CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206769Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Edvardas Kaminskas, M.D.
Subject	Deputy Division Director Summary Review
NDA# **Supplement #**	NDA 206769
Applicant Name	Teva Pharmaceuticals USA
Date of Submission	February 28, 2014
PDUFA Goal Date	December 25, 2014
Proprietary Name / **Established (USAN) Name**	Argatroban Injection
Dosage Forms / Strength	Injection, solution; single use polyolefin bag containing 250 mg argatroban in 250 mL aqueous sodium chloride solution (1 mg/mL)
Proposed Indications	1. 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).
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Hyon-Zu Lee, Pharm.D./Virginia Kwitkowski, M.S.N.
CMC Review	William M. Adams, B.S./Janice Brown, M.S./Ali Al-Hakim, Ph.D.
Product Quality Microbiology Review	Jessica G. Cole, Ph.D./Brian S. Riley, Ph.D.
Nonclinical Pharmacology/Toxicology	Shwu-Luan Lee, Ph.D./Christopher Sheth, Ph.D.
Clinical Pharmacology	Young Jin Moon, Ph.D./Bahru Habtemariam, Pharm.D.
CDTL Review	Janice Brown, M.S.
OSE/DMEPA	Michelle Rutledge, Pharm.D./Yelena Maslov, Pharm.D.
OPDP	James S. Dvorsky, Pharm.D.

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader
OSE=Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OPDP=Office of Prescription Drug Promotion

Signatory Authority Review Template

1. Introduction

Argatroban is a small molecule, a synthetic direct thrombin inhibitor derived from L-arginine and 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 250 mg/ 250 mL aqueous solution is submitted as a 505(b)(2) NDA.

2. Background

The proposed drug product differs from the listed drug in total drug content per container and packaging componenets. The reference drug is supplied as two single-use use vials, each vial containing 125 mL of Argatroban Injection, 1mg/mL. The applicant's drug product is 250 mg/250 mL (1 mg/mL) argatroban solution-filled polyolefin bag with a single port packaged into an aluminum overpouch. The applicant is seeking approval for all listed drug indications.

3. CMC/Device

Argatroban Injection is supplied as a 1 mg/mL ready-to-use, premixed, sterile solution in 250 mL of 9 mg/mL Sodium Chloride (b) (4), 3.0 mg/mL Sorbitol (b) (4) and Water for Injections (b) (4) in a single port 250 mL (b) (4) bag. The CMC information for the drug substance was provided in DMF No. (b) (4) from (b) (4)
The applicant provided adequate reference to their Type II DMF (b) (4) for information pertaining to the drug substance, argatroban. DMF (b) (4) was reviewed and found acceptable to support the NDA. Drug product information was reviewed. No CMC issues which preclude approval were found and the CMC reviews recommended approval of the NDA.

The Product Quality Microbiology Review concluded that the applicant has provided data sufficient that the risks for non-sterility and excessive endotoxin have been mitigated, and recommended approval of the NDA.

I concur with the conclusions reached by the chemistry and microbiology reviewers.

4. Nonclinical Pharmacology/Toxicology

No nonclinical pharmacology/toxicology information was submitted in this application. The excipients used by the sponsor are (b) (4) of the listed drug. The specifications for 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 recommended approval of the NDA.

5. Clinical Pharmacology/Biopharmaceutics

The proposed drug product differs from the reference listed drug (RLD, Sandoz, Inc., NDA 22485) in total drug content per container (125 mg/125 mL) and package components. In support of a waiver of *in vivo* bioequivalence, the applicant conducted an *in vitro* bridging sstudy to assess *in vitro* equivalence of the anticoagulant pharmacodynamic activity (as assessed by activated partial thromboplastin time (aPTT), prothrombin time (PT), and thrombin time (TT) in pooled plasma samples) between Teva's and Sandoz's products. The 90% CI of the ratios of means between Teva and the RLD were within the pre-specified confidence bound of 90% to 110%. Therefore, the biowaiver request for Argatroban Injection, 250 mg/250 mL (1 mg/mL) is granted.

There are no outstanding biopharmaceutics issues related to the Argatroban injection product and the reviewers recommended approval.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A.

7. Clinical/Statistical-Efficacy

No clinical efficacy information is included in this submission. No clinical issues which preclude approval were found. The Clinical Review recommended tentative approval of the NDA, pending an approval recommendation from the other disciplines.

8. Safety

No clinical safety information is included in this submission.

9. Advisory Committee Meeting

This application was not presented at an Advisory Committee meeting.

10. Pediatrics

There is no new information in the resubmission that would require a Pediatric and Maternal Health Staff (PMHS) review.

11. Other Relevant Regulatory Issues

An Establishment Evaluation Request (EER) was submitted to the Office of Compliance, and an overall "Approve" recommendation was issued.

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).

13. Decision/Action/Risk Benefit Assessment

- Recommended Regulatory Action

Approval.

- Risk Benefit Assessment

The risk/benefit assessment is the same as for the listed drug. 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 information requests and the application has received an "Approve" recommendation from the Office of Compliance. There are no outstanding regulatory issues that preclude approval.

There are no recommendations for Postmarketing Risk Management Activities or other Postmarketing Study Commitments.

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/s/

EDVARDAS KAMINSKAS
12/04/2014