CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212035Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 212035
Argatroban in Sodium Chloride Injection
Review #2

Drug Name/Dosage Form	Argatroban Injection in Sodium Chloride, 50 mg/50 mL
Strength	50 mg/50 mL (1 mg/mL)
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Accord Healthcare, Inc.
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resubmission, Sequence 0012	4/7/21	Drug product, Manufacturing, Microbiology

Quality Review Team

Discipline	Reviewer/Secondary	Branch/division
Drug Product	Theodore Carver/ David J. Claffey	Branch V/New Drug Products III of Office of New Drug Products
Process/ Facility	Vidya Pai/Rose Xu	Branch II/ Office of Pharmaceutical Manufacturing Assessment
Microbiology	Jianli Xu/ Neil Sweeney	Office of Pharmaceutical Manufacturing Assessment
Regulatory Business Process Manager	GraftonAdams/Hamet Toure	Branch I/Regulatory Business Process Management I
Application Technical Lead	Theodore Carver	Branch V/New Drug Products III of Office of New Drug Products

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

B.

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	2/13/2019	Reviewed in conjunction with NDA
	Type III			n/a	No Review	Adequate information provided in the NDA (Review #1)
	Type III			n/a	No Review	Adequate information provided in the NDA (Review #1)
	Type V			n/a	No Review	Adequate information provided in the NDA (Review #1)

*Sufficient information provided in the NA

C. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	22434	Listed Drug

2. CONSULTS:

None.

Executive Summary

1. **Recommendations and Conclusions on Approvability**

The Office of Pharmaceutical Quality Review team has assessed NDA 212035 with respect to Chemistry, Manufacturing, and Controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports to have. As such OPQ recommends approval of this NDA from a quality perspective.

2. **Background Summary**

Argatroban Injection in Sodium Chloride is an aqueous solution of 50 mg Argatroban in 50 mL 0.9 sodium chloride and sorbitol for intravenous infusion. Argatroban was previously 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 of HIT while undergoing percutaneous coronary intervention. The basis for tentative approval of the original 505(b)(2) application was a biowaiver granted based on qualitative and quantitative sameness to Argatroban injection in 0.9% sodium chloride, (b) (4); however, for paragraph IV patent certification to a pharmaceutically equivalent product, the listed drug in the NDA resubmission is Argatroban in Sodium Chloride, NDA 022434.

The drug product consists of a 50 mL aqueous solution of argatroban and excipients. Each mL contains 1 mg argatroban, 3 mg sorbitol (NF) (b) (4), and 9 mg sodium chloride (USP) (b) (4), (b) (4) Water for Injection (USP). (b) (4)

NDA 212035 was tentatively approved on 2/28/2019 with a paragraph IV patent certification from the Applicant. The Integrated Quality Assessment for the original NDA concluded that there were no approvability issues with the drug substance, drug product, microbiology, manufacturing, or facilities. On 4/7/2021, the Applicant resubmitted the NDA with a request for final approval.

In the resubmission amendment, the Applicant states that the only changes to the application are (b) (4) that was previously approved. The Applicant certifies that there are no other changes made to the chemistry, manufacturing, and controls section of the application after the issuance of the tentative approval letter. No changes to CMC information have been submitted to the NDA since the tentative approval letter was issued. There have been no changes to drug substance and manufacturing information provided in the original submission, and

therefore, the original reviews for these disciplines remain supportive of recommendation to approve this NDA. The drug product, microbiology, and facilities reviews of information provided in the resubmission and subsequent facility evaluations are summarized below.

3. **Summary of Quality Assessments**

A. Drug product (Argatroban in Sodium Chloride): Dr. Theodore Carver reviewed the drug product and quality aspects of the product labeling. The drug product is a clear, colorless to pale yellow solution in a 50 mL clear (b) (4) glass vial with (b) (4) (b) (4) rubber stopper and aluminum crimp with green flip-off seal. Argatroban is administered as an intravenous bolus dose followed by continuous infusion dosing. The drug product container closure is a 50 mL vial that may be inverted prior to intravenous infusion.

B. Microbiological Aspects: Dr. Jianli Xu performed the quality microbiology review of the drug product information in the resubmission amendment to NDA 212035. The resubmission including a single manufacturing change (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) The same summary of changes provided in the resubmission amendment was reviewed in microbiology review (b) (4) (adequate) dated 9/19/2018 and deemed adequate. The microbiology review concluded that the microbiological information is adequate to support the NDA.

