CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209552Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	25-Oct-18
From	Sherita McLamore, Ph.D.
Subject	Cross-Discipline Team Leader (CDTL) Review
NDA	209552
Type of Application	505(b)(2)
Applicant	Aurobindo Pharma Limited
Date of Receipt	29-May-2018
PDUFA Goal Date	29-Nov-2018
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:	**APPROVAL**

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

- Clinical (George Shashaty, M.D.); in DARRTS, dated 13-Apr-2017
- Pharmacology/Toxicology (Ramadevi Gudi, Ph.D.); in DARRTS, dated 13-Apr-2017
- DEMPA (Idalia Rychlik, Pharm. D.); in DARRTS, dated 17-Oct-2018
- Drug Product (William Adams, Ph.D.); in Panorama, dated 27-Apr-2017
- Drug Substance (Hari Sarker, Ph.D.); in Panorama, dated 28-Apr-2017
- Microbiology (Daniel Schu, Ph.D.); in Panorama, dated 05-Apr-2017
- Manufacturing Facilities (Ebrin Doddin, Ph.D.); in Panorama, dated 18-Oct-2018
- Manufacturing Process (Steve Rhieu, Ph.D.); in Panorama, dated 27-Feb-2017
- Quality Biopharmaceutics (Gerlie Gieser, Ph.D.); in Panorama, dated 14-Apr-2017

1. Introduction

Aurobindo Pharma Ltd. has submitted NDA 209552 in support of a 50 mg/ 50 mL (1 mg/mL) formulation for Argatroban Injection in 0.9% Sodium Chloride in a single dose vial. The application was submitted as a 505(b)(2) NDA under the Federal Food, Drug and Cosmetic Act referencing Argatroban Injection in 0.9% Sodium Chloride, 125 mg/125 mL (1 mg/mL) manufactured by Sandoz Inc. as the listed drug (LD). The Sandoz formulation was approved under NDA 22485 in 2011 as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT). The Sandoz Argatroban product is supplied as a sterile, non-pyrogenic, clear, colorless to pale yellow isotonic solution in a single-dose clear glass vial containing 125 mg of the active in 125 mL of sodium chloride (1 mg/mL). The Aurobindo product and the LD have the same indications and route of administration. They are qualitatively and quantitatively (b) (4) have the same concentration differing only in the drug substance supplier, vial size and fill volume. The Aurobindo product is presented as sterile, colorless to pale yellow solution in a single-dose vial containing 50 mg of the active in 50 mL of sodium chloride and Sorbitol, NF in Water for Injection, USP with 0.1% drug load. The Aurobindo Argatroban Injection (b) (4)

2. Background

Argatroban is a small molecule, anticoagulant direct thrombin inhibitor. 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 on the Agency's determination of safety and efficacy for the listed drug, Argatroban Injection in 0.9% Sodium Chloride, 125 mg/125 mL (1 mg/mL) which was previously approved for marketing under NDA 22485. The indications, active ingredient, inactive ingredients, route of administration, dosage form, and concentration of argatroban are the same as those of the LD.

3. Product Quality

With the exception of facilities, there was no new product quality information included in this submission. NDA 209552 was recommended for approval from the drug substance, drug product and drug process perspectives at the conclusion of the first review cycle (see CDTL memo dated 5/09/2017). The application remains acceptable from a drug substance, drug product and process perspectives and is therefore recommended for approval from drug substance, drug product and process. NDA 209552 included three sites: Aurobindo Pharma Limited of Hyderabed, India which is responsible for manufacturing, packaging, labeling, release and stability testing of the drug product; Aurobindo Pharma Limited of (b) (4) which is responsible for testing (b) (4) which is responsible for manufacturing, packaging, labeling, release and stability testing of the drug substance. At this time, all sites are acceptable and are recommended for approval to perform the functions included in the application.

4. Product Quality Microbiology

No new microbiology data was included in this submission. NDA 209552 was recommended for approval from a biopharm perspective at the end of the first review cycle (see CDTL memo dated

5/09/2017). The application remains acceptable from a microbiology perspective and is therefore recommend for approval.

5. Biopharmaceutics

No new biopharmaceutics data was include in this submission. NDA 209552 was recommended for approval from a biopharm perspective at the end of the first review cycle (see CDTL memo dated 5/09/2017). The application remains acceptable from a biopharm perspective and is therefore recommend for approval.

Overall CMC Recommendation: The Office of Pharmaceutical Quality recommends **APPROVAL** of NDA 209552 from a product quality perspective based on the recommendations from the Drug Product, Drug Substance, Drug Process, Biopharm, Microbiology and Facilities reviewers.

