pharmacology/Toxicology Review (Shwu-Luan Lee, Ph.D., final signature January 11, 2013) stated, “The NDA is recommended for approval from a pharmacology/toxicology perspective.” No pharmacology/toxicology issues which preclude approval were found and the review recommended approval.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology information was included in the resubmission. No clinical pharmacology review was done for this cycle.

6. Clinical Microbiology

There was no clinical microbiology review for this cycle.

7. Clinical/Statistical- Efficacy

No new efficacy information is included in the resubmission. No statistical review was done for this cycle.

8. Safety

There are no new safety concerns from a review of the recent literature. Clinical Review of the resubmission was completed by Firoozeh Alvandi, M.D. (January 7, 2013). The reviewer found no new safety concerns and stated, “The recommended regulatory action is approval from the clinical perspective.” The review also stated the following statement be retained in the applicant’s label for Argatroban Injection, “The safety and effectiveness of Argatroban, including the appropriate anticoagulation goals and duration of therapy, have not been established among pediatric patients”. The proposed labeling has retained this statement. The clinical reviewer recommends an approval action for this NDA.

9. Advisory Committee Meeting

There was no Advisory Committee meeting held for this application.

10. Pediatrics

There is no new information in the resubmission that would require another Pediatric and Maternal Health Staff (PMHS) review.

11. Other Relevant Regulatory Issues

Manufacturing Facilities

On January 18, 2013 the Office of Compliance issued an overall withhold recommendation for this application.

12. Labeling

 (b) (4)

The formatting of the applicant's proposed labeling has been constructed to comply with the requirements of the Physician's Labeling Rule (PLR).

The exact wording of the labeling in the PLR format has been reviewed and comments from all disciplines were conveyed to the applicant.

13. Recommendations/Risk Benefit Assessment

No pharmacology/toxicology issues or clinical pharmacology issues have been found to preclude approval. Clinical Review finds the application adequate and recommends approval. CMC did not recommend approval due to the withhold recommendation from the Office of Compliance for the facility used to manufacture the Argatroban drug product and minor CMC deficiencies.

- Recommended Regulatory Action

A "Complete Response" action is recommended for this NDA based on the withhold recommendation from the Office of Compliance and minor CMC deficiencies.

- Risk Benefit Assessment

Due to the withhold recommendation from the OC and the minor CMC deficiencies associated with this application, this product is currently unsuitable for commercial production and marketing.

- Recommendation for Postmarketing Risk Management Activities:

None

- Recommendation for other Postmarketing Study Commitments:

None identified

- Recommended Comments to Applicant

Insert the following language into the action letter:

1. During a recent inspection of the APP Pharmaceuticals, LLC., Grand Island, NY facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.
2. Provide the Analytical Procedure and Validation of Analytical Procedure for the method used in the Identification Test cited in “Table 3.2.S.5-1 Specification for Individual Isomers Argatroban 21-S and 21-R” and demonstrated adequacy of the method to distinguish the individual isomers.
3. Provide drug product stability data for all attributes, utilizing all test methods listed in the specifications.

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/s/

JANICE T BROWN
03/21/2013

ALI H AL HAKIM
03/21/2013

FILE MEMORANDUM

MEMO DATE: 01/07/2013 PM: Beatrice Kallungal

TO NDA: 201811
Submission Date: 10/12/2012
FDA Received Date: 10/12/2012
SDN / SN:
eCTD number: Non-eCTD SDN 17

Network path in edr: <\\CDSesub1\EVSPROD\IND076594\076594.enx>

Other reviewers: Clinical Pharmacology: Zhang, Lillian
Non-Clinical: Lee, Shwu Luan
Product Quality: Leutzinger, Eldon E.
Product Quality Microbiology: Metclafe, John

FROM: Firoozeh Alvandi, MD, Medical Reviewer; Division of Hematology Products

SUBJECT: Argatroban

Via: Virginia Kwitkowski, MS, RN, ACNP-BC
Clinical Team Leader, DHP, OHOP

ISSUE: NA

ACTIONS RECOMMENDED: The recommended regulatory action is approval from the clinical perspective.

SUMMARY OF REVIEWER FINDINGS: No new safety concerns arise from review of recent literature. No clinical efficacy or safety data were submitted in this NDA application. Review of the label submitted in the PLR format found the label to be acceptable. For details and recommendations regarding this NDA submission, refer to reviews by other disciplines.

Background:

The applicant, previously APP Pharmaceuticals, LLC, now Fresenius Kabi USA LLC, has resubmitted NDA 201811 after receipt of Complete Response issued 07/23/2012 by the Agency based on CMC deficiencies. The applicant has developed an argatroban formulation that differs from the reference listed drug (RLD) in its inert ingredient. The inert ingredient in the applicant's proposed argatroban is 954 mg propylene glycol (the inert ingredients in the RLD are (b) (4) mg D-sorbitol, (b) (4) mg dehydrated alcohol).

