CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212035Orig1s000

SUMMARY REVIEW

Cross Discipline Team Leader Memo

Submission Date:	April 7, 2021
NDA #	212035
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)
Regulatory Action Recommendation	Approval

The following summary is taken from the clinical review by Dr. Carrie Diamond.

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 reference listed drug label (NDA 022434 for ARGATROBAN by Eagle Pharmaceuticals Inc). Revisions were recommended based on the most recently approved reference listed drug.

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. The clinical team recommends approval and there are no clinical post marketing requirements or post

marketing commitments for this application (NDA 212035).

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/s/

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Cross-Discipline Team Leader Review

Date	22-Feb-2019
From	Sherita McLamore, Ph.D.
Subject	Cross-Discipline Team Leader (CDTL) Review
NDA	212035
Type of Application	505(b)(2)
Applicant	Accord Healthcare Inc.
Date of Receipt	30-Apr-2018
PDUFA Goal Date	28-Feb-2019
Proposed Proprietary Name	None
Dosage forms / Strength	Injection/50 mg/50 mL (1 mg/mL)
Route of Administration	Intravenous
Proposed Indication(s)	Indicated for prophylaxis or treatment of thrombosis in adult patients with heparin- induced thrombocytopenia (HIT). Indicated as an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI)
Recommended:	**TENATIVE APPROVAL**

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Clinical (Laurel Menapace, M.D.); in DARRTS, dated 20-Dec-2018
- Pharmacology/Toxicology (Emily Place, Ph.D.); in DARRTS, dated 24-Jan-2018
- DEMPA (Casmir Ogbonna, Pharm. D.); in DARRTS, dated 04-Dec-2018
- Drug Product (William Adams, Ph.D.); in Panorama, dated 29-Jan-2019
- Drug Substance (Gaetan Ladouceur, Ph.D.); in Panorama, dated 18-Dec-2018
- Microbiology (Jianli Xue, Ph.D.); in Panorama, dated 11-Dec-2018
- Manufacturing Facilities (Diane Goll, Ph.D.); in Panorama, dated 22-Jan-2019
- Manufacturing Process (Diane Goll, Ph.D.); in Panorama, dated 30-Nov-2018
- Quality Biopharmaceutics (Yang Zhao, Ph.D.); in Panorama, dated 22-Jan-2018

1. Introduction

NDA 212035 was submitted by Accord Healthcare Inc. for Argatroban Injection in 0.9% sodium chloride, 1 mg/mL, 50 mL in accordance with section 505(b)(2) of the Food, Drug and Cosmetic Act. Argatroban is a small molecule anticoagulant that was originally approved by the FDA in (b) (4) (NDA 20883) for the treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT). NDA (b) (4) was submitted for Argatroban in Sodium Chloride (b) (4) by (b) (4) and approved in (b) (4) 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). Argatroban in Sodium Chloride manufactured by (b) (4) is the Listed Drug (LD) for this application. The (b) (4) product is supplied as a sterile, non-pyrogenic, clear, colorless to pale yellow isotonic solution in a single-dose

clear glass vial containing (b) (4) the active in (b) (4) sodium chloride (1 mg/mL). The Accord drug product, Argatroban injection in 0.9% sodium chloride, 1 mg/mL (50 mL) is presented as a non-pyrogenic, clear, colorless to pale yellow sterile isotonic aqueous solution containing the active, sorbitol and sodium chloride in a single use glass vial solution. The Accord product is qualitatively and quantitatively identical to the LD (b) (4) It has the indications, route of administration, dosage form, and dosing regimen as the LD. The Accord product is designed to (b) (4) (b) (4)

The recommended dosing regimen for Argatroban Injection in 0.9% Sodium Chloride for patients with heparin-induced thrombocytopenia consists of an initial dose of 2 mcg/kg/min administered as a continuous infusion. For patients with percutaneous coronary intervention, the initial dose is 25 mcg/kg/min and a bolus of 350 mcg/kg administered via a large bore intravenous line over 3 to 5 minutes.