4. **Assessment of Manufacturing Facilities:** Facility compliance information for the drug substance and drug product in the NDA resubmission were reviewed by Dr. Vidya Pai. No new manufacturing facilities were introduced in the resubmission. The inspection history and compliance status were reviewed for each facility and no new concerns were noted that would affect their suitability to support the NDA. The facilities review concluded that all facilities are in a favorable compliance status and are acceptable to support the NDA. See the table below for a summary of the recommendation for each facility. As a lifecycle management consideration, the OPMA facilities review recommended (b) (4) (b) (4)

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Table of Manufacturing Facilities for NDA 212035:

Establishment Name and Address	FEI Number	Responsibilities and Profile Codes	Initial Assessment	Final Recommendation
(b) (4)				**RECOMMEND APPROVE; Acceptable for the functions and responsibilities listed in the application.**
Intas Pharmaceuticals Limited Plot No : 5 to 14, Pharmez, Near Village Matoda, Sarkhej-Bavla Highway, No. 8-A, Taluka : Sanand, Ahmedabad Gujarat, India 382213	(b) (4)	LCP – Also a Testing Facility of Drug Product Manufacturer (b) (4)	Low Risk Identified. Experience in testing operations. Acceptable compliance history.	**RECOMMEND APPROVE; based on acceptable regulatory history and ability to perform the proposed analytical test**
Intas Pharmaceuticals Limited Plot No : 457/458, Village – Matoda, Sarkhej-Bavla Highway, Taluka - Sanand, Ahmedabad Gujarat, India 382210	(b) (4)	(b) (4) Drug Product Manufacturing and Testing (b) (4) - Testing: Release and Stability testing for DP (b) (4)	Low Risk Identified. Facility has history manufacturing (b) (4) Acceptable compliance history.	**Acceptable for the functions and responsibilities listed in the application.**

5. **Environmental Assessment**: No new changes in drug product manufacturing or scale have been submitted since the review of the original NDA submission; therefore, the claim for categorical exclusion under 21 CFR 25.31(a), which was reviewed by William Adams, the drug product reviewer, on 1/28/2019, remains acceptable and is granted.

6. **Expiration Dating and Storage Conditions**: No new drug substance or drug product stability data have been submitted since the tentative approval of the original NDA. The drug substance has a retest period of (b) (4) months when stored at (b) (4). The drug product stability data were previously reviewed and found to be adequate to support the 24-month shelf life requested by the Applicant for the drug product. An expiration dating period of 24 months is acceptable for the drug product when stored at stored at controlled room temperature20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to86°F). The drug product should be protected from light and stored in original carton. DO NOT FREEZE.

7. **Quality Labeling**: The container and carton label were reviewed as part of the review of the drug product and labeling reviews. The dosage form description, strength, established name, NDC #, Lot #/Expiry, and storage conditions are adequately described in the carton and container label, which meets relevant regulatory requirements for labeling. Refer to the labeling review for additional information.

1. **List of CMC Deficiencies:** None

OVERALL ASSESSMENT AND SIGNATURES:

At present, there are no outstanding deficiencies related to the drug substance, drug product, process, microbiology, and environmental analysis sections of this NDA. The OPQ overall recommendation for NDA 215014 is *approval.*

Theodore Carver, Ph.D. 5/26/2021

Application Technical Lead Name and Date:

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CHAPTER II: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: The below review is for the USPI submitted on 5/17/21 for the NDA 212035 resubmission. This version of the labeling was previously edited based on suggested revisions earlier in the review cycle.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	**ARGATROBAN IN SODIUM CHLORIDE injection, for intravenous use**	Adequate.
Established name(s)		Adequate.
Route(s) of administration		Adequate.
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Injection: 50 mg per 50 mL (1 mg/mL) (b) (4) in single-dose vial (3)	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"		N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient use). Other package		Adequate.

terms include pharmacy bulk package and imaging bulk package.		

