# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 209552Orig1s000

# PRODUCT QUALITY REVIEW(S)

## Executive Summary

### I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 209552 Argatroban Injection in 0.9% NaCl, 50 mg/50 mL (1 mg/mL). As part of this action, OPQ grants a (b) (4) re-test period for the drug substance when stored (b) (4) a 36-month drug product expiration period when stored at 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.

### II. Summary of Quality Assessments

#### A. Product Overview

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). In 2011 argatroban was approved under NDA 22485 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 Sandoz (125 mg/125 mL) approved under NDA 22485 is the Listed Drug (LD) for this application. The proposed drug product (b) (4) (b) (4) differs only in the fill volume and vial size (i.e. 125 mg/125 mL vs. 50 mg/50 mL). The proposed drug product is designed to avoid waste (50 mL vs 125 mL).

The 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 209552 and grants a (b) (4) re-test period for the drug substance and a **36-month expiration period** for the drug product when stored at USP controlled room temperature in the proposed commercial packaging (do not freeze and protect from light).

| | |
|---|---|
| **Proposed Indication(s) including Intended Patient Population** | • For prophylaxis or treatment of thrombosis in adult patients with HIT<br>• As an anticoagulant in adult patients with or at risk |

| | |
|---|---|
| | for HIT undergoing PCI |
| **Duration of Treatment** | Undefined |
| **Maximum Daily Dose** | 560 mg |
| **Alternative Methods of Administration** | None |

**B. Quality Assessment Overview**

**Facilities:**

NDA 209552 was originally submitted to the Agency in July of 2016 and resubmitted in September 2017. Both submissions resulted in a Compete Response (CR) as a result of Withhold recommendations from the Office of Compliance. The July 2016 submission was issued a withhold recommendation as a result of deficiencies identified during inspections of (b) (4) and Aurobindo Pharma Limited, (b) (4) (FEI 3008461619) manufacturing facilities. The responded to the CR and the application was resubmitted in September 2017. At that time the (b) (4) was deemed acceptable; however, the Aurobindo Pharma Ltd was not. In conjunction with the September 2017, the Aurobindo Pharma site was re-inspected in (b) (4). At that time, the site was issued a 9-item FDA Form 483 for deficiencies observed. The deficiencies included inadequate (b) (4) (b) (4) (b) (4) As a result, the Division of Inspectional Assessment (DIA) recommended Withhold.

NDA 209552 was resubmitted to the agency in May 2018 (Class 2 resubmission due to the outstanding facilities issues). The Office of Compliance reviewed the firm's (Aurobindo Pharma Ltd) responses to the deficiencies that were observed during the 2018 inspection. It was concluded that and a satisfactory resolution of all deficiencies had been provided and there were no risks identified that would preclude the firm from successfully performing the proposed responsibilities. The firm's responses were deemed adequate and the application was recommended for approval from a facility perspective (see appended facility review).

There were no other product quality changes to the application and no outstanding product quality issues. Accordingly, NDA 209552 is recommended for approval from a product quality perspective.

**C. Special Product Quality Labeling Recommendations (NDA only)**

**n/a**

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

**Appended at the end of the original drug product review.**

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## Executive Summary

### I. Recommendations and Conclusion on Approvability

OPQ recommends **COMPETE RESPONSE** of NDA 209552 Argatroban Injection in 0.9% NaCl, 50 mg/50 mL (1 mg/mL) as the Facilities reviewer issued a WITHOLD recommendation for this application as a result of deficiencies associated with the drug product manufacturing site.

### II. Summary of Quality Assessments

#### A. Product Overview

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). In 2011 argatroban was approved under NDA 22485 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 Sandoz (125 mg/125 mL) approved under NDA 22485 is the Listed Drug (LD) for this application. The proposed drug product (b) (4) (b) (4) differs only in the fill volume and vial size (i.e. 125 mg/125 mL vs. 50 mg/50 mL). The proposed drug product is designed to avoid waste (50 mL vs 125 mL).

The 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 recommendation from the Facilities reviewer, OPQ recommends a COMPLETE RESPONSE for NDA 209552,

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

## B. Quality Assessment Overview

**Facilities:**

NDA 209552 was originally submitted to the Agency in July of 2016. This application was issued a Complete Response (CR) as a result of a Withhold recommendation from the Office of Compliance. The withhold recommendation was issued as a result of deficiencies identified during inspections of (b) (4) and Aurobindo Pharma Limited, (b) (4) (FEI 3008461619) manufacturing facilities. (b) (4) was responsible for drug substance manufacturing, packaging, testing and release testing. Aurobindo Pharma Ltd was responsible for drug product manufacture, chemical and microbiological testing of the drug substance and drug product release and stability testing.