No clinical studies were performed with the proposed drug product as this submission relies on the LD, Argatroban in Sodium Chloride, (b) (4) for safety and efficacy. Accordingly, approval of NDA 212035 from clinical, non-clinical and clinical pharmacology perspectives will be primarily based on publicly available information.

2. Background

There are seven approved NDAs for Argatroban (NDAs 20883, 201811, 201743, 203049, 206769, 22434, 22485 and 209552). This application presents a formulation that is a new strength of Argatroban hydrochloride. Argatroban is a small molecule, synthetic, direct thrombin inhibitor derived from L-arginine that is manufactured by (b) (4). Argatroban is approved 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). The current application contains no additional or independent clinical studies or PK data but instead relies upon information in the public domain and on the Agency's determination of safety and efficacy for the Listed Drug, Argatroban Injection in 0.9% Sodium Chloride, (b) (4) (1 mg/mL) which was previously approved for marketing under NDA (b) (4) The indications, active ingredient, (b) (4) route of administration, dosage form, and concentration of argatroban are the same as those of the LD.

3. Chemistry, Manufacturing and Controls (CMC)

Argatroban drug substance is a white or almost white non-hygroscopic, crystalline solid manufactured by (b) (4) It has four asymmetric centers and shows isomerism at C21 (produced at *ca.* 65/35 of R and S at C21). As the drug product is formulated as clear solution in which the drug substance is in a solubilized form, the polymorphic form of the drug substance does not affect the quality of the drug product. The drug substance will be packaged in (b) (4) (b) (4) The drug substance currently has a retest period of (b) (4) months when stored at (b) (4) The applicant crossed referenced DMF (b) (4) for all aspects pertaining to the manufacture and control of the drug substance. DMF (b) (4) was reviewed in conjunction with this NDA and was considered adequate to support the approval of this NDA.

The drug product, Argatroban Injection in 0.9% Sodium Chloride, 1 mg/mL, 50 mL is presented as a non-pyrogenic, clear, colorless to pale yellow sterile isotonic aqueous solution containing the active, sorbitol and sodium chloride in a single-use glass vial solution. The drug product is qualitatively and quantitatively identical to Listed Drug (ARGATROBAN injection in 0.9% Sodium Chloride, 1 mg/mL, (b) (4) Like the LD, the proposed product is ready to use and does not require dilution. The drug product (b) (4) (b) (4) contains no antimicrobial preservatives (b) (4). The applicant requested an *in vivo* biowaiver for the drug product in accordance with 21 CFR 320.22(b)(1). Based on the provided information, the biopharmaceutics reviewer concluded that the waiver of the requirement to conduct in vivo bioavailability or bioequivalence should be granted as the proposed product is a parenteral solution intended solely for intravenous administration; and the proposed product contains the same active and inactive ingredients in the same concentration as the LD product.

Argatroban Injection in 0.9% Sodium Chloride, 1 mg/mL, 50 mL is manufactured, packaged and release tested by Intas Pharmaceuticals Limited, Matoda, India at a commercial batch size of (b) (4) L, which corresponds to (b) (4) vials. The drug product will be manufactured by (b) (4) (b) (4) (b) (4) The description of the manufacturing process includes well defined CQAs and CPPs. The proposed process parameters and in-process controls are described in sufficient detail and are justified. The applicant demonstrated the suitability of the manufacturing process for the drug product at the commercial scale and the description of the manufacturing process includes appropriate in-process controls and operating parameters.

In support of the proposed 24-month expiry, 24 months of long-term (25°C/60% RH) and 6 months accelerated (40°C/75% RH) primary stability data. The available stability data demonstrates consistency over time and supports the proposed expiry. Accordingly, based on the 24 months of stability data included in this application for Argatroban injection in 0.9% sodium chloride, 1 mg/mL, Accord Healthcare Inc. proposed and the FDA accepts the expiration dating period of **24 months** for the drug product when stored at stored at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). The label includes the statements "Do not freeze" and "(b) (4)".