1.2 FULL PRESCRIBING INFORMATION

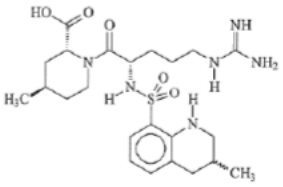
1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Each 50 mL glass vial contains 50 mg argatroban (1 mg/mL); and, as supplied, is ready for intravenous infusion. Dilution is not required. Argatroban in Sodium Chloride injection is a clear, colorless to pale yellow solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if solution is cloudy, contains precipitates, or if the flip (b) (4) is not intact. Vial may be inverted for use with a medical infusion set.	Adequate. The instructions for inverting the vial were discussed with the review team, because some drug products include vial attachments to facilitate inversion of the vial. In response to an information request, the Applicant indicated that no vial attachments or other devices are included or copackaged with the drug product. After discussion with the review division and review of the container closure information, it was determined that the 50 mL container will work with marketed infusion sets without a co-packaged adapter.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Injection: 50 mg per 50 mL (1 mg/mL) clear solution in a single–dose vial. The solution is ready for intravenous infusion.	Adequate.
Strength(s) in metric system		Adequate.
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance		Adequate.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting		Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"		N/A
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.		Adequate.

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Argatroban is a synthetic direct thrombin inhibitor and the chemical name is 1-[(2S)-5-[(aminoimino-methyl)amino]-1-oxo-2-[[(1,2,3,4-tetrahydro-3-methyl-8-quinolinyl)sulfonyl]amino]pentyl]-4-methyl-,(2R,4R)- 2-piperidinecarboxylic acid. Argatroban has 4 asymmetric carbons. One of the asymmetric carbons has an *R* configuration (stereoisomer Type I) and an *S* configuration (stereoisomer Type II). Argatroban consists of a mixture of *R* and *S* stereoisomers at a ratio of approximately 65:35.	Adequate.
Dosage form(s) and route(s) of administration		Adequate.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.		N/A, not a salt.
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.		Adequate.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	The molecular formula of argatroban is $C_{23}H_{36}N_6O_5S$. Its molecular weight is 508.63 g/mol. The structural formula is:  Argatroban in Sodium Chloride injection is a sterile, non-pyrogenic, clear, colorless to pale yellow, (b) (4) solution. It is supplied in a single-dose, clear glass vial containing 50 mg of argatroban in 50 mL solution. Each mL, contains 1 mg argatroban, 9 mg sodium chloride, USP and 3 mg sorbitol, NF in water for injection, USP. The pH of the solution is between 3.2 to 7.5.	Adequate. The information aligns with information submitted in Module 3 of the NDA.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol		N/A
Statement of being sterile (if applicable)		Adequate.
Pharmacological/ therapeutic class		Adequate.

Chemical name, structural formula, molecular weight		Adequate.
If radioactive, statement of important nuclear characteristics.		N/A
Other important chemical or physical properties (such as pKa or pH)		N/A

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	None.	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	None.	Adequate.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		

Available dosage form(s)	**16 HOW SUPPLIED/STORAGE AND HANDLING** Argatroban in Sodium Chloride injection is supplied in a single-dose vial containing 50 mg argatroban in 50 mL of aqueous solution (1 mg/mL). NDC 16729-430-11 – Package containing one vial of Argatroban in Sodium Chloride injection (each vial contains 50 mg of argatroban). NDC 16729-430-43 – Package containing 10 vials of Argatroban in Sodium Chloride injection (each vial contains 50 mg of argatroban). **Storage** Store the vials in original cartons at 20°C to 25°C (68°F to 77°F): excursion permitted between 15°C to 30°C (59°F to 86°F). Do not refrigerate or freeze. Protect from light and store in carton. Do not use if solution is cloudy or contains a precipitate.	Adequate
Strength(s) in metric system		Adequate.
Available units (e.g., bottles of 100 tablets)		Adequate.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number		Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	N/A	N/A

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	See above.	Adequate.

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)		Adequate. The shelf life and storage conditions are supported by stability results.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	N/A

Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	See above.	Adequate.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	No information included.	N/A
Include information about child-resistant packaging	No Information included.	Not applicable

1.2.5 Other Sections of Labeling N/A

1.2.6 **Manufacturing Information After Section 17 (for drug products)**

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	**Manufactured For:** Accord Healthcare, Inc., 1009, Slater Road, Suite 210-B, Durham, NC 27703, USA. **Manufactured By:** Intas Pharmaceuticals Limited, Plot No.: 457, 458, Village – Matoda, Bavla Road, Ta. - Sanand, Dist.- Ahmedabad – 382 210. India.	Adequate.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): N/A

3.0 CARTON AND CONTAINER LABELING

Assessment of Container and Carton labeling: Adequate

3.1 Container Label

(b) (4)

3.2 Carton Labeling

(b) (4)

10X vial Carton sticker label:

ITEMS FOR ADDITIONAL ASSESSMENT

N/A

Overall Assessment and Recommendation:

The labeling/labels are adequate from a quality perspective.