6. Clinical Pharmacology

No new clinical/pharmacology information provide in the resubmission.

7. Non-Clinical Pharmacology/Toxicology

The proposed formulation, 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 125 mg/125 mL. This application included no new non-clinical pharmacokinetic or toxicology information and 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 125 mg/125 mL (NDA 22485) for safety and efficacy and no additional or independent clinical studies were performed with the proposed drug product (Argatroban Injection in 0.9% Sodium Chloride, 50 mg/50 mL). The clinical reviewer has recommended approval NDA 209552 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 labeling review was performed by DMEPA, DDMAC, Clinical, Non-Clinical and CMC. There were no new labeling recommendations for this submission. Please refer to CDTL memo dated 5/09/2017 for detailed labeling recommendations.

Overall Labeling Recommendation:
The labeling for Aurobindo's Argatroban Injection in 0.9% Sodium Chloride, 50 mg/50 mL remains acceptable.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

This product relies on the safety and efficacy of the listed product, Argatroban Injection in 0.9% Sodium Chloride, 125 mg/125 mL. The Aurobindo product has the same active ingredient and inactive ingredient, is the same dosage form, same concentration and route of administration as the LD, Argatroban Injection in 0.9% Sodium Chloride, 125 mg/125 mL. There were no new clinical or nonclinical studies conducted for this 505(b)(2) application.

NDA 209552 was originally submitted to the Agency in July of 2016. With the exception of the Facilities (OPF), at the conclusion of the review cycle, all disciplines recommended approval of this NDA. The Facilities reviewer entered a withhold recommendation for this NDA because it was determined that both the drug substance and drug product manufacturing sites (b) (4) Aurobindo Pharma Limited) were not in compliance with CGMPs. Accordingly, the CDTL recommended a COMPLETE RESPONSE (CR) for the application**.** The NDA was resubmitted in September of 2017 and at that time the (b) (4) site was acceptable; however, the Aurobindo Pharma Limited site was re-inspected and was deemed inadequate to perform the responsibilities listed in the application (site was issued a 9-item 483 for deficiencies observed). As a result, the Division of Inspectional Assessment (DIA) issued a WITHHOLD recommendation and the CDTL again recommended a CR for the application. In this submission (May 2018), the applicant responded and the Office of Compliance reviewed the firm's (Aurobindo Pharma Ltd) responses to the deficiencies observed and conveyed during the 2018 inspection. It was concluded that a satisfactory resolution of all deficiencies had been provided and that there were no risks identified that would preclude the firm from successfully performing the proposed responsibilities. As such, the application was recommended for approval from a facility perspective. As there were no outstanding issues precluding the approval of this application and all disciplines have recommended approval of this NDA the CDTL recommends **APPROVAL** of NDA 209552**.**

- **Risk Benefit Assessment**

Please refer to NDA 22485.

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

/s/

SHERITA D MCLAMORE
10/25/2018

Cross-Discipline Team Leader Review

Date	08-May-17
From	Sherita McLamore, Ph.D.
Subject	Cross-Discipline Team Leader (CDTL) Review
NDA	209552
Type of Application	505(b)(2)
Applicant	Aurobindo Pharma Limited
Date of Receipt	28-Jul-16
PDUFA Goal Date	28-May-2017
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:	**COMPLETE RESPONSE**

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

- Clinical (George Shashaty, M.D.); in DARRTS, dated 13-Apr-2017
- Pharmacology/Toxicology (Ramadevi Gudi, Ph.D.); in DARRTS, dated 13-Apr-2017
- DEMPA (Idalia Rychlik, Pharm. D.); in DARRTS, dated 17-Mar-2017
- Drug Product (William Adams, Ph.D.); in Panorama, dated 27-Apr-2017
- Drug Substance (Hari Sarker, Ph.D.); in Panorama, dated 28-Apr-2017
- Microbiology (Daniel Schu, Ph.D.); in Panorama, dated 05-Apr-2017
- Manufacturing Facilities (Ebrin Doddin, Ph.D.); in Panorama, dated 08-May-2017
- Manufacturing Process (Steve Rhieu, Ph.D.); in Panorama, dated 27-Feb-2017
- Quality Biopharmaceutics (Gerlie Gieser, Ph.D.); in Panorama, dated 14-Apr-2017