This is a 505(b)(2) because the applicant is relying on reference product (Argatroban by Pfizer [originally by Encysive]; NDA 20-883) to provide pharmacological equivalence. There were no clinical efficacy/safety data submitted for review.

The applicant completed the following studies:

1. An *in vitro* study to compare argatroban from two different formulations (APP and RLD) on aPTT, PT and TT clotting test using human pooled plasma, performed as a bridge-study to demonstrate bioequivalence between the Reference Listed Drug (RLD) “Argatroban Injection” and APP’s proposed drug product. This study evaluated the activated partial thromboplastin time (aPTT), prothrombin time (PT) and thrombin time (TT) for the RLD and APP’s argatroban drug product using pooled human plasma. The test and reference products were evaluated at 0.3, 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 µg/mL of argatroban for the aPTT and PT coagulation tests and at 0.05, 0.1, 0.2, 0.3 and 0.5 µg/mL of argatroban for the TT coagulation test (test and RLD were evaluated at the same plasma concentrations). The test placebo and reference placebo at excipient concentrations corresponding to 3.0 µg/mL argatroban were also evaluated to confirm that the excipients have no effect on coagulation tests. Plasma was collected from 24 healthy non-smoking adult subjects. Plasma samples were pooled into 6 pools with plasma from 4 subjects per pool. See CMC review and Clinical Pharmacology review.

2. A pilot *in vitro* study, performed prior to the main *in vitro* study, to ensure that the selected range of Argatroban concentrations, previously published by the innovator, was adequate to assess aPTT, PT and TT coagulation tests. The *in vitro* pilot study evaluated the impact of the chosen argatroban concentrations on aPTT, PT and TT using pooled citrated human plasma, spiked with the argatroban at seven plasma drug concentrations (0.04, 0.12, 0.4, 1.2, 2.0, 3.0, and 5.0 µg/mL) (test and RLD were evaluated at the same plasma concentrations). Test Placebo and Reference Placebo at excipients’ concentrations corresponding to 5.0 µg/mL argatroban were also evaluated. Whole blood samples from four (4) healthy non-smoking volunteers were collected in citrated tubes for this study. See CMC review and Clinical Pharmacology review.

The label in the PLR format appears acceptable from the clinical perspective. It contains the required information on pediatric experience and dosing of argatroban in accordance with 505A(o) (1)(2)(A)(B), allowing protected information as pertains to Contraindications, Warnings, and Precautions, or Use in Specific Populations/Pediatric Use portions to be retained in generic drug labels. The pediatric use summary statement “The safety and effectiveness of Argatroban, including the appropriate anticoagulation goals and duration of therapy, have not been established among pediatric patients” has also been included in the label as required.

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/s/

FIROOZEH ALVANDI
01/07/2013

VIRGINIA E KWITKOWSKI
01/07/2013

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA #	201811
Supplement #	
Applicant Name	APP Pharmaceuticals, Inc.
Date of Submission	January 31, 2012
PDUFA Goal Date	July 31, 2012
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:	Complete Response

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Firoozeh Alvandi, M.D./ Virginia Kwitkowski, RNP
Statistical Review	N/A
Pharmacology Toxicology Review	Shwu Luan Lee Ph.D./ Haleh Saber, Ph.D.
CMC Review/Biopharmaceutics Review	Anne Marie Russell, Ph.D./Janice Brown, M.S./Angelica Dorantes, Ph.D.
Microbiology Review	J. Metcalfe, Ph.D./ Stephen Langille, Ph.D.
Clinical Pharmacology Review	Young J. Moon, Ph.D./ Julie Bullock, Pharm.D.
DDMAC	
OSI	N/A
CDTL Review	Janice Brown, M.S. and Sarah Pope Miksinski, Ph.D.
OSE/DMEPA	
OSE/DDRE	
OSE/DSRCS	
Other -MHT	

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 201811 is a 505 b2 application for argatroban which was submitted to the Agency on April 30, 2010. The Agency filed the application and granted a standard review with a PDUFA goal date of February 28, 2011. The Agency issued a Complete Response letter to the original application based on Chemistry, Manufacturing and Control issues. This submission is a class 2 submission to address outstanding issues.

2. Background

The Reference Listed Drug (RLD) for this submission is Argatroban Injection (NDA 20-883), which is currently marketed by Pfizer.

3. CMC/Device

From Ms. Brown's review:

CMC: While some of the deficiencies in the Complete Response letter were satisfactorily addressed, the applicant did not provide acceptable responses to all the deficiencies. The remaining significant outstanding issues include inadequate drug product specifications, lack of comparative purity profile data for RLD, and incomplete drug product stability data. The complete list of CMC deficiencies is not duplicated here and can be found in the CMC review by Anne Marie Russell (final signature July 6, 2012).