NDA 209552 was resubmitted to the agency in September 2017. At which time it was concluded that this application would be a Class 2 resubmission due to the outstanding facilities issues.

Since the initial review of this NDA, the Office of Compliance reviewed (b) (4) (b) (4) responses to the deficiencies observed and conveyed during the 2017 inspection and it was determined that the firm's responses were adequate. Accordingly, this firm is ACCEPTABLE and the reviewer recommended the facility for approval for the functions listed in the application.

The Aurobindo Pharma Ltd site was re-inspected in (b) (4). During this most recent inspection, nine observations were documented and the site was issued a 483. The current CGMP classification for this site is pOAI. The results of the recent inspection are currently under review. Accordingly, the Division of Inspectional Assessment (DIA) recommended **Withhold** and a satisfactory resolution of all deficiencies is required before this NDA may be approved.

**Drug Product:**

While not identified as an issue during the initial review of this NDA, the firm was asked to either establish a validated test method for elemental impurities as part of the drug product specification or to provide appropriate risk assessment consistent with ICH Q3D and USP <232/233>. This IR was sent in response to the January 2018 implementation of the mandatory compliance with USP <232>/<233>. On February 27, 2018, the applicant provided a risk assessment for elemental impurity consistent with ICH Q3D. The data indicated that the total elemental impurities are present at levels in the drug product significantly lower than the 30% of permitted daily exposure (PDE) (see attached elemental impurities risk memo). Based on the applicant's evaluation of the Risk Assessment of Elemental Impurities the drug product review team continues to recommend approval of this application form a drug product perspective.

## C. Special Product Quality Labeling Recommendations (NDA only)

**n/a**

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

**n/a**

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 05, 2018

**FROM: Branch 2/DNDP1/ONDP/OPQ**

**SUBJECT: Evaluation of the Risk Assessment of Elemental Impurities for NDA 209552**

**APPLICATION/DRUG: NDA 209552 Argatroban Injection in 0.9% Sodium Chloride, 50 mg/50 mL (1 mg/mL) Single Dose Vial**

**Background:**
In response to the Agency's email dated February 26, 2018, the applicant submitted an amendment on February 27, 2018 providing a risk assessment for elemental impurities in the proposed drug product in accordance with ICH Q3D and USP<232/233>. The applicant also committed to reassess compliance with ICH Q3D if ingredient suppliers, container closure systems, and/or equipment contact surfaces are changed post-approval.

**Applicant's Evaluation of Risk Assessment for Elemental Impurities:**
Per ICH Q3D, the following elemental impurities should be assessed for parenteral products: (b) (4) (b) (4)
The applicant provided a risk assessment of all the metals indicated above along with that of (b) (4) which was used in the manufacturing of the drug substance (controlled at NMT (b) (4) in the drug substance specifications). The applicant provided a risk assessment of the potential sources for the elemental impurities in this submission: intentionally added (b) (4) container closure system, manufacturing equipment, and raw materials (drug substance and excipients).
The applicant provided elemental impurities data from their evaluation of each of the potential sources (except for the intentionally added (b) (4) which is controlled in the drug substance specifications). The data provided by the applicant shows significantly lower levels of these impurities compared to the control threshold set at 30% of permitted daily exposure (PDE). The applicant indicated that the results

show very low risk of elemental impurities per ICH Q3D option 2b. The summary report from the applicant is shown below.

Elemental Impurities Risk Assessment – Evaluation Report for the Drug Product:

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|
| Element | Intentionally added (if used in the process) | Elemental impurities in Raw materials *(Drug Substance and Excipients)* | Manufacturing equipment | Leached from container closure systems | Total elemental impurity contribution µg/day (2 +3 +4) | Control* threshold | Action |
| (b) (4) | No | (b) (4) | 0.0 | 0.0 | | (b) (4) | |
| | No | | 0.0 | 0.0 | | | |
| | No | | 0.0 | 0.0 | | | |
| | No | | 0.0 | 0.0 | | | |
| | No | | 0.0 | 0.0 | | | |
| | No | | 0.0 | 0.0 | | | No further controls required |
| | No | | 0.0 | 0.0 | | | |
| | No | | 0.0 | 0.0 | | | |
| | No | | 0.0 | 0.0 | | | |
| | No | | 0.0 | 0.0 | | | |
| | Yes | | 0.0 | 0.0 | | | |

*Control threshold is 30% PDE of Each elemental impurity.

