CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212035Orig1s000

CLINICAL REVIEW(S)

Clinical Review of 505(b)(2) Application

Submission Date:	April 7, 2021
NDA #	212035
SD#	14
Applicant	Accord Healthcare Inc.
Drug Name: non-proprietary (Proprietary, if appl.)	Argatroban injection in 0.9% sodium chloride, 1 mg/mL, 50 mL
Indication(s) Sought	• For prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT) • As an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI)
Clinical Reviewer	Carrie Diamond, MD
Clinical Team Leader	Tanya Wroblewski, MD

Actions Recommended: Approval

Background of Application:
Pursuant to Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, Accord Healthcare originally submitted NDA 212035, for Argatroban injection in 0.9% sodium chloride, 1 mg/mL, 50 mL on 04/30/2018. During the first review cycle the Reference Listed Drug (RLD) was changed from (b) (4) (b) (4) to Eagle Pharmaceuticals Inc. (NDA 022434). NDA 212035 currently refers to the RLD, for ARGATROBAN injection in 0.9% Sodium Chloride, 1 mg/mL, 50 mL, by Eagle Pharmaceuticals Inc (NDA 022434).

The Division conducted labeling negotiations during the first review cycle. Dr. Laurel Menapace completed a clinical review of the initial application submission on 12/20/2018 and there were no clinical issues identified at that time with the application. The application was issued a tentative approval letter on 02/28/2019. The tentative approval letter states, "this application is not eligible for approval because the 45-day period described in section 505(c)(3)(C) of the Federal Food, Drug and Cosmetic Act (the Act) has not yet expired. This ineligibility reflects your failure to comply the with the statutory requirements for the timing of sending notice of paragraph IV certification as set forth in section 505(b)(3)(B) of the Act."

The Applicant submitted a Class 1/Resubmission of NDA 212035 on 04/07/2021. In the cover letter the Applicant states, "The reference listed drug (RLD), ARGATROBAN IN SODIUM CHLORIDE [Argatroban; Injectable; Intravenous; 50 mg/50 mL (1 mg/mL)] of Eagle Pharmaceuticals Inc., (NDA 022434) is subject to periods of patent protection. The following patents and expiration dates are currently listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"):

US Patent No.	Patent Expiration
7589106	Sep 26, 2027
7687516	Sep 26, 2027

Accord Healthcare Inc. has filed a paragraph IV certification under section 505(b)(2)(A)(iv) of the FD&C Act stating that US patents Nos. 7589106 and 7687516 are invalid, unenforceable, or will not be infringed by manufacture, use, or sale of Argatroban in 0.9% Sodium Chloride Injection, 1 mg/mL, 50 mL under this NDA. Patent certification containing Paragraph IV certification was submitted to USFDA on January 29, 2019 under Module 1.3.5.2 of previous sequence #0007. Accord Healthcare Inc. had notified the Agency that Accord Healthcare Inc. complied with the requirements of section 505(b)(3)(A) of the FD&C Act, and that the infringement suit for the above mentioned US patents was brought against Accord Healthcare Inc. within the statutory 45-day period". Details of the lawsuits were provided, and the lawsuits were dismissed.

Documents Reviewed:
The original submission SD-1 (4/30/18) and clinical review by Dr. Laurel Menapace on 12/20/2018 was reviewed. In addition, the current submission SD-14 (4/7/21) was reviewed. No clinical studies were submitted with this submission.

Module 1:

- Form FDA 356h
- Cover Letter
- Labeling (draft, annotated, and Listed Drug Labeling)

Literature Review: A literature review for new safety information regarding Argatroban was conducted to determine whether the current labeling was sufficient to provide adequate instructions for use.

Orange Book Status/Outstanding Exclusivities:
There are 6 actively marketed NDAs for Argatroban. Their numbers are 20883, 201811, 203049, 22434, 22485, and 209552. There are two NDAs for Argatroban that are listed as discontinued (201743 and 206769). There are 6 ANDAs for Argatroban.

There are outstanding patent numbers 7589106 and 7687516 for NDA 22434 that expire on 09/26/2027.

Summary of Review Findings:
This reviewer conducted a PubMed database search for recent publications regarding Argatroban safety, and no new safety issues were identified.