From Dr. Russell's review:

APP has not yet provided acceptable responses to the deficiencies identified in the Complete Response letter dated 24-FEB-2011. As a result, the application cannot be recommended for approval at this time.

From Dr. Russell's review the following deficiencies should be communicated to the Applicant.

1. During a recent inspection of the APP Pharmaceuticals manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved
2. The HPLC method for determination of argatroban and impurities and identification of argatroban (10-08-03-6457) and validation report PR-08-00037 contain acceptance criteria for impurities in the raw material and finished product with unjustifiably high values [for example, the percent relative standard deviation (RSD) for precision of NMT (b) (4) % at an impurity level of more than (b) (4) and the percent RSD for precision of NMT (b) (4) % at an impurity level of less than (b) (4)]. The same high values are observed in the proposed acceptance criteria for the percent RSD for intermediate precision as well as the percent change in solutions from the initial timepoint. Therefore, revise the acceptance criteria to more accurately match your analytical data ((b) (4) %) and conduct the proposed future validation utilizing the revised criteria prior to future testing.
3. Provide the certificates of analysis and control testing data for all argatroban, API lots used in the preparation of the drug product for any proposed manufacturing site(s), utilizing the proposed NDA test methods. Note that the Summary of Test Results (SOTR) submitted for lots of drug substance (1002935, 1009636 and 1002937) used to manufacture the exhibit lots of drug product (R340-032, R340-033 and R340-034), reported test results using the defunct isomeric ratio test method (10-08-03-6457) instead of the current method (10-08-03-6689).
4. Include full quality control specifications for the individual 21-R and 21-S isomers of argatroban as part of the methodology proposed for isomeric ratio. The proposal to submit manufacture's Certificate of Analysis and to confirm the structure of using proton NMR is does not provide sufficient quality control for these reference standards. Provide specifications, including attribute, test method and acceptance criteria.
5. Provide comparative purity profile data for the RLD and the proposed product. The file of the referenced Report #PD11-NPA-018 in the Complete Response was not included in the submission.
6. Provide specifications at release and during stability for impurities (b) (4). Refer to ICH Q3B(R2) - Impurities in New Drug Products. The file of the referenced Report #PD11-NPA-018 in the Complete Response, submitted to support the proposal to omit impurities, was not included in the submission.
7. In the drug product stability protocol, revise the specifications to include other individual impurities. The proposal to omit the impurities was not supported due to the absence of Report #PD11-NPA-018 from the submission.
8. Report the test method (including version) and indicate the date testing was conducted on all submitted data – including Summary of Test Result (SOTR), certificates of analysis, batch analysis reports and stability reports.
9. Provide acceptance, release and stability test data conducted using the current submitted methods for all lots of drug substance and drug product. Identify any test

data conducted using outdated test methods.

10. Provide drug product stability data for all attributes, utilizing all test methods listed in the specifications.

The Office of New Drug Quality Assessment Biopharmaceutics Review did not find any issues that would preclude approval.

The Office of Compliance issued: *Overall OC Recommendation NDA 201811/000 Decision: WITHHOLD, Decision Date: 02/22/2012.* This recommendation was based on the APP Pharmaceuticals site in Grand Island NY which manufactures the drug product and performs quality control testing.

After reading Dr. Russell's and Ms. Brown's reviews, I concur that these issues preclude approval.

4. Nonclinical Pharmacology/Toxicology

During the original review, the pharmacology/toxicology team became aware of an impurity that was above the threshold in ICHQ3B. The sponsor did not address this deficiency in the submission and the following language was placed in the Complete response 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 the current submission, the applicant addressed this deficiency. The following text is from Dr. Lee's review dated June 4, 2012:

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

5. Clinical Pharmacology/Biopharmaceutics

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

6. Microbiology

The previously identified microbiology deficiencies have been resolved and the review team recommends approval.

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 Office of Compliance issued a Withhold recommendation. Therefore this application cannot be approved.

12. Labeling

All disciplines made recommendations for labeling.

13. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action
Complete Response letter will include deficiencies from CMC including the withhold recommendation from the Office of Compliance
- 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
07/20/2012

Cross-Discipline Team Leader Review

Date	July 17, 2012
From	Janice Brown for Sarah Pope Miksinski, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 201811 (2 nd review cycle)
Applicant	APP Pharmaceuticals, Inc.
Date of Submission	January 31, 2012 (received January 31 2012)
PDUFA Goal Date	July 31, 2012
Proprietary Name / Established (USAN) names	Argatroban Injection
Dosage forms / Strength	100 mg/mL (250 mg/2.5 mL vial)
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:	Complete Response

1. Introduction

Argatroban is a small molecule, synthetic direct thrombin inhibitor derived from L-arginine and approved for intravenous administration for treatment and prevention of thrombosis in patients with heparin-induced thrombocytopenia (HIT) and for anticoagulation in patients with HIT who are undergoing percutaneous coronary interventions (PCI). The current application for Argatroban Injection 100 mg/mL (250 mg/2.5 mL vial) aqueous solution was submitted as a 505(b)(2) NDA. The product must be diluted 1:100 fold prior to administration (infusion) in 0.9% sodium chloride injection, 5% dextrose injection, or Lactated Ringer's injection to a final concentration of 1 mg/mL. The innovator product (Argatroban Injection, 250 mg/2.5 mL, (NDA 20-883) is also a concentrated solution which must be diluted prior to use.