NDA 212035 included 5 manufacturing, testing, and packaging facilities. All facilities were found acceptable for the responsibilities listed in the application.

Overall Product Quality Recommendation: The Office of Pharmaceutical Quality (drug substance, drug product, drug process, microbiology, biopharmaceutics and facilities) recommends **APPROVAL** for NDA 212035.

6. Clinical Pharmacology

n/a

7. Non-Clinical Pharmacology/Toxicology

The proposed (b) (4) indication, route of administration, concentration, and duration of administration of Argatroban Injection in 0.9% Sodium Chloride, 50 mg/50 mL will be the same as those of the LD, Argatroban Injection in 0.9% Sodium Chloride (b) (4) This application included no new non-clinical pharmacokinetic or toxicology information. Therefore, reliance on the pharmacology/toxicology information required for the approval of this product is based on previous FDA findings for the safety of the LD. The proposed product, Argatroban Injection in 0.9% Sodium Chloride, 50 mg/50 mL, is approvable from the perspective of pharmacology/toxicology.

8. Clinical/Statistical-Efficacy

The application was submitted as a 505(b)(2) NDA under the Food Drug and Cosmetic Act. As such this submission relies on the LD, Argatroban Injection in 0.9% Sodium Chloride (b) (4) (b) (4) for safety and efficacy and no additional or independent clinical studies were performed with the proposed drug product (Argatroban Injection in Sodium Chloride, 1 mg/mL). The clinical reviewer conducted a PubMed database search for recent publications regarding argatroban safety and no new issues were identified. Accordingly, the clinical reviewer has recommended approval NDA 212035 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).

9. Safety N/A

10. Advisory Committee Meeting **N/A**

11. Pediatrics N/A

12. Other Relevant Regulatory Issues N/A

13. Labeling

The label was updated to comply with Pregnancy and Lactation Labeling Rule (PLLR) content and format requirements. The labeling review was completed by DMEPA, Clinical, Non-Clinical and CMC.

Clinical Recommendations:

- No labeling comments noted.

DMEPA Recommendations:

A. Prescribing Information

1. Dosage and Administration Section

a. Consider stating numbers greater than or equal to 1,000 in tables 2 and 3 with a comma to prevent the reader from misinterpreting thousands “1000” as hundreds “100” or ten-thousands “10000” (e.g. 1,000 mg instead of 1000 mg, 10,000 units instead of 10000 units), per Draft Guidance: Container and Carton April 2013 (lines 475-476), and ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations.

b. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise those abbreviations, symbols, and dose designations as follows:

• In Section 2.3, replace the symbol **"≥"** with the intended meaning to prevent misinterpretation and confusion.

Additional recommendations were made to the Carton Labeling and Container Label and to the Carton Sticker Label

Non-Clinical Recommendations:

The label was updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR) content and format requirements

CMC Recommendations:

Minor edits made in the PI

Overall Labeling Recommendation:

Multiple labeling recommendations and edits were proposed to ensure that the prescribing information is clear and concise and is based on our current regulations and guidance (see Virginia Kwitkowski's review dated 10/05/18). The applicant accepted all changes recommended by the agency. The labeling for Accord's Argatroban Injection in 0.9% Sodium Chloride, 50 mg/50 mL is acceptable.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

This product relies on the safety and efficacy of the Listed Drug, Argatroban in Sodium Chloride (125 mg/125 mL). The Accord product is nearly identical to the Listed Drug, as the Accord product has the same active ingredient and inactive ingredient, is the same dosage form and has the same routes of administration and concentration of argatroban following as the Listed Drug.

While all disciplines recommended approval of NDA 212035 the CDTL recommends **TENATIVE APPROVAL.** This application is not eligible for full approval because the 45-day period described in section 505(c)(3)(C) of the Federal Food, Drug, and Cosmetic Act has not yet expired. This ineligibility is based on the applicant's failure to comply 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.

- **Risk Benefit Assessment**

Please refer to NDA 22485.

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/s/

SHERITA D MCLAMORE
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