1. Introduction

Aurobindo Pharma Ltd. has submitted NDA 209552 in support of a 50 mg/ 50 mL (1 mg/mL) formulation for Argatroban Injection in 0.9% Sodium Chloride in a single dose vial. The application was submitted as a 505(b)(2) NDA under the Federal Food, Drug and Cosmetic Act referencing Argatroban Injection in 0.9% Sodium Chloride, 125 mg/125 mL (1 mg/mL) manufactured by Sandoz Inc. as the listed drug (LD). The Sandoz formulation was approved under NDA 22485 in 2011 as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT). The Sandoz Argatroban product is supplied as a sterile, non-pyrogenic, clear, colorless to pale yellow isotonic solution in a single-dose clear glass vial containing 125 mg of the active in 125 mL of sodium chloride (1 mg/mL). The Aurobindo product and the LD have the same indications and route of administration. They are qualitatively and quantitatively (b) (4) the same concentration differing only in the drug substance supplier, vial size and fill volume. The Aurobindo product is presented as sterile, colorless to pale yellow solution in a single-dose vial containing 50 mg of the active in 50 mL of sodium chloride and Sorbitol, NF in Water for Injection, USP with 0.1% drug load. The Aurobindo Argatroban Injection (b) (4).

2. Background

Argatroban is a small molecule, anticoagulant direct thrombin inhibitor. 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 on the Agency's determination of safety and efficacy for the L D, Argatroban Injection in 0.9% Sodium Chloride, 125 mg/125 mL (1 mg/mL) which was previously approved for marketing under NDA 22485. The indications, active ingredient, inactive ingredients, route of administration, dosage form, and concentration of argatroban are the same as those of the LD.

3. Chemistry, Manufacturing and Controls (CMC)

The drug substance for this NDA is argatroban. The drug substance is a white or almost white, crystalline, non-hygroscopic powder free from foreign particles. The drug substance is chiral and is manufactured by (b) (4). As the drug product is a clear solution (b) (4) will not affect the quality of the drug product. (b) (4) The applicant referenced DMF (b) (4) for all aspects pertaining to the manufacture and control of the argatroban drug substance. The drug substance has a (b) (4) (b) (4) retest date. For additional detail pertaining to the manufacturing and control of the drug substance, refer to the DMF (b) (4) reviews. DMF (b) (4) was most recently review in support of this NDA (April 28, 2017) and was deemed adequate to support the approval of this NDA.

(b) (4)

The drug product, Argatroban Injection in 0.9% Sodium Chloride 50 mg/50 mL, is presented as a 1 mg/mL, clear to pale yellow, sterile aqueous solution containing the active, sorbital and sodium chloride in a single-dose glass vial. The formulation contains no novel excipients and all excipients are within the allowed range in the (b) (4)

The drug product is manufactured, packaged and release tested by Aurobindo Pharma of India at a commercial batch size (b) (4) vials. The exhibit batches were manufactured at (b) (4) vials). The manufacturing process for the drug product consists of (b) (4)

The drug product is packaged in a 50 mL clear molded (b) (4) glass vial with 20 mm gray (b) (4) rubber stopper and 20 mm aluminum overseal having a sky blue (b) (4) disc. This packaging configuration is consistent with the packaging configuration for the LD. Extractable and leachable studies demonstrate that level of leachables in drug product would be less than the acceptable intake limits. As such, there are no leachable substances that require monitoring on stability. Stability studies demonstrate that the Aurobindo product behaves comparably to the LD and will remain within the proposed specification through the proposed 36 month shelf-life.

Six months accelerated and 36 month long term stability data were included for three exhibit batches (batches AB1301, EAB1302 and EAB1303) of the drug product stored inverted and upright. All batches were manufactured with (b) (4) drug substance lot IE1200379A and were packaged in the proposed container closure system. At the time tested, data for all attributes remained within the proposed acceptance criteria with no significant changes or noteworthy trends. Forced degradation studies demonstrate that he drug product is very sensitive to acid hydrolysis, base hydrolysis and photolysis. The results of the stability studies indicate that the drug product behaves comparably to the LD and is expected to remain within the proposed specification for the proposed shelf life. Accordingly, a 36 month shelf life will be granted for the product when stored

at 20° to 25°C (68° to 77°F) based on the real time stability data. It is noted that the label includes "Do not freeze" and "Retain in original carton to protect from light".

The drug substance, drug product and process, reviewers recommended approval of the NDA 209552.