2. Background

The applicant for this NDA is relying upon information in the public domain (labeling for approved argatroban product and published studies and information about argatroban) to support the safety and efficacy of the new product.

This NDA was originally submitted on April 5, 2010. This is the second review cycle for this application. See the Cross-Discipline Team Leader (CDTL) review dated February 16, 2011 by Dr. Sarah Pope-Miksinski for details of the regulatory history prior to this NDA resubmission and reviews cited therein for a summary and details of the application review history prior to this cycle. On February 24, 2011 the Division issued a Complete Response letter to the sponsor citing an unresolved nonclinical and chemistry, manufacturing and controls (CMC) deficiencies and manufacturing facility issues that remained to be resolved before the product can be approved.

The sponsor submitted a response to the CR letter on January 31, 2012.

3. CMC

CMC: While some of the deficiencies in the Complete Response letter were satisfactorily addressed, the applicant did not provide acceptable responses to all the deficiencies. The remaining significant outstanding issues include inadequate drug product specifications, lack of comparative purity profile data for listed drug, and incomplete drug product stability data. Since numerous changes to the proposed drug substance and drug product specification were requested, reanalysis of all drug substance and drug product batches is required. The applicant included a justification for the omission of impurity testing and comparative purity analysis with the listed drug; however, the supporting documents were not included in the submission. The complete list of CMC deficiencies is not duplicated here and can be found in the CMC review by Anne Marie Russell (final signature July 6, 2012).

BIOPHARMACEUTICS: APP Pharmaceuticals requested that the Agency waive the CFR's requirement to submit in vivo bioavailability/bioequivalence (BA/BE) data for their product. To support their BA/BE waiver request, APP Pharmaceuticals provided information showing that the proposed Argatroban Injection will be administered at the same dosage level, for the same duration, and for the same indications as the listed drug, Argatroban Injection approved under NDA 20-883.

Angelica Dorantes, Ph.D. ONDQA Biopharmaceutics reviewer granted a biowaiver for the proposed Argatroban Injection. To support the BA/BE waiver request, APP Pharmaceuticals provided information showing that the proposed Argatroban Injection in vitro pharmacodynamic activity (aPTT, PT, and TT) is similar to the activity of the RLD product, the difference in the inactive ingredients would not have an impact on the bioavailability or represent a safety concern, is same dosage form, administered at the same dosage level, for the same duration, and for the same indications as the RLD product, Argatroban Injection under NDA 20-883.

MICROBIOLOGY: In the resubmission, no microbiology issues were identified and the review recommended approval (John Metcalfe, Ph.D., final signature June 29, 2012).

4. Nonclinical Pharmacology/Toxicology

The February 24, 2012 CR letter cited the following nonclinical 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 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.”

The nonclinical review of information in the resubmission by Shwu-Luan Lee, Ph.D. (final signature June 4, 2012) concluded that the deficiency was resolved stating, “The proposed specification of Impurity (b) (4) set at NMT (b) (4) % is acceptable. There are no pending pharmacology/toxicology issues to preclude the approval of this 505(b)(2) NDA.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology information was included in the resubmission. No clinical pharmacology review was done for this cycle.

6. Clinical Microbiology

There was no clinical microbiology review for this cycle.

7. Clinical/Statistical- Efficacy

No new efficacy information is included in the resubmission. No statistical review was done for this cycle.

8. Safety

There are no new clinical data provided in the current submission. The clinical reviewer (Firoozeh Alvandi, M.D., final signature June 29, 2012) recommends a “Complete Response” action for this NDA based on CMC deficiencies.

9. Advisory Committee Meeting

There was no Advisory Committee meeting held for this application.

10. Pediatrics

As discussed in the previous CDTL Review for this application (Sarah Pope-Miksinski, Ph.D., February 16, 2012), the labeling for the RLD contains information in the Pediatric Use section based upon a study conducted by the RLD applicant. The study was not sufficient to support an indication for pediatric use. However, information from the study regarding pediatric experience was placed into the label based on concerns for safety should the product be used off label in pediatric patients. Consequently, this information should be retained in the label for the new APP argatroban product.

11. Other Relevant Regulatory Issues

Manufacturing Facilities: In this resubmission, APP transferred the manufacture of the drug product from the APP Pharmaceuticals, LLC at the Barceloneta, PR site to the Grand Island, New York manufacturing facility. The overall recommendation from the Office of Compliance is Withhold (final recommendation on February 22, 2012).

