

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**201811Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	See Electronic Date Stamp
<b>From</b>	Janice Brown M.S.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA # Supplement#</b>	NDA 201811 (5 <sup>th</sup> review cycle)
<b>Applicant</b>	Fresenius Kabi USA, LLC
<b>Date of Submission</b>	January 23, 2015 (received January 23, 2015) Original NDA submitted on 02-Apr-2010 (received 05-Apr-2010)
<b>PDUFA Goal Date</b>	March 23, 2015
<b>Proprietary Name / Established (USAN) names</b>	Argatroban Injection
<b>Dosage forms / Strength</b>	Injection, solution, concentrate/250 mg/2.5 mL vial (100 mg/mL)
<b>Proposed Indication(s)</b>	<ol style="list-style-type: none"> <li>1. Indicated for prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT).</li> <li>2. As an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI).</li> </ol>
<b>Recommended:</b>	Approval, pending acceptance of the final labeling revisions by the applicant

## 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 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

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 2, 2010 (received on April 5, 2010). This is the fifth review cycle for this application. See the Cross-Discipline Team Leader (CDTL) reviews dated February 16, 2011, July 20, 2012, March 21, 2013, and February 05, 2014 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 February 28, 2014 the Division issued a Complete Response letter to the applicant citing manufacturing facility issues that remained to be resolved before the product can be approved. The Applicant submitted a Class 1 resubmission on January 23, 2015 to address complete response issues with the 505(b)(2) application. The complete response issue has been resolved with the Applicant's resubmission.

## 3. CMC

CMC: The previous CMC reviewer (Anne Marie Russell, Ph.D.) recommended a complete response due to the Withhold recommendation from the Office of Compliance on February 4, 2014.

There is no new CMC information in the resubmission. The facilities listed in this application received an "approve" recommendation from the Office of Process and Facilities, and the product quality reviewer (Nina Ni, Ph.D.), recommended approval pending final acceptance of the container/carton labeling and the PI by the applicant in her review dated March 9, 2015 (signed March 9, 2015).

Microbiology: The quality microbiology reviewer previously recommended approval of this NDA in the review dated June 29, 2012. The reviewer (Denise A. Miller, Ph.D.) filed an updated memo dated February 24, 2015 (signed February 25, 2015) indicating that there is no new product quality microbiology information in the resubmission and recommended approval of the NDA.

Facilities: In this cycle, the facility issues have been resolved. The Office of Process and Facilities reviewer (Stephen Fong, Ph.D.) has given an overall “approve” recommendation for this NDA.

Issues with the Panorama “Inspection View” prevented the facility reviewer to enter an Overall Manufacturing Inspection Recommendation for this NDA. The final facility approval recommendation was sent in an email that is reproduced in attachment 1 in the drug product primary quality assessment review (Nina Ni, Ph.D.) in Panorama.

## **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. There is no pharmacology-toxicology information in the resubmission and the nonclinical reviewer recommended approval of the NDA in her review dated March 2, 2015 (signed March 10, 2015).

## **5. Clinical Pharmacology/Biopharmaceutics**

The biopharmaceutics reviewer (Angelica Dorantes, Ph.D.) previously recommended approval of the NDA in her review dated April 24, 2012. The reviewer filed an updated memo dated January 23, 2015 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 new clinical pharmacology information in the resubmission, the reviewer (Martina Sahre, Ph.D.) indicated that there was no action necessary and recommended approval in her DARRTS entry on February 26, 2015.

## **6. Clinical Microbiology**

Not applicable.

## **7. Clinical/Statistical- Efficacy**

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

## **8. Safety**

The previous clinical review (Adam George, Pharm.D., signed 31-Jan-2014) did not identify any clinical deficiencies in the NDA.

The safety review of the resubmission was completed by Hyon-Zu Lee, Pharm.D. on February 02, 2015. The safety reviewer found no safety issues from the review of the recent literature and recommends tentative approval of the NDA pending an approval recommendation from the other disciplines.

## **9. Advisory Committee Meeting**

There was no Advisory Committee meeting held for this application.

## **10. Pediatrics**

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 is retained in the label for the new Fresenius argatroban product.

## **11. Other Relevant Regulatory Issues**

- Application Integrity Policy (AIP): There were no AIP issues raised during the pre-approval inspections for this NDA.
- Exclusivity or patent issues of concern: No issues were noted for this NDA.
- 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*

The proposed labeling for the Fresenius Kabi argatroban injection is essentially the same in content as that of the innovator listed drug product, except for the relevant sections of the Dosage and Administration, How Supplied, Description, and Storage and Handling sections of the labeling. The label has also been revised to comply with the Pregnancy and Lactation Labeling Rule (PLLR) (section 8 – USE IN SPECIFIC POPULATIONS).

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

***OSE/DMEPA.*** The DMEPA review for the revised container label, carton labeling and Prescribing labeling was found acceptable from a medication error perspective (see review by Mishale Mistry, PharmD dated January 23, 2015).

***Proprietary name:*** There was no proprietary name proposed for this product.

***Issues not resolved at the time of CDTL memo completion:*** Acceptance of the final PI label and container/carton labeling by the applicant.

***Patient labeling/Medication guide:*** Not required for this product.

## **13. Recommendations/Risk Benefit Assessment**

No product quality, pharmacology/toxicology or clinical pharmacology issues have been found to preclude approval. Clinical safety review finds the application adequate and recommends approval of the NDA. The Office of Process and Facilities recommends approval of the application for the facilities used to manufacturing and control the product.

- Recommended Regulatory Action: Approval, pending acceptance of the final labeling revisions by the applicant.
- Risk Benefit Assessment

The review of this NDA is based primarily on chemistry, manufacturing and controls and clinical pharmacology/biopharmaceutics data. The Applicant has satisfactorily responded to the CMC deficiency and the application has received an approve recommendation from the Office of Process and Facilities. There are no outstanding regulatory issues for this NDA. This application may be approved pending acceptance of the revised labeling by the applicant.

- Recommendation for Postmarketing Risk Management Activities: None
- Recommendation for other Postmarketing Study Commitments: None
- Recommended Comments to Applicant: None

Janice T. Brown -A  Digitally signed by Janice T. Brown A  
DN: cn=US, o=U.S. Government, ou=HHS, ou=FDA,  
ou=People, o.9.2342.19200300.100.1.1=1300101685,  
cn=Janice T. Brown A  
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