**Comment: Acceptable**

The data provided by the applicant is consistent with the applicant's conclusion that the product has a very low risk of contamination from the elemental impurities in the drug product as per ICH Q3D Option 2b.

**CONCLUSION: The applicant's evaluation of the Risk Assessment of Elemental Impurities for NDA 209552 is acceptable for ICH Q3D.**

Anamitro Banerjee, Ph.D.
Acting Branch Chief, Branch 2,
Division of New Drug Product I (DNDPI)
Office of New Drugs Products (ONDP)
Office of Pharmaceutical Quality/CDER/FDA

Sherita McLamore

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**Recommendation: COMPLETE RESPONSE**

# NDA 209552
# Review #1

| | |
|---|---|
| Drug Name/Dosage Form | Argatroban Injection in 0.9% NaCl |
| Strength | 50 mg/50 mL (1 mg/mL) |
| Route of Administration | Intravenous |
| Rx/OTC Dispensed | Rx |
| Applicant | Sandoz, Inc. |
| US agent, if applicable | n/a |

| SUBMISSION(S) REVIEWED | DOCUMENT DATE | DISCIPLINE(S) AFFECTED |
|---|---|---|
| Original Submission | 7/28/16 | all |
| SN-002: Labeling | 10/24/16 | Drug Product |
| SN-003: Response to IR | 11/21/16/ | Drug Product |
| SN-004: Response to IR | 01/05/17 | Process |
| SN-005: Response to IR | 01/06/17 | Process |
| SN-006: Labels and Labeling | 03/10/17 | Drug Product |
| SN-007: Response to IR | 03/16/17 | Drug Product |
| SN-008: Final Printed Labeling | 04/14/17 | Drug Product |
| SN-009: Response to IR | 04/21/17 | Drug Product |

**Quality Review Team**

| DISCIPLINE | PRIMARY REVIEWER | SECONDARY REVIEWER |
|---|---|---|
| Drug Master File/Drug Substance | Haripada Sarker | Benjamin Stevens |
| Drug Product | William Adams | Anamitro Banerjee |
| Process | Steve Rhieu | Edwin Jao |
| Microbiology | n/a | n/a |
| Facility | Ebern Dobbin | Christina Capacci-Daniel |
| Biopharmaceutics | Gerlie Gieser | Okponanabofa Eradiri |
| Regulatory Business Process Manager | Rabiya Laiq | n/a |

| | | |
|---|---|---|
| Application Technical Lead | Sherita McLamore | n/a |
| Laboratory (OTR) | n/a | n/a |
| ORA Lead | n/a | n/a |
| Environmental | William Adams | Anamitro Banerjee |

# Quality Review Data Sheet

## 1. RELATED/SUPPORTING DOCUMENTS

**. DMFs:**

| | Type | | Item Referenced | Status | Date Review Completed | Comments |
|---|---|---|---|---|---|---|
| (b) (4) | Type II | (b) (4) | | Adequate | 4/28/17 | n/a |
| | Type III | | (b) (4) | 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 |

**. Other Do** , *pplications*

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| NDA | 22485 | RLD |

## 2. CONSULTS

**N/A**

## Executive Summary

### I. Recommendations and Conclusion on Approvability

OPQ recommends **COMPETE RESPONSE** of NDA 209552 Argatroban Injection in 0.9% NaCl, 50 mg/50 mL (1 mg/mL) as the Facilities reviewer has provided a WITHOLD recommendation for this application due to deficiencies associated with the drug product and drug substance manufacturing sites.

### II. Summary of Quality Assessments

#### A. Product Overview

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). In 2011 argatroban was approved under NDA 22485 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 Sandoz (125 mg/125 mL) approved under NDA 22485 is the Listed Drug (LD) for this application. The proposed drug product (b) (4) (b) (4) differs only in the fill volume and vial size (i.e. 125 mg/125 mL vs. 50 mg/50 mL). The proposed drug product is designed to avoid waste (50 mL vs 125 mL).

The 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 recommendation from the Facilities reviewer, OPQ recommends a COMPLETE RESPONSE for NDA 209552.

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

## B. Quality Assessment Overview

(b) (4)

(b) (4)

(b) (4)

(b) (4)

in i clud d i h p lic t o . DM (b) (4) was e iewed in co j nc ion wit h s NDA (review dated 4/28/17) and was consider adequate to support the approval of this NDA.