12. Labeling

 (b) (4)

The formatting of the applicant’s proposed labeling has been constructed to comply with the requirements of the Physician’s Labeling Rule (PLR).

The exact wording of the labeling in the PLR format has been reviewed and comments from all disciplines were conveyed to the applicant.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action: Complete Response due the significant CMC and manufacturing facility deficiencies.

Risk Benefit Assessment: There are significant CMC and manufacturing deficiencies associated with this application. Therefore, this product is currently unsuitable for commercial production and marketing.

Recommendation for Postmarketing Risk Management Activities: Not applicable

Recommendation for other Postmarketing Study Commitments: None identified

Recommended Comments to Applicant: There are numerous deficiencies that need to be inserted into the action letter. For clarity and brevity, these deficiencies are not duplicated here and are located in the CMC review.

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/s/

JANICE T BROWN
07/20/2012

SARAH P MIKSINSKI
07/20/2012

FILE MEMORANDUM

MEMO DATE: 6/29/2012 PM: Lara Akinsanya

TO NDA: 201811
Submission Date: 1/31/2012
FDA Received Date: 1/31/2012
SDN / SN:
eCTD number: non-eCTD

Network path in edr: <\\CDSesub1\EVSPROD\IND076594\076594.enx>

Other reviewers: Clinical Pharmacology: Moon, Young-Jin
Non-Clinical: Lee, Shwu Luan
Product Quality: Russell, Anne Marie
Biopharmacology: Dorantes, Angelica
Product Quality Microbiology: Metcalfe, John

FROM: Firoozeh Alvandi, MD, Medical Reviewer; Division of Hematology Products

SUBJECT: Argatroban

Via: Virginia Kwitkowski, MS, RN, ACNP-BC
Clinical Team Leader, DHP, OHOP

ISSUE: NA

ACTIONS RECOMMENDED: The recommended regulatory action is a Complete Response (CR) based on CMC deficiencies.

SUMMARY OF REVIEWER FINDINGS: No new safety concerns arise from review of recent literature. No clinical efficacy or safety data were submitted in this NDA application. Review of the label submitted in the PLR format found the label to be acceptable. For details and recommendations regarding this NDA submission, refer to reviews by other disciplines.

Background:

The applicant, APP Pharmaceuticals, LLC, has resubmitted NDA 201811 with responses to the Complete Response issued by the Agency 2/24/2011, pertaining to CMC deficiencies (as the recommended regulatory action was Complete Response based on CMC deficiencies). The applicant has developed an argatroban formulation that differs from the reference listed drug (RLD) in its inert ingredients. The inert ingredient in the APP argatroban is 954 mg propylene glycol (the inert ingredients in the RLD are (b) (4) mg D-sorbitol, (b) (4) mg dehydrated alcohol).

This is a 505(b)(2) because the applicant is relying on reference listed drug (Argatroban by Pfizer [originally by Encysive]; NDA 20-883) to provide pharmacological equivalence. There were no clinical efficacy/safety data submitted for review.

The applicant completed the following studies:

1. An *in vitro* study to compare argatroban from two different formulations (APP and RLD) on aPTT, PT and TT clotting test using human pooled plasma, performed as a bridge-study to demonstrate bioequivalence between the Reference Listed Drug (RLD) “Argatroban Injection” and APP’s proposed drug product. This study evaluated the activated partial thromboplastin time (aPTT), prothrombin time (PT) and thrombin time (TT) for the RLD and APP’s argatroban drug product using pooled human plasma. The test and reference products were evaluated at 0.3, 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 µg/mL of argatroban for the aPTT and PT coagulation tests and at 0.05, 0.1, 0.2, 0.3 and 0.5 µg/mL of argatroban for the TT coagulation test (test and RLD were evaluated at the same plasma concentrations). The test placebo and reference placebo at excipient concentrations corresponding to 3.0 µg/mL argatroban were also evaluated to confirm that the excipients have no effect on coagulation tests. Plasma was collected from 24 healthy non-smoking adult subjects. Plasma samples were pooled into 6 pools with plasma from 4 subjects per pool. See CMC review and Clinical Pharmacology review.

2. A pilot *in vitro* study, performed prior to the main *in vitro* study, to ensure that the selected range of Argatroban concentrations, previously published by the innovator, was adequate to assess aPTT, PT and TT coagulation tests. The *in vitro* pilot study evaluated the impact of the chosen argatroban concentrations on aPTT, PT and TT using pooled citrated human plasma, spiked with the argatroban at seven plasma drug concentrations (0.04, 0.12, 0.4, 1.2, 2.0, 3.0, and 5.0 µg/mL) (test and RLD were evaluated at the same plasma concentrations). Test Placebo and Reference Placebo at excipients’ concentrations corresponding to 5.0 µg/mL argatroban were also evaluated. Whole blood samples from four (4) healthy non-smoking volunteers were collected in citrated tubes for this study. See CMC review and Clinical Pharmacology review.

