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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 206769
Supporting document/s:	1
Applicant's letter date:	February 28, 2014
CDER stamp date:	February 28, 2014
Product:	Argatroban Injection
Indication:	Treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT) / as an anticoagulant in patients with HIT undergoing percutaneous coronary intervention
Applicant:	TEVA Pharmaceuticals USA
Review Division:	Division of Hematology Oncology Toxicology (DHOT) for Division of Hematology Products (DHP)
Reviewer:	Christopher Sheth, Ph.D.
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1 Executive Summary

1.1 Introduction

Argatroban is a direct thrombin inhibitor. Argatroban binds to the thrombin active site and does not require the co-factor antithrombin III for antithrombotic activity. Further information on the pharmacology of the drug could be found in the label.

Teva has submitted this 505(b)(2) NDA for the drug product Argatroban Injection, 250 mg/ 250 mL (1 mg/mL). Teva is relying on the Agency's previous findings of safety and effectiveness for Sandoz's approved drug product Argatroban Injection (in 0.9% Sodium Chloride), 125 mg/ 125 mL, NDA 022485. Teva's proposed product will differ from Sandoz's product in total drug content per container and in packaging components. Teva's presentation is a bag product containing 250 mL of Argatroban Injection (1 mg/mL), whereas the listed drug (LD) is supplied as two single use vials in a package, each vial containing 125 mL of Argatroban Injection (1 mg/mL).

No pharmacology/toxicology studies have been submitted to this NDA. There are no pharmacology/toxicology concerns with this application. The excipients used by Teva are identical to those in the LD. The specifications that Teva has proposed for their drug product impurities are acceptable. The levels of all leachables identified in the argatroban infusion bags were toxicologically justified.

1.2 Brief Discussion of Nonclinical Findings

No nonclinical pharmacology or toxicology studies were submitted with NDA 206769. Teva is relying on the Agency's previous finding of safety and effectiveness for Sandoz's approved drug product Argatroban Injection (in 0.9% Sodium Chloride), 125 mg/125 mL, NDA 022485. Teva requested a waiver of evidence of in vivo bioavailability requirements for their drug product in accordance with 21 CFR §320.22(b)(1), which is located in eCTD module 1.12.15.

The specifications for impurities in the drug substance and in the drug product were reviewed, along with the justifications provided by Teva. The drug substance impurity specifications proposed by Teva were adopted from those set by drug substance manufacturer (see Drug Master File (DMF) (b) (4) for further details on potential and actual impurities found). The specification limits proposed by Teva for related (b) (4) (NMT (b) (4) %) and any unknown impurity (NMT (b) (4) %) are in accordance with ICH Q3B, and the specification limit for total impurities (NMT 1.0%) is based on the specification for total impurities of the drug substance and the drug product stability data collected to date.

The CMC team asked Pharmacology/Toxicology to review the Toxicological Qualification of Leachables in Argatroban document provided by Teva (located in eCTD module 3.2.P.2). From the Pharmacology/Toxicology perspective, the levels of all leachables identified in the Argatroban infusion bags were toxicologically justified.

1.3 Recommendations

1.3.1 Approvability

From the Pharmacology/Toxicology perspective, Argatroban Injection 250 mg/250 mL (1 mg/mL) may be approved for the proposed indications.

1.3.2 Additional Non Clinical Recommendations

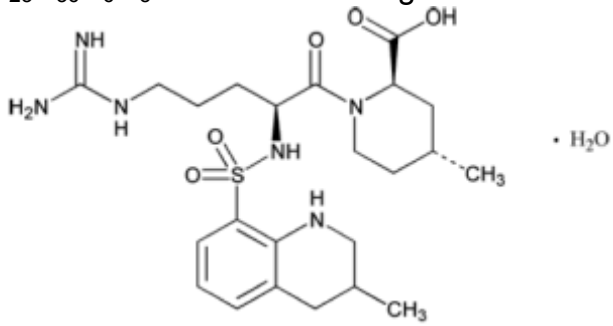
None

1.3.3 Labeling

The information presented in nonclinical sections of the label is similar to that of the listed drug.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional)	141396-28-3
Generic Name	Argatroban
Code Name	N/A
Chemical Name	2-Piperidinecarboxylic acid, 1-[5-[(aminoiminomethyl)amino]-1-oxo-2-[[(1,2,3,4-tetrahydro-3-methyl-8-quinolinyl)sulfonyl]amino]pentyl]-4-methyl-, monohydrate
Molecular Formula/Molecular Weight	$C_{23}H_{36}N_6O_5S \cdot H2O$ / 526.65 g/mol
Structure or Biochemical Description	
Pharmacologic Class	Direct thrombin inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND (b) (4); DMF (b) (4) (argatroban drug substance)