**Drug Product**

The drug product, Argatroban Injection in 0.9% Sodium Chloride, 50 mg/50 mL (1 mg/mL) is presented as a clear to pale yellow, sterile aqueous solution containing the active, sorbitol and sodium chloride in a single dose glass vial. The drug product is (b) (4) to the listed drug, Argatroban Injection in 0.9% NaCl, 125 mg/125 mL (1 mg/mL) manufactured by Sandoz. As such there are no novel excipients and all excipients are fall within the IIG limit for the proposed route of administration (i.e. IV).

The drug product is manufactured, packaged and release tested by Aurobindo Pharma of India at a commercial batch size (b) (4) vials). The drug product is packaged in a clear, (b) (4) glass 50 mL vial with a 20 mm neck and capped with a 20 mm gray (b) (4) rubber stopper aluminum and a 20 mm aluminum overseal having a sky blue (b) (4) flip-off disc.

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.

The Applicant included thirty-six months of primary stability data for three exhibit batches packaged in commercial packaging presentation and stored inverted and upright. The available stability data shows consistency over time and supports a ***36 month shelf-life when stored under USP controlled room temperature, do not freeze and protect from light***.

**Process**

The manufacturing process consists of (b) (4)

(b) (4)

(b) (4)

efficacy. The proposed drug product (b) (4) to the Listed Drug in terms of (b) (4) composition, dosage form, concentration at the point of patient contact, indications and route of administration. The applicant requested a BA/BE waiver per 21 CFR § 320.22(b)(1). The BA/BE waiver was granted and as such the application is recommended for approval from a biopharmaceutics perspective.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

**Facilities**

Following completion of review of this application, it was determined that both the drug substance and drug product manufacturing sites are not in compliance with CGMPs. Accordingly, this application is recommended for **Withhold** from a compliance perspective due to deficiencies identified during the most recent inspections of (b) (4) and Aurobindo Pharma Limited, (b) (4). A satisfactory resolution of all deficiencies is required before this NDA may be approved.

**Environmental Assessment**

The applicant provided a claim for categorical exclusion from conducting an environmental impact statement (EIS) or environmental assessment (EA) is made under 21 Code of Federal Regulations (CFR) Sections 25.31(a). The drug product will not be administered at a higher dosage level or for a longer duration or for different indications that were previously in effect and applicant is in compliance with all

federal, state, and local environmental protection laws.

The request for categorical exclusion is granted.

**C. Special Product Quality Labeling Recommendations (NDA only)**

**n/a**

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

**Appended at the end of the drug product review.**

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# LABELING
*{For NDA only}*

**R Regional Information**

1.14 Labeling

***Amendment SN-008***
**Package Insert**
ARGATROBAN injection, for intravenous use
Initial U.S. Approval: 2000
----------INDICATIONS AND USAGE----------
Argatroban is a direct thrombin inhibitor indicated:
• For prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT) (1.1)
• As an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI) (1.2)
----------DOSAGE AND ADMINISTRATION----------¬
• Argatroban 50 mg in 50 mL aqueous sodium chloride solution (1 mg/mL) is intended for administration to adult patients (2.1)

Heparin-Induced Thrombocytopenia (2.2)
The dose for heparin-induced thrombocytopenia without hepatic impairment is 2 mcg/kg/min administered as a continuous infusion (2.2)

Percutaneous Coronary Intervention (2.3)
The dose for patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention is started at 25 mcg/kg/min and a bolus of 350 mcg/kg administered via a large bore intravenous line over 3 to 5 minutes (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 50 mg/50 mL (1 mg/mL) single dose vial (3)

See 17 for PATIENT COUNSELING INFORMATION
Revise: 04/2017

**FULL PRESCRIBING INFORMATION**
**2 DOSAGE AND ADMINISTRATION**
2.1 Preparation for Intravenous Administration
Each 50 mL glass vial contains 50 mg of argatroban (1 mg/mL); and, as supplied, is ready for intravenous infusion. Dilution is not required.

Argatroban 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 the solution is cloudy, contains precipitates, or if the cap/over seal is not intact.

Vial may be inverted for use with medical infusion set.

## 3 DOSAGE FORMS AND STRENGTHS

Injection: 50 mg/50 mL (1 mg/mL) ready for intravenous infusion (b) (4)

## 11 DESCRIPTION

Argatroban is a synthetic direct thrombin inhibitor.