Theodore Carver

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David Claffey

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	212035
Assessment Cycle Number	MR02
Drug Product Name/ Strength	Argatroban in 0.9% Sodium Chloride Injection/1 mg/mL, 50 mL
Route of Administration	Intravenous Infusion
Applicant Name	Accord Healthcare Inc.
Therapeutic Classification/ OND Division	CDER/OND/OCHEN/DNH
Manufacturing Site	Intas Pharmaceuticals Limited, Plot No: 457/458, Village-Matoda, Bavla Road, Ta.-Sanand, Ahmedabad, Gujarat, India 382210
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Amendment	4/7/2021

Highlight Key Issues from Last Cycle and Their Resolution: None

Remarks: None

Concise Description of Outstanding Issues: None

Supporting Documents: Microbiology review (b) (4) (adequate) dated 9/19/2018 for the proposed changes regarding (b) (4) (b) (4)

The amendment is to "request for final approval" of NDA 212035 after receiving a tentative approval on 2/28/2019. The original submission was reviewed in microbiology review N212035MR01.doc (adequate) dated 12/11/2018 and deemed adequate.
The subject drug product (b) (4) is manufactured on the (b) (4) (b) (4)

(b) (4)

(b) (4) (b) (4)

(b) (4)

(b) (4) The same summary of changes are provided in this amendment, reviewed in microbiology review (b) (4) .pdf (adequate) dated 9/19/2018 and deemed adequate. The sponsor certifies that there are no other changes made to the CMC section of the application after the issuance of the tentative approval letter.

Primary Microbiology Assessor Name and Date:
Jianli Xue, Ph.D.
CDER/OPQ/OPMA/DMA I/BII
5/3/2021

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Neal J. Sweeney, Ph.D.
CDER/OPQ/OPMA/DMA I/BII
5/3/2021

Neal Sweeney

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Jianli Xue

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Date: 5/04/2021 03:23:39PM
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/s/

THEODORE E CARVER
05/28/2021 12:44:51 PM

DAVID J CLAFFEY
05/28/2021 02:04:02 PM

Recommendation: APPROVAL

NDA 212035
Review #1

Drug Name/Dosage Form	Argatroban injection in 0.9% NaCl, 50 mg/50 mL
Strength	1 mg/mL
Route of Administration	IV
Rx/OTC Dispensed	Rx
Applicant	Accord Healthcare Inc.
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	30-Apr-18	All
Amendment	14-May-18	DP
Amendment	31-May-18	DP, Process, Facility,
Amendment	05-Nov-18	DP, Process, Micro, Facility

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Gaetan Ladouceur	Suong Tran
Drug Product	William Adams	Anamitro Banerjee
Process	Diane Goll	David Anderson
Microbiology	Jianli Xue	Neal Sweeney
Facility	Diane Goll	David Anderson
Biopharmaceutics	Yang Zhao	Banu Zolnik
Regulatory Business Process Manager	Rabiya Laiq	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a
Environmental	William Adams	Anamitro Banerjee

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	n/a		Reviewed in conjunction with NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type V			n/a	No Review	Adequate information provided in the NDA

B. Other Documents: *IND, LD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	(b) (4)	Listed Drug

2. CONSULTS

N/A

Executive Summary

1. Recommendations and Conclusion on Approvability

OPQ recommends APPROVAL of NDA 212035 for Argatroban Injection in 0.9% NaCl, 1 mg/mL. As part of this action, OPQ grants a (b) (4)-month re-test period for the drug substance when stored (b) (4) and a 24-month expiration period for the drug product when stored at "20°C to 25°C (68°F to 77°F) excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature]". There are no outstanding issues and no post-approval quality agreements to be conveyed to the applicant.

2. Summary of Quality Assessments

1. Product Overview

NDA 212035 was submitted 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 by Accord Healthcare Inc. Argatroban is a small molecule anticoagulant that was originally approved by the FDA in 2000 (NDA 20883) for the treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT). (b) (4) argatroban was approved under (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) was approved under (b) (4) is the Listed Drug (LD) for this application.

Argatroban drug substance is a synthetic direct thrombin inhibitor derived from (b) (4) and is manufactured by (b) (4) 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, sorbital 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 same route of administration, dosage form, and dosing regimen as the LD. The Accord product is designed to minimize waste (50 mL vs 125 mL).