The label in the PLR format appears acceptable from the clinical perspective. It contains the required information on pediatric experience and dosing of argatroban in accordance with 505A(o) (1)(2)(A)(B), allowing protected information as pertains to Contraindications, Warnings, and Precautions, or Use in Specific Populations/Pediatric Use portions to be retained in generic drug labels. The pediatric use summary statement “The safety and effectiveness of Argatroban, including the appropriate anticoagulation goals and duration of therapy, have not been established among pediatric patients” has also been included in the label as required.

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/s/

FIROOZEH ALVANDI
06/29/2012

VIRGINIA E KWITKOWSKI
06/29/2012

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Acting Division Director
Subject	Division Director Summary Review
NDA/BLA #	201811
Supplement #	
Applicant Name	APP Pharmaceuticals, Inc.
Date of Submission	April 30, 2010
PDUFA Goal Date	February 28, 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:	Complete Response

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	Milagros Driver, Ph.D./Janice Brown, Ph.D.
Microbiology Review	J. Metcalfe, Ph.D./ Bryan S. Riley
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 -MHT	1. Tammie Brent-Howard RN, MSN/Karen Feibus, M.D. 2. Jeannie Best MSN, RN, PNP/ Hari Sachs, M.D.

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DSI=Division of Scientific Investigations

DDRE= Division of Drug Risk Evaluation

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CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

NDA 201811 is a 505 b2 application for argatroban which was submitted to the Agency on April 30, 2010. The Agency filed the application and granted a standard review with a PDUFA goal date of February 28, 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

From the CMC CDTL memo:

NDA 201811 was initially submitted on 02-APR-2010 as a 505(b)(2) application. At the time of the filing determination, the NDA appeared to include a full (and fileable) dossier of CMC information, along with proposed container/carton and PI labeling. Subsequent to the Agency's filing determination, the Agency's PAI inspection process uncovered a grave inconsistency in that the Applicant's proposed drug product manufacturing site (APP Pharmaceuticals, LLC, Barceloneta, PR) was no longer in operation. The Agency discussed this discrepancy with the Applicant via a 19-NOV-2010 teleconference in which the Applicant confirmed that the proposed site was no longer in operation. The Applicant confirmed that the site closure was a business decision but provided minimal further details. While the Applicant provided a general strategy for the proposal of a new (undetermined) site, the Applicant also confirmed that no specific and identified drug product manufacturing site was (or could be) proposed at that time.

During the 19-NOV-2010 teleconference, the Agency clarified that a “Complete Response” action was highly likely, as the totality of Module 3 applied to a site no longer manufacturing the drug product. The Applicant acknowledged this clarification. Official meeting minutes can be located in DARRTS.

- **General product quality considerations**
There are significant quality concerns with this application. Most significantly, the Applicant has no drug product manufacturing site in place for the proposed commercial product, and the majority of Module 3 information and data is applicable only to the previously-closed site. While a full CMC review was conducted (see Chemistry Review #1 dated 16-FEB-2011, by Dr. M. Salazar), the reviewed information applies to a closed site. There is no alternate drug product manufacturing site proposed. In the absence of an acceptable path forward regarding the proposal and establishment of an operational drug product manufacturing site, the submitted Module 3 is essentially obsolete to support the proposed commercial product.
- **Facilities review/inspection**
An Establishment Evaluation Request (EER) was submitted to the Office of Compliance, and an overall withhold recommendation was issued for the application on 07-OCT-2010 due to the non-operational status of the proposed drug product manufacturing site (see above).
- **Microbiology**
Argatroban Injection is a (b) (4) and (b) (4) product. The microbiology reviewer (Dr. J. Metcalfe) does not recommend approval of this NDA in his review dated 13-JAN-2011. There are significant outstanding microbiology issues related to the manufacturing process and/or overall sterility assurance, as the provided information applies to a site no longer in operation.

I concur with the CDTL that these issues preclude approval.

4. Nonclinical Pharmacology/Toxicology

During the review, the pharmacology/toxicology team became aware of an impurity that was above the threshold in ICHQ3B. The sponsor did not address this deficiency in the submission and the following language will be placed in the Complete response 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.

5. Clinical Pharmacology/Biopharmaceutics

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

6. Microbiology

The Microbiology review team does not recommend approval. The language reproduced below is from page 20 of their review:

Comment

It is understood by this reviewer that the Barceloneta facility referenced in the subject submission for manufacture of the subject drug product closed during the summer of 2010 (after submission of the NDA). Consequently, the drug product sterilization validation information and data sets are irrelevant if the applicant chooses to manufacture the product at an alternate facility.

Deficiencies

- 1. Provide sterilization validation methods and data sets representative of the drug product manufacturing process at the alternate manufacturing facility.*
- 2. Provide container closure integrity test methods and data sets using the (b) (4) vial presentation if this vial will be used for marketed product.*
- 3. With regard to the drug product label, the storage statement should be modified as follows (modifications are shown in italics):*

(b) (4)

(b) (4)

20 to 25 C (68 to 77 F) (see USP),

(b) (4)

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.