The chemical name for Argatroban monohydrate is 1-[5-[(aminoiminomethyl)amino]-1-oxo-2-[[(1,2,3,4-tetrahydro-3-methyl-8-quinolinyl)sulfonyl]amino]pentyl]-4-methyl-2-piperidinecarboxylic acid, monohydrate. 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.

The molecular formula of argatroban is $C_{23}H_{36}N_6O_5S \cdot H_2O$. Its molecular weight is 526.66 g/mol. The structural formula is:

[molecular structure]

Argatroban Injection is a sterile, non-pyrogenic, clear, colorless to pale yellow isotonic solution. It is supplied in a clear glass single dose vial containing 50 mg of argatroban in 50 mL sodium chloride solution. Each mL contains 1 mg argatroban, 9 mg sodium chloride, USP, 3 mg sorbitol, NF in water for injection, USP. The pH of the solution is between 4.0 to 7.5.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Argatroban Injection is supplied as a single dose vial containing 50 mg argatroban in 50 mL of aqueous solution (1 mg/mL).

| | |
|---|---|
| 50 mL single dose vials | NDC 55150-241-00 |
| packaged in cartons of 10 vials | NDC 55150-241-10 |

*Storage and Handling:*
Store the vials in original cartons at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Do not refrigerate or freeze. Retain in the original carton to protect from light. If the solution is cloudy, or if an insoluble precipitate is noted, the vial should be discarded.

The vial stopper is not made with natural rubber latex.

Distributed by:
AuroMedics Pharma LLC
279 Princeton-Highstown Rd.
East Windsor, NJ 08520

Manufactured by:
Aurobindo Pharma Limited
Hyderabad – 500038
India

***Reviewer's Assessment:***

Adequate for CMC information. The proposed labeling matches the labeling for the reference product, except for the product revisions. The requisite CMC information in sections 2, 3, 11, and 16 is present and correct. The label storage statement is that supported by the studies in NDA modules 3.2.P.2 and 3.2.P.8. The sites listed in the "Distributed by" and


d to include the complete USP CRT statement and to include the 'do not refrigerate or freeze' statement. "Mfg in India" permits import from India into U.S. The listed manufacturing site matches that on the package insert. Batch# and expiry date will be placed in the Coding Zone.

***Amendment SN-006***
*Carton Labeling*

(b) (4)

[redacted]

(b) (4)

(b) (4) statements which are not on the vial label. Does not include the (b) (4) statement as on the vial label. The label storage statement has been corrected to include the complete USP CRT statement and to include the (b) (4) statements. (b) (4) (b) (4) permits import from India into US. Manufacturing site matches that on the package insert. Batch# and expiry date will be placed in the Coding Zone.

***List of Deficiencies***: None

**SIGNATURES**

| | | |
|---|---|---|
| Primary Reviewer | William M. Adams, OPQ/ONDP/DNDP branch 2 | 04/27/17 |
| Secondary Reviewer | Anamitro Banerjee, OPQ/ONDP/DNDPI branch 2 | 04/27/17 |

William Adams

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Anamitro Banerjee

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# BIOPHARMACEUTICS

**Product Background:**

**NDA:** 209552-ORIG-1

**Drug Product Name / Strength:** Argatroban Injection, contains 50 mg argatroban in 50 mL aqueous sodium chloride solution (1 mg/mL)

**Route of Administration:** For Intravenous Infusion

**Applicant Name:** Aurobindo Pharma Limited

***Review Recommendation:***
The Applicant's biowaiver request in relation to NDA 209552 for Argatroban Injection 1 mg/mL is granted, based on 21 CFR § 320.22(b)(1). The Division of Biopharmaceutics therefore recommends the APPROVAL of NDA 209552 for Argatroban Injection, 1 mg/mL.

***Review Summary:***
This 505(b)(2) NDA submission for Argatroban Injection (50 mg/50 mL) relies for approval on FDA's findings of safety and effectiveness established for the Listed Drug approved under NDA 22485, Argatroban Injection (125 mg/125 mL). The Applicant requested a BA/BE waiver per 21 CFR § 320.22(b)(1). The proposed drug product is the same as the listed drug in terms of (b) (4) composition, dosage form (parenteral solution in single-dose vials), concentration (1 mg/mL) at the point of patient contact, indications, and administration route (for IV bolus injection and infusion). To avoid waste, the fill volume of the proposed drug product is smaller than that of the listed drug (50 mL vs 125 mL).