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.

Based on the information provided in this application (original submission and in responses to information requests), OPQ considers all review issues adequately addressed

and potential risks to patient safety, product efficacy, and product quality mitigated appropriately. Accordingly, OPQ recommends APPROVAL of NDA 212035 and grants a (b)(4)-month re-test period for the drug substance (as outlined in the referenced DMF) and a **24**-month expiration period for the drug product when stored at 20°C to 25°C (68°F to 77°F) excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature]. Protect from light and store in original carton. DO NOT FREEZE.

Proposed Indication(s) including Intended Patient Population	• For prophylaxis or treatment of thrombosis in adult patients with HIT • As an anticoagulant in adult patients with or at risk for HIT undergoing PCI
Duration of Treatment	undefined
Maximum Daily Dose	560mg
Alternative Methods of Administration	None

2. Quality Assessment Overview

Drug Substance

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). Because the drug product is formulated as clear solution in which the drug substance is in solubilized form, the polymorphic form of the drug substance does not affect the quality of the drug product. Argatroban is sparingly soluble in ethanol, insoluble in acetone, ethyl acetate, and in ether. The drug substance will be packaged in (b) (4) (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. Accordingly, limited information was included in the application. DMF (b) (4) was reviewed in conjunction with this NDA and was considered adequate to support the approval of this NDA.

Drug Product and Drug Process

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. It has the same route of administration, dosage form and dosing regimen as the LD.

The drug product contains no antimicrobial preservatives (b) (4) The manufacturing process was developed by (b) (4) and drug product quality attributes. It 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 NDA exhibit batch size is identical to the proposed commercial batch size. Argatroban Injection will be manufactured by (b) (4) (b) (4) The manufacturing process includes: (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. The description of the manufacturing process includes appropriate in-process controls and operating parameters.

The drug product specifications included description, identification, pH, container content, particulate matter, bacterial endotoxins, sterility color and achromicity of solution, osmolality, assay and related substances. The applicant included a risk assessment for elemental impurities as per ICH Q3D/USP <232>. The results of the risk assessment are acceptable and therefore a test for an elemental impurity in the drug product release specifications was not proposed and is not required (see drug product review for details). The drug product specifications are consistent with ICH Q6A and are based on batch analyses and stability data. The drug product specifications are adequate to establish the drug product identity, potency and purity and provide adequate controls to ensure the quality of the drug product throughout the proposed product expiry. The proposed specification and acceptance criteria for the drug product, together with controls for impurities in the drug substance are adequate to ensure that the critical quality attributes of this product are well controlled.

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 were provided for three registration batches of the drug product. The registration batches were manufactured at commercial scale by the commercial process and were stored inverted and upright in the commercial container closure system.

The applicant requested a 24-month expiry for the drug product when stored under controlled room temperature. The available stability data shows consistency over time and supports the proposed expiry. 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 products 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 drug product should be protected from light and stored in original carton. DO NOT FREEZE.

NDA 212035 is recommended for approval from a drug product and drug process perspective with an assigned drug product expiry of 24-months.

Biopharmaceutics

The applicant requested a waiver of *in vivo* bioavailability and bioequivalence of 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 is granted based on the following:

1. the proposed product is a parenteral solution intended solely for intravenous administration; and
2. the proposed product contains the same active and inactive ingredients in the same concentration as the LD product.

Accordingly, based on the information provided, the biowaiver is granted and this application is recommended for approval from a biopharmaceutics perspective.

Quality Microbiology

The drug product manufacturing process includes (b) (4)

(b) (4)

(b) (4) Accordingly, this application is recommended for approval from a quality microbiology perspective.

Facilities

NDA 212035 included 3 sites and all sites were listed as ready for inspection:

- **Intas Pharmaceuticals Limited of India (FEI 3003157498)**– Manufacture, release and stability testing of drug product
- **Intas Pharmaceuticals Limited of India (FEI** (b) (4)**)-** (b) (4) for drug product

(b) (4)

All facilities listed in NDA 212035 were deemed acceptable for the responsibilities listed in the application; however, the facility reviewer notes the following Lifecycle Management Considerations:

(b) (4)

NDA 212035 is recommended for approval from a compliance perspective.

