CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206769Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	See electronic date stamp
From	Janice Brown M.S.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	206769
Applicant	Teva Pharmaceuticals, USA
Date of Submission	28-Feb-2014
PDUFA Goal Date	28-Dec-2014
Proprietary Name / Established (USAN) names	argatroban
Dosage forms / Strength	Injection, solution; single use polyolefin bag containing 250 mg argatroban in 250 mL aqueous sodium chloride solution (1 mg/mL)
Proposed Indication(s)	1. Prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT). 2. As an anticoagulant in adults patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI)
Recommended:	Approval

Include the following statement in the action letter:

A 24-month expiration dating period is granted for the drug product when stored at room temperature [20°C - 25°C (68°C - 77°F); excursions permitted to 15° to 30°C (59° to 86°F)]. Do not freeze.

1. Introduction

Argatroban is a small molecule, synthetic direct thrombin inhibitor derived from L-arginine, is approved for intravenous administration for treatment and prevention of thrombosis in patients with heparin-induced thrombocytopenia (HIT) and for anticoagulation in patients with HIT who are undergoing percutaneous coronary interventions (PCI). The current application for Argatroban Injection is submitted as a 505(b)(2) NDA. The proposed drug product differs from the listed drug in total drug content per container and packaging components. The reference product is supplied as two single use vials, each vial containing 125 mL of Argatroban Injection (1 mg/mL). Teva's drug product is a 250mg/250ml (1 mg/mL) argatroban solution filled a polyolefin bag with a single port packaged into an aluminum overpouch.

Argatroban Injection is administered as an intravenous infusion. The drug product should not be diluted prior to administration. The applicant is seeking approval for all listed drug indications.

2. Background

The subject of the current NDA application has the same active and inactive ingredients, strength, dosage form, route of administration, and conditions of use as the listed drug in NDA (b) (4). The applicant for this NDA is relying upon information in the public domain (labeling for approved argatroban product and published studies and information about argatroban) to support the safety and efficacy of the new product. No primary clinical data was submitted to support the application.

3. CMC

Argatroban is a direct thrombin inhibitor synthesized from the naturally occurring amino acid, L-arginine. There are four chiral centers, one of which is not defined (*i.e.*, both stereoisomers are present). Type I (21-*R*) and Type II (21-*S*) isomers are present in a 2:1 molar ratio. The ratio is controlled by the drug substance specification.

Drug Substance

The CMC information for the drug substance was provided in DMF No. (b) (4) from (b) (4) (b) (4) The applicant provided adequate reference to their Type II DMF (b) (4) for information pertaining to the drug substance, argatroban. The DMF contains the necessary information related to manufacturing, characterization, physical properties, manufacture, process controls, analytical methods, specifications, validation, container closure system, reference standard and stability data for argatroban. DMF (b) (4) was reviewed and found acceptable to support the NDA.

Drug Product

The manufacturing process for Argatroban injection utilizes (b) (4)

The submitted primary and supportive study data is sufficient to support the proposed expiry period of 24 months with a label storage statement of "Store the bag in (b) (4) original carton at 20° to 25°C (68° to 77°F) (see USP Controlled Room Temperature). Do not freeze. Retain in the original carton to protect from light". No CMC issues which preclude approval were found and the CMC Reviews (Mike Adams, B.S., final signature November 18, 2014 and November 24, 2014) recommended approval of the NDA.

Microbiology

The applicant has provided data sufficient to demonstrate that the risks for non-sterility and excessive endotoxin have been mitigated. These data include the validation studies and controls for the (b) (4) process, the container closure integrity studies, and the controls for endotoxins and bioburden in the raw materials, container closure components, and finished product. The product quality microbiology review completed by Jessica Cole, Ph.D. (signed August 19, 2014) found the microbiological information acceptable and recommended approval of the NDA from a quality microbiology standpoint.

Facilities review and inspection

An Establishment Evaluation Request (EER) was submitted to the Office of Compliance, and an overall "Approve" recommendation was issued in Panorama. The overall application re-evaluation date is September 19, 2014.

4. Nonclinical Pharmacology/Toxicology

No pharmacology/toxicology studies were submitted in the NDA. The excipients used by Teva are (b) (4) in the listed drug. The specifications that Teva has proposed for their drug product impurities and degradants were acceptable. The level of leachables from the polyolefin bags found in the argatroban drug product was toxicologically justified. No pharmacology/toxicology issues which preclude approval were found and the Pharmacology/Toxicology Review (Christopher Sheth, Ph.D., final signature May 23, 2014) recommended approval of the NDA.

5. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology

In support of a waiver of *in vivo* bioequivalence (BE), Teva submitted an *in vitro* bridging study to assess *in vitro* equivalence of the anticoagulant pharmacodynamic activity between Teva's Argatroban injection and the listed drug, Sandoz Argatroban Injection, The results indicate that an acceptable *in vitro* bridge between Teva's product and the Sandoz product was established. The Clinical Pharmacology reviewer, Young Jin Moon, Ph.D. recommended approval (signed November 19, 2014) of the NDA from a clinical pharmacology perspective.

Biopharmaceutics

The Applicant requested a waiver of *in vivo* bioavailability/bioequivalence (BA/BE) requirements for Argatroban for Injection based on 21 CFR § 320.22 (b). To support the biowaiver request, the applicant stated that the proposed changes in the drug product strength (total drug content per container) and packaging components do not pose questions of safety or efficacy because the formulation, the indications, the doses, and the route of administration of the proposed drug product are the same as those of the listed drug. The Biopharmaceutics review found the Applicant's justification acceptable. The supportive in vitro study assessing the equivalence of the anticoagulant pharmacodynamics (PD) activity between the proposed Argatroban product and the listed drug was evaluated and found acceptable by the Clinical Pharmacology Reviewer, Dr. Young Jin Moon. Therefore, the biowaiver request for Argatroban Injection, 250 mg/250 mL (1 mg/mL) is granted. The Biopharmaceutics reviewer, Houda Mahayni, Ph.D. recommended approval (signed November 21, 2014) of the NDA from a biopharmaceutics perspective.

6. Clinical Microbiology

No Clinical Microbiology review was required for this NDA.

7. Clinical/Statistical- Efficacy

This application is submitted as a 505(b)(2) NDA relying on previous determination of efficacy and safety of RLD argatroban for its labeled indications. Argatroban is indicated as an anticoagulant for:

- Prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT).
- As an anticoagulant in adults patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI).

No clinical studies have been conducted with Teva's argatroban product. No clinical issues which preclude approval were found and the Clinical Review (Hyon-Zu Lee. Pharm D, final signature September 30, 2014) recommended tentative approval of the NDA, pending an approval recommendation from the other disciplines.

No Statistical Review was done for this NDA.

8. Safety

No safety evaluation was performed for this NDA.

9. Advisory Committee Meeting

There was no Advisory Committee meeting held for this application.

10. Pediatrics

There was no Pediatric Review of this NDA.

11. Other Relevant Regulatory Issues

- Application Integrity Policy (AIP): There were no AIP issues raised during the pre-approval inspections for this NDA.
- Exclusivity or patent issues of concern: No issues were noted for this NDA.
- Financial disclosures: Not applicable
- Other GCP issues: None
- DSI audits: Not applicable
- Other discipline consults: None
- Any other outstanding regulatory issues: None

12. Labeling

The formatting of the applicant's proposed labeling has been constructed to comply with the requirements of the Physician's Labeling Rule (PLR). The proposed labeling for the Teva Argatroban injection is essentially the same in content as that of the innovator product except for changes required due to (1) the change in total drug content and packaging components (2) the drugs are produced and distributed by different manufacturers. Differences in labeling affect sections 3 (Dosage Forms and Strengths), 11 (Description), and 16 (How Supplied).

The exact wording of the labeling in the PLR format has been reviewed and comments from all disciplines were conveyed to the applicant. The applicant submitted revised labeling incorporating the Division's recommendations.

Proprietary name: There was no proprietary name proposed for this product.

DMEPA comments: In an initial review dated October 2, 2014, the DMEPA reviewer (Michelle Rutledge, Pharm.D.) identified several specific deficiencies in the prescribing information, and container/carton labeling. These deficiencies were conveyed to the firm. The applicant submitted revised labeling incorporating the DMEPA's recommendations on October 8, 2014.

Patient labeling/Medication guide: Not required for this product.

13. Recommendations/Risk Benefit Assessment

Clinical, CMC, pharmacology/toxicology, and clinical pharmacology recommend approval of this NDA. This application may be approved.

- **Recommended Regulatory Action**

Approval

- **Risk Benefit Assessment**

The review of this NDA is based primarily on chemistry, manufacturing and controls and clinical pharmacology/biopharmaceutics data. The Applicant has satisfactorily responded to the CMC deficiencies and the application has received an approve recommendation from the Office of Compliance. There are no outstanding regulatory issues for this NDA. This application may be approved.

- **Recommendation for Postmarketing Risk Management Activities**

This does not apply to this NDA.

- **Recommendation for other Postmarketing Study Commitments**

None

- **Recommended Comments to Applicant**

None

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/s/

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12/01/2014

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12/01/2014