Based on OPQ recommendation, the Finished Product Release and Shelf-life Specifications of the proposed drug product were revised to include QC tests and the corresponding appropriate acceptance limits that would ensure comparability to the Listed Drug's quality attributes including assay, minimum fill volume, particulates, sterility, pH, non-pyrogenicity, osmolality/isotonicity of the solution intended for parenteral administration.

**List of Submissions reviewed:**
SDN-1, 7/28/2016 Original NDA Submission
SDN-3, 11/21/2017 (Response to Quality Information Request)

**Highlight of Key Outstanding Issues from Last Cycle:**

Not Applicable (Original NDA Submission)

**Concise Description of Outstanding Issues :**
None

***List of Deficiencies:***

*None*

***Primary Biopharmaceutics Reviewer Name and Date: Gerlie Gieser, PhD (4/13/2017)***

***Secondary Reviewer Name and Date: Okpo Eradiri, PhD (4/13/2017)***

Gerlie Gieser

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Okponanabofa Eradiri

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# MICROBIOLOGY

**Product Background:**

**NDA:** 209552

**Drug Product Name / Strength:** Argatroban Injection in 0.9% Sodium Chloride; 50 mg/50 mL (1 mg/mL)

**Route of Administration:** Intravenous

**Applicant Name:** Aurobindo Pharma Limited
The Water Mark Building, Plot No: 11
Survey No: 9, Kondapur, Hi-tech City, Hyderabad,
Telangana 500084, India

**US Agent:** Vincent P. Andolina
**Telephone:** (609) 642-1136
**Email:** vandolina@aurobindousa.com

**Manufacturing Site:** Aurobindo Pharma Limited, (b) (4)
(b) (4) Hyderabad,
Telangana 502307, India

**Method of Sterilization:** (b) (4)

**Review Summary: Adequate**
**The drug product is** (b) (4) **sterilized. The submission is recommended for approval on the basis of product quality microbiology.**

**List Submissions being reviewed:** 07/28/2016 (original submission): 10/24/2016 (Filing review issues-Labeling); 01/06/2017 (response to microbiology Information Request)

**Concise Description Outstanding Issues Remaining:** N/A.

**Supporting/Related Documents:**

- Microbiology Reviews of DMF (b) (4) dated 21 November 2016 and 05 April 2017, respectively, for sterility assurance information (b) (4) of

**Remarks Section:** The submission was provided in the eCTD format.

**S Drug Substance-** N/A.

**Reviewer's Assessment:** The drug substance manufacturing process is not the subject of this product quality microbiology review as the drug product is (b) (4) sterilized (b) (4) (b) (4)

**P.1 Description of the Composition of the Drug Product**

- **Description of drug product –**
  (See Section 3.2.P.1– *Description and Composition of the Drug Product.pdf*)

  The subject drug product is a clear, colorless to pale yellow solution.

- **Drug product composition –**
  (See Section 3.2.P.1– *Description and Composition of the Drug Product.pdf*)

  A table was provided in the submission for the composition of the subject drug product, which has been reproduced below.

| Ingredients | Function | Composition | | |
|---|---|---|---|---|
| | | Per mL (mg/mL) | Per Container (mg/50 mL) | % |
| Argatroban | Active Ingredient | 1.0* | | (b) (4) |
| Sodium Chloride USP | | | | (b) (4) |
| Sorbitol USNF | | | | |
| Water for Injection USP/Ph.Eur/IH | | | | |
| | | | | (b) (4) |

- **Description of container closure system –**
  (See 3.2.P.7-*Summary of Container/Closure System.pdf*)

  The subject container-closure system for commercial production will consist of the following:
  - Container: (b) (4) (b) (4)
  - Closure: Rubber stoppers (b) (4) (b) (4)
  - Seal: Aluminum Seal (b) (4) (b) (4)

**Acceptable**

**P.2.5 Microbiological Attributes**

- **Container/Closure and Package Integrity**
  (See Section 3.2.P.2- *Microbial Attributes.pdf*)

**Comparability Protocols-** N/A.

## 2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

### 2.A. Package Insert

The subject drug product is a single dose vial that is ready for intravenous infusion. Dilution is not required. The proposed storage condition for subject drug product is 20 to 25°C (68 to 77°F).

**Acceptable**

**Post-Approval Commitments –** N/A.

***Primary Microbiology Reviewer Name and Date:*** Daniel J. Schu, Ph.D. 3/30/2017
***Secondary Reviewer Name and Date:*** Marla Stevens-Riley, Ph.D. 3/30/17
"I concur."

Daniel Schu

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Marla Stevens Riley

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Sherita McLamore

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