Environmental Assessment

The applicant provided a claim for categorical exclusion and a statement of no extraordinary circumstances under 21 Code of Federal Regulations (CFR) Sections 25.31(a). The categorical exclusion cited is appropriate based on the estimated amount of drug to be produced for direct use. The claim of categorical exclusion is therefore acceptable and granted.

3. Special Product Quality Labeling Recommendations (NDA only)

n/a

4. **Final Risk Assessment (see Attachment)**

Attached.

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Dist.- Ahmedabad – 382 210.
India.

Reviewer's Assessment:
Package Insert
Highlights: Established name is acceptable for CMC. A trade name is not proposed.
Section 2 & 3: Acceptable for CMC. The description, dosage form, and strength are correct.
Section 11: The IUPAC chemical name is edited for clarity. Ingredient names are edited to include the USP/NF designations to be consistent with other approved Argatroban applications.
Section 16: Information is complete and correct. The storage statement is supported by information in module 3.2.P.8.
"Mfg for" and "Mfg by" statements are accurate, and the use of both statements is acceptable.
Content meets 21 CFR 201.56 and 201.57.
CMC revisions were noted at the labeling meetings and forwarded to the applicant.

Vial Label

(b) (4)

Reviewer's Assessment:
Vial Label: Draft label is acceptable from the CMC perspective. The established name, strength (1 mg/mL), composition statement and storage statement are the same as the reference product. Content statement (50 mg/50mL) is supported by the proposed application. There is no proposed trade name. "Mfg for" and "Mfg by" statements are acceptable. Content meets 21 CFR 201.56 and 201.57.

Single Vial Carton Labeling

(b) (4)

10 Vial Carton Labeling

(b) (4)

Reviewer's Assessment:

Single Vial Carton: Draft label is acceptable rom the CMC perspective. The established name, strength (1 mg/mL), and storage statement are the same as the reference product. Content statement (50mg/50mL) is supported by the proposed application. There is no proposed trade name. "Mfg for" and "Mfg by" statements are acceptable. Content meets 21 CFR 201.56 and 201.57.

10 Vial Carton: Draft label is acceptable from the CMC perspective and the information is the same as accepted for the single vial carton.

List of Deficiencies: None

Primary Labeling Reviewer Name and Date:

William Adams, CMC-DP Reviewer/DNDP 01/28/19

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Anamitro Banerjee, Branch Chief/DNDP 01/28/19

William Adams

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Anamitro Banerjee

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BIOPHARMACEUTICS REVIEW

Application No: NDA-212035-ORIG-1

Drug Product Name, Strength: Argatroban injection in 0.9% sodium chloride, 1 mg/mL, 50 mL

Route of Administration: Intravenous Injection (infusion)

Indication: A direct thrombin inhibitor indicated (1) 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).

Applicant Name: Accord Healthcare Inc.

List of Submission being Reviewed:
Original NDA-212035 submission dated 4/30/18

Primary Biopharmaceutics Reviewer:
Yang Zhao, Ph.D., Division of Biopharmaceutics-Branch 1

Secondary Biopharmaceutics Reviewer:
Banu Zolnik, Ph.D., Division of Biopharmaceutics-Branch 1

Review Summary:

Submission: Accord Healthcare Inc. submitted this NDA seeking approval for Argatroban injection in 0.9% sodium chloride, 1 mg/mL, 50 mL under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The Listed Drug (LD) is (b) (4) Argatroban injection in 0.9% sodium chloride, 1 mg/mL, (b) (4)

Review's Objective: The Biopharmaceutics Review focuses on the evaluation of the Applicant's waiver request of in vivo bioavailability and bioequivalence studies.

Biowaiver: No safety or efficacy clinical studies were submitted to support this application. The Applicant is relying on FDA's findings of safety and effectiveness of the LD product.

The Applicant requests a waiver of evidence of in vivo bioequivalence of Argatroban injection in 0.9% sodium chloride, 1 mg/mL, 50 mL relative to the above LD. Per 21 CFR 320.22(b)(1), a waiver of the requirement to conduct in vivo bioavailability or bioequivalence studies is applicable for the proposed drug product, because (1) the proposed product is a parenteral solution intended solely for intravenous administration; and (2) the proposed product contains the same active and inactive ingredients in the same concentration as the LD product. It should be noted that the proposed drug product is qualitatively and quantitatively same as the LD (b) (4)

(b) (4)

(b) (4) Based on the provided information, waiver of the requirement to conduct in vivo bioavailability or bioequivalence studies for the proposed drug product is **granted.**