Facilities: This application included three sites: Aurobindo Pharma Limited of Hyderabed, India which is responsible for manufacturing, packaging, labeling, release and stability testing of the drug product; Aurobindo Pharma Limited of (b) (4) which is responsible for testing (b) (4) which is responsible for manufacturing, packaging, labeling, release and stability testing of the drug substance. After completion of review of the aforementioned facilities, it was determined that both the drug substance and drug product manufacturing sites (Aurobindo Pharma Ltd and (b) (4) 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 these sites. A satisfactory correction of the deficient conditions is required in order for the firm to be given an acceptable recommendation from a compliance perspective.

4. Product Quality Microbiology

This drug product is (b) (4) sterilized and contains no antimicrobial preservatives (single-dose). During the manufacturing process (b) (4) The drug product specification includes tests and acceptance criteria for bacterial endotoxins and sterility as per USP <85> and USP <71>, respectively. There are no pending microbiological concerns for the NDA and this application is recommended for approval on the basis of sterility assurance.

5. Biopharmaceutics

As this is a 505(b)(2) application, the applicant relies on findings for the LD [Argatroban Injection (125 mg/125 mL) approved under NDA 22485] for safety and efficacy. The proposed drug product is identical to the LD in terms of qualitative and quantitative composition, dosage form, concentration, 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 reviewer recommended approval of NDA 209552 from the Biopharmaceutics perspective.

Overall CMC Recommendation: The Office of Pharmaceutical Quality recommends **Complete Response** for NDA 209552 from a product quality perspective based on the withhold recommendation from the Facilities reviewer.

6. Clinical Pharmacology

n/a

7. Non-Clinical Pharmacology/Toxicology

The proposed formulation, 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 125 mg/125 mL. 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 125 mg/125 mL (NDA 22485) for safety and efficacy and no additional or independent clinical studies were performed with the proposed drug product (Argatroban Injection in 0.9% Sodium Chloride, 50 mg/50 mL). The clinical reviewer has recommended approval NDA 209552 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 labeling review was performed by DMEPA, DDMAC, Clinical, Non-Clinical and CMC.

Clinical Recommendations:

- The length of highlights (HL) must be one-half page or less unless a waiver has been granted.
- The prescribing information (PI) must comply with the Pregnancy and Lactation Labeling Rule (PLLR) content and format requirements [see *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014), codified at 21 CFR 201.56 and 201.57(c)(9)]. Therefore, resubmit labeling in PLLR format by October 28, 2016. The submission should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1 Refer to the draft guidance for industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format

- For each recent major change listed in HL section, the corresponding new or modified text in the full prescribing information must be marked with a vertical line on the left edge.

DMEPA Recommendations:

No comments noted

DDMAC Recommendations:

- Reviewer noted typographical error in sections 5.1 and 6.1 (i.e. word "in" omitted in section 5.1 and the word "(b) (4)" deleted from section 6.1)
- Reveiwer notes that this section is consistent with other recently revised argatroban labels; however recommend revision of this section to be consistent with the Guidance for Industry *Patient Counseling Information Section of Labeling for Human Prescription Drugs and Biological Products—Content and Format* dated December, 2014. Specifically, this section should be revised to include subheadings in order to allow the reader to quickly identify the major concepts

Non-Clinical Recommendations:

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

CMC Recommendations:

No comments noted

Overall Labeling Recommendation:

The applicant accepted the changes recommended by the agency. The labeling for Aurobindo'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 product, Argatroban Injection in 0.9% Sodium Chloride, 125 mg/125 mL. The Aurobindo product is identical to the LD except for the amount of the product in the single-dose vial. The Aurobindo product has the same active ingredient and inactive ingredient, is the same dosage form, same concentration and route of administration as the LD, Argatroban Injection in 0.9% Sodium Chloride, 125 mg/125 mL. There were no new clinical or nonclinical studies conducted for this 505(b)(2) application.

With the exception of the Facilities (OPF), all disciplines recommended approval of this NDA. The Facilities reviewer entered a withhold recommendation for this NDA because it was determined that both the drug substance and drug product manufacturing sites were not in compliance with CGMPs. Accordingly, the CDTL recommendation for this NDA is a **COMPLETE RESPONSE.** A satisfactory correction of the deficient conditions is required in order for the firm to be given an acceptable recommendation from a compliance perspective.

Complete Response Comment to be Conveyed to the applicant:

During recent inspections of (b) (4) Aurobindo Pharma Limited,

(b) (4) (FEI 3008461619) manufacturing facilities for this NDA, our field investigator conveyed deficiencies to the representatives of the facilities. Satisfactory resolution of these deficiencies is required before this NDA may be approved.

- **Risk Benefit Assessment**

Please refer to NDA 22485.

Sherita McLamore

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