Labeling:

The labeling submitted was previously negotiated with the Sponsor. We conducted labeling meetings during this resubmission. Labeling was resubmitted and reviewed based on the currently listed RLD label (NDA 022434 for ARGATROBAN by Eagle Pharmaceuticals Inc). Revisions were recommended based on the most recently approved RLD.

Regulatory Conclusion:

The 505(b)(2) Committee agreed that this application was acceptable for approval based on the 505(b)(2) pathway. NDA 212035 is recommended for approval from the clinical perspective. There are no clinical PMRs or PMCs for this Argatroban application (NDA 212035).

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CARRIE E DIAMOND
05/26/2021 08:33:05 AM

TANYA M WROBLEWSKI
05/26/2021 10:42:25 AM

Clinical Review of 505(b)(2) Application

Submission Date:	April 30, 2018
NDA #	212035
SD#	1
Applicant	Accord Healthcare Inc.
Drug Name: non-proprietary (Proprietary, if appl.)	Argatroban injection in 0.9% sodium chloride, 1 mg/mL, 50 mL
Indication(s) Sought	• For prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT) • As an anticoagulant in adults patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI)
Clinical Reviewer	Laurel Menapace, MD
Clinical Team Leader	Virginia Kwitkowski, MS, ACNP-BC

Actions Recommended: Approval

Background of Application:

Pursuant to Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, Accord Healthcare has submitted NDA 212035, for Argatroban injection in 0.9% sodium chloride, 1 mg/mL, 50 mL.
This NDA refers to the Reference Listed Drug (RLD), (b) (4) for ARGATROBAN injection in 0.9% Sodium Chloride, 1 mg/mL, (b) (4)

Documents Reviewed:

SD-1 (4/30/18)

Module 1:

- Form FDA 356h
- Cover Letter
- Administrative Information
- Other Correspondence
- Labeling (draft, annotated, and Listed Drug Labeling)

Literature Review: A literature review for new safety information regarding argatroban was conducted to determine whether the current labeling was sufficient to provide adequate instructions for use.

Review of other Argatroban labelings:
There are 7 actively marketed NDAs for Argatroban. Their numbers are 20883, 201811, 201743, 203049, 206769, 22434, 22485 (the RLD), and 209552 (recently approved on 11/27/18). There is 1 NDA that is tentatively approved (22359). There is one NDA for argatroban that is listed as discontinued (201743). There are 6 ANDAs for argatroban (one of them is listed as a tentative approval).

Recently, all of the NDAs labelings for Argatroban were sent supplement request letters requesting the removal of pediatric-specific text that implied a pediatric indication (while one does not exist). The last of these was approved on 11/27/18.

Summary of Review Findings:

This reviewer conducted a PubMed database search for recent publications regarding argatroban safety, and no new issues were identified.

Orange Book Status/Outstanding Exclusivities for Approved NDAs:

NDA #	Outstanding Exclusivities	Outstanding Patents
(b) (4) (RLD)	There is no unexpired exclusivity for this product in the Orange Book database.	There are no unexpired patents for this product in the Orange Book database.
203049	None	None
20883	None	None
201811	None	None
206769	None	None
22434	None	Patent # 7589106 expiring 09/26/27 (use codes U-1163 and U-1164)
209552	None	None

Labeling:

The labeling was submitted in PLR and PLLR format. We conducted a filing meeting. We have two multi-disciplinary labeling meetings scheduled (01/16/19 & 02/13/19) and a wrap-up meeting planned on 1/22/19 for this submission. We consulted OSE (DMEPA) for review of this labeling and their review by Casmir Ogbonna was archived on 10/16/18, comments were sent to the Applicant and an updated review was archived on 12/06/18 stating that they have no further recommendations for the carton and container labeling.

Labeling discussions have not yet begun, but we will recommend revisions based upon guidances published since the approval of the last version of the RLD labeling and based upon revisions made to previously approved Argatroban products. For details regarding the rationale for specific proposed labeling changes, refer to the Labeling Review by Virginia Kwitkowski archived on 10/05/18.

The 505(b)(2) committee should be consulted for this application.

Regulatory Conclusion:

NDA 212035 is recommended for approval from the clinical perspective. There are no clinical PMRs or PMCs for this Argatroban application. We defer to the CMC discipline for review issues from their perspective.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

VIRGINIA E KWITKOWSKI on behalf of LAUREL A MENAPACE
12/20/2018