Overall Review Recommendation:
From the Biopharmaceutics perspective, NDA 212035 for Argatroban injection in 0.9% sodium chloride, 1 mg/mL, 50 mL is recommended for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

1. Background:

Argatroban injection in 0.9% sodium chloride, 1 mg/mL, 50 mL is a sterile, clear, colorless to pale yellow isotonic solution. It is supplied in a single-dose clear glass vial containing 50 mg of argatroban in 50 mL sodium chloride solution for intravenous infusion use. The vial is sealed with a gray rubber stopper and a green aluminum flip-off seal. Dilution is not required. The excipients present are sorbitol (b) (4), sodium chloride (b) (4), and water (b) (4).

The Applicant reported that argatroban drug substance is soluble in bulk solution containing (b) (4) sodium chloride (b) (4), but the Applicant did not provide solubility data of argatroban.

The Listed Drug (LD) is Argatroban injection in 0.9% sodium chloride, 1 mg/mL, (b) (4) (b) (4)

2. Assessment of Waiver Request of In Vivo Bioavailability and Bioequivalence Studies:

The Applicant requested a waiver of the requirement to conduct in vivo bioavailability or bioequivalence studies for Argatroban injection in 0.9% sodium chloride, 1 mg/mL, 50 mL in accordance with 21 CFR 320.22(b)(1) (\\cdsesub1\evsprod\nda212035\0001\m1\us\request-waiver-in-vivo-bioavailability-studies.pdf).

The proposed drug product has the same indications, route of intravenous administration, dosage form and dosing regimen as those for the LD product of Argatroban injection in 0.9% sodium chloride, 1 mg/mL, (b) (4) The proposed drug product contains the same active ingredient and inactive ingredients in same concentration (mg per mL) as the LD product (Table 1).

Table 1. Formulation comparison between the proposed Argatroban injection in 0.9% sodium chloride, 1 mg/mL, 50 mL and LD Argatroban injection in 0.9% sodium chloride, (b) (4) mL

Sr. No.	Ingredients	Accord's formulation: Argatroban Injection in 0.9% Sodium chloride, 1 mg/mL, 50 mL		RLD and RS formulation's: Argatroban Injection in 0.9% Sodium chloride, 1 mg/mL, (b) (4) (b) (4)	
		Concentration per mL	Concentration per vial (50 mL)	Concentration per mL	Concentration per vial (b) (4)
1	Argatroban	1.0 mg	50.0 mg	(b) (4)	
2	Sorbitol	3.0 mg	150.0 mg		
3	Sodium chloride	9.0 mg	450.0 mg		
4	Water for injection				

In addition, the Applicant provided comparative physico-chemical data of assay, pH, osmolality, specific gravity and viscosity for the proposed product and the LD product (Table 2). These parameters are very similar between the proposed product and the LD product.

Table 2. Comparative physico-chemical parameters between the proposed drug product and the LD product

Product	**ARGATROBAN injection in 0.9% sodium chloride,** (b) (4)	**Argatroban injection in 0.9% sodium chloride, (Accord Healthcare)**		
Presentation		1 mg/mL, 50 mL [50 mg/50 mL]		
Batch number		R09373	R09538	R11755
Mfg. date		Aug 2014	Aug 2014	Oct 2014
Exp. Date		July 2016	July 2016	Sep 2016
AR. Nos.		890104930 ASARGPU4 0004	890105287 ASARGPU4 0005	890107202 ASARGPU4 0006
Storage condition		g term (20°-25°C (68°-77°F)		
Tests	**Limit**	**Results**		
Assay of Argatroban	(b) (4)			(b) (4)
pH				
Osmolality				
Specific gravity				
Viscosity				

The difference between the proposed product and LD is that the proposed drug product is packaged differently (50 mg/50 mL) as compare to that for the LD product (b) (4)

Reviewer's Assessment: A biowaiver per 21 CFR 320.22(b)(1) is supported by the following information/data: (1) the proposed product is a parenteral solution intended solely for intravenous administration, (2) the proposed product contains the same active and inactive ingredients in the same concentration as the LD product, and (3) similar physico-chemical properties of pH, osmolality, gravity, viscosity. Therefore, the biowaiver request for Argatroban injection in 0.9% sodium chloride, 1 mg/mL, 50 mL is granted.

Yang Zhao

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Banu Zolnik

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Sherita McLamore

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