12. Labeling

All disciplines made recommendations for labeling.

13. Decision/Action/Risk Benefit Assessment

- - Recommended regulatory action
Complete Response letter will include deficiencies from CMC including lack of a facility for inspection
 - 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
02/24/2011

Cross-Discipline Team Leader Review

Date	16-FEB-2011
From	Sarah Pope Miksinski, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	201811
Applicant	APP Pharmaceuticals, Inc.
Date of Submission	02-APR-2010
PDUFA Goal Date	28-FEB-2011
Proprietary Name / Established (USAN) names	Argatroban Injection
Dosage forms / Strength	100 mg/mL (250 mg/2.5 mL vial)
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:	Complete Response

1. Introduction

NDA 201811 was submitted to the Agency on 02-APR-2010. The Agency filed the application and granted a standard review with a PDUFA goal date of 28-FEB-2011. There were two Clinical Pharmacology filing review issues conveyed in the Agency's 02-JUL-2011 filing letter.

This CDTL memo serves to highlight the critical approvability issues discussed in all review disciplines and recommends a "Complete Response" action for this application. All individual discipline reviews may be found in DARRTS. Final container/carton and PI labeling were not negotiated due to the intended "Complete Response" action.

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 and D-sorbitol were removed from the currently proposed product, and propylene glycol was added as a (b) (4). The Applicant proposed that the formulation revisions result in an (b) (4)

(b) (4). The Chemistry Review contains (page 53) 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 201811 was initially submitted on 02-APR-2010 as a 505(b)(2) application. At the time of the filing determination, the NDA appeared to include a full (and fileable) dossier of CMC information, along with proposed container/carton and PI labeling. Subsequent to the Agency's filing determination, the Agency's PAI inspection process uncovered a grave inconsistency in that the Applicant's proposed drug product manufacturing site (APP Pharmaceuticals, LLC, Barceloneta, PR) was no longer in operation. The Agency discussed this discrepancy with the Applicant via a 19-NOV-2010 teleconference in which the Applicant confirmed that the proposed site was no longer in operation. The Applicant confirmed that the site closure was a business decision but provided minimal further details. While the Applicant provided a general strategy for the proposal of a new site (Grand Island, NY), the Applicant also confirmed that the newly-intended site had not been submitted in the initial NDA submission.

During the 19-NOV-2010 teleconference, the Agency clarified that a "Complete Response" action was highly likely, as the totality of Module 3 applied to a site no longer manufacturing the drug product. The Applicant acknowledged this clarification. Official meeting minutes can be located in DARRTS.

- **General product quality considerations**
There are significant quality concerns with this application. Most significantly, the Applicant has no drug product manufacturing site in place for the proposed commercial product, and the majority of Module 3 information and data is applicable only to the previously-closed site. While a full CMC review was conducted (see Chemistry Review #1 dated 16-FEB-2011, by Dr. M. Salazar), the reviewed information applies to a closed site. There is no alternate drug product manufacturing site proposed. In the absence of an acceptable path forward regarding the proposal and establishment of an operational drug product manufacturing site, the submitted Module 3 is essentially obsolete to support any viable commercial product.
- **Facilities review/inspection**
An Establishment Evaluation Request (EER) was submitted to the Office of Compliance, and an overall withhold recommendation was issued for the application on 07-OCT-2010 due to the non-operational status of the proposed drug product manufacturing site (see above).

- Microbiology
Argatroban Injection is a (b) (4) and (b) (4) product. The microbiology reviewer (Dr. J. Metcalfe) does not recommend approval of this NDA in his review dated 13-JAN-2011. There are significant outstanding microbiology issues related to the manufacturing process and/or overall sterility assurance, as the provided information applies to a site no longer in operation.
- 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 02-FEB-2011 and captures a recommendation of non-approval for the NDA (see review by Dr. S. Lee). The recommendation is based on the inadequacy of the proposed specification (NMT (b) (4) %) for Impurity (b) (4). The Pharmacology/Toxicology reviewer confirms that insufficient information and justification were submitted in the NDA to support the proposed acceptance criterion.

5. Clinical Pharmacology

There were no clinical pharmacology data submitted to this NDA, with the exception of an *in vitro* 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 16-FEB-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 a “Complete Response” action for this NDA based on CMC deficiencies, in a 09-FEB-2011 memorandum.

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 deferred during the current cycle, and no labeling discussions were conducted due to the major deficiencies associated with the application.

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: Not applicable as this is an intended “Complete Response” action.
- Financial disclosures: Not applicable
- Other GCP issues: None
- DSI audits: Not applicable
- Other discipline consults: None
- Any other outstanding regulatory issues: None

12. Labeling

Due to the significant CMC, Pharmacology/Toxicology, and Microbiological deficiencies associated with this application, labeling discussions were not conducted. Some labeling comments are captured in the separate discipline reviews; however, full labeling (including both the PI and container/carton labeling) was not discussed internally and will need to be revisited during subsequent review cycles.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action
This reviewer does not recommend approval of this NDA based on the presence of significant CMC, Microbiology, and Pharmacology/Toxicology deficiencies.
- Risk Benefit Assessment
There are substantial review deficiencies associated with this application. Therefore, this product is currently unsuitable for commercial production and marketing.
- Recommendation for Postmarketing Risk Management Activities
Not discussed during the current review cycle.

- Recommendation for other Postmarketing Study Commitments
Not discussed during the current review cycle.
- Recommended Comments to Applicant
There are numerous deficiencies that need to be inserted into the action letter. For clarity and brevity, these deficiencies are not duplicated here and are located in the respective Pharmacology/Toxicology, CMC, and Microbiology reviews.

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/s/

SARAH P MIKSINSKI
02/16/2011

FILE MEMORANDUM

MEMO DATE: 02/09/2011 PM: Ebla Ali-Ibrahim

TO NDA: 201811
Submission Date: 04/30/2010
FDA Received Date: 05/03/2010
eCTD number: non-eCTD

Network path in edr: <\\CDSESUB1\EVSPROD\NDA201811\201811.enx>

Other reviewers: Biometrics: Lee, Kyung Y.
Clinical Pharmacology: Zhang, Hua
Non-Clinical: Lee, Shwu Luan
Product Quality: Leutzinger, Eldon E.
Product Quality Microbiology: Langille, Stephen E.

FROM: Firoozeh Alvandi, MD, Medical Reviewer; Division of Hematology Products

SUBJECT: Argatroban

Via: Virginia Kwitkowski, MS, RN, ACNP-BC
Acting Clinical Team Leader, DHP, OODP

ISSUE: Complete Response

ACTIONS RECOMMENDED: The recommended regulatory action is a Complete Response (CR) based on CMC deficiencies.

SUMMARY OF REVIEWER FINDINGS: No new safety concerns arise from review of recent literature. No clinical efficacy or safety data were submitted in this NDA application. For details and recommendations regarding this NDA submission, refer to reviews by other disciplines.

Background:

APP has developed an argatroban formulation that differs from the reference listed drug (RLD) in its inert ingredients. The inert ingredient in the APP argatroban is 954 mg propylene glycol (the inert ingredients in the RLD are (b) (4) mg D-sorbitol, (b) (4) mg dehydrated alcohol).

This is a 505(b)(2) because the applicant is relying on reference product (Argatroban by Pfizer [originally by Encysive]; NDA 20-883) to provide pharmacological equivalence. There were no clinical efficacy/safety data submitted for review.

The applicant completed the following studies:

1. An *in vitro* study to compare argatroban from two different formulations (APP and RLD) on aPTT, PT and TT clotting test using human pooled plasma, performed as a bridge-study to demonstrate bioequivalence between the Reference Listed Drug (RLD) "Argatroban Injection" and APP's proposed drug product. This study evaluated the activated partial thromboplastin time (aPTT), prothrombin time (PT) and thrombin time (TT) for the RLD and APP's argatroban drug product using pooled human plasma. The test and reference products were evaluated at 0.3, 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 µg/mL of argatroban for the aPTT and PT coagulation tests and at 0.05, 0.1, 0.2, 0.3 and 0.5 µg/mL of argatroban for the TT coagulation test (test and RLD were evaluated at the same plasma concentrations). The test placebo and reference placebo at excipient concentrations corresponding to 3.0 µg/mL argatroban were also evaluated to confirm that the excipients have no effect on coagulation tests. Plasma was collected from 24 healthy non-smoking adult subjects. Plasma samples were pooled into 6 pools with plasma from 4 subjects per pool.

See CMC review and Clinical Pharmacology review.

2. A pilot *in vitro* study, performed prior to the main *in vitro* study, to ensure that the selected range of Argatroban concentrations, previously published by the innovator, was adequate to assess aPTT, PT and TT coagulation tests. The *in vitro* pilot study evaluated the impact of the chosen argatroban concentrations on aPTT, PT and TT using pooled citrated human plasma, spiked with the argatroban at seven plasma drug concentrations (0.04, 0.12, 0.4, 1.2, 2.0, 3.0, and 5.0 µg/mL) (test and RLD were evaluated at the same plasma concentrations). Test Placebo and Reference Placebo at excipients' concentrations corresponding to 5.0 µg/mL argatroban were also evaluated. Whole blood samples from four (4) healthy non-smoking volunteers were collected in citrated tubes for this study.

See CMC review and Clinical Pharmacology review.

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/s/

FIROOZEH ALVANDI
02/09/2011

VIRGINIA E KWITKOWSKI
02/09/2011