2.3 Drug Formulation

The finished drug product, Argatroban Injection, 250 mg/250 mL (1 mg/mL) is supplied as a clear, colorless to pale yellow solution, packaged in 250 mL (b) (4) bag with single port, closed by stopper and cap, put into aluminum foil overpouch with clear window. Argatroban Injection, 250 mg/250 mL (1 mg/mL) is administered as intravenous infusion. The drug product should not be diluted prior to administration. A summary of the formulation is presented in Table 1.

Table 1 Unit Composition for Teva's Argatroban Injection, 250 mg /250 mL (1 mg/mL)

Components	Concentration (mg/mL)	Each 250 mL bag contains [2] (mg)	Function	Reference to quality standard
Argatroban (as Argatroban monohydrate)	1.0 (1.035)	250.0 (258.75)	Active ingredient	In-house
Sorbitol	3.0	750.0	[redacted]	NF
Sodium chloride	9.0	2250.0	[redacted]	USP
Water for Injections	Ad to 1 mL [1]	Ad to 250 mL [1]	[redacted]	USP

[redacted]

(Excerpted from Applicant's submission)

2.4 Comments on Novel Excipients

None. The excipients used by Teva are the same as those used for the LD (Table 2).

Table 2 Comparison of Teva's product with the listed drug

Components	Reference product: Argatroban Injection in 0.9% Sodium chloride, 125 mg/125 mL (1 mg/mL)		TEVA product: Argatroban Injection, 250 mg/250 mL (1 mg/mL)	
	Concentration[1] / 1.0 mL	Concentration /125.0 mL	Concentration /1.0 mL	Concentration /250.0 mL
Argatroban (as Argatroban monohydrate)	1.0 mg (1.035 mg)	125.0 mg (129.38 mg)	1.0 mg (1.035 mg)	250.0 mg (258.75mg)
Sorbitol	3.0 mg	375.0 mg	3.0 mg	750.0 mg
Sodium chloride	9.0 mg	1125.0 mg	9.0 mg	2250.0 mg
Water for injections	ad 1.0 mL	ad 125.0 mL	ad 1.0 mL	ad 250.0 mL

1 reference to Sandoz's label for the LD

(Excerpted from Applicant's submission)

2.5 Comments on Impurities/Degradants of Concern

Impurities

The argatroban drug substance used in Teva's formulation is manufactured by the holder of DMF [redacted]. A letter of authorization to cross reference DMF [redacted] for argatroban drug substance was provided by the drug substance manufacturer and included in the Application (eCTD module 1.4.1). The manufacturer is controlling for impurities in the drug substance in accordance with ICH guidelines. The drug substance manufacturer has identified 6 potential impurities. The potential impurities

originating from the synthesis of argatroban include: [redacted] (Table 3). Related [redacted] was identified as a degradation product of argatroban. The other potential impurities are synthesis impurities that are being controlled in the drug substance (Table 4).

With regards to the drug product, Teva is monitoring for and reporting related [redacted] in addition to any unknown impurity and total impurities. An ultra performance liquid chromatography-based analytical method was validated for the determination of related substances in Teva's Argatroban Injection using argatroban as a working standard and related [redacted] as marker; under unstressed and stressed (i.e., light-, base-, acid-, heat- and [redacted]-stressed) conditions.

Table 5 summarizes the comparative impurity profiles of Teva's Argatroban Injection exhibit batches and the LD. According to Teva, their exhibit batches were stored at controlled conditions (25±2°C/40±5% RH) for 12 months and the LD lot was stored at recommended conditions (room temperature, upright position) according to the label until the study. Table 6 summarizes Teva's proposed specifications/justifications for controlling impurities in their drug product.

Table 3 Potential impurities originating from the synthesis

Impurity	Chemical name	Structure	Origin
(b) (4)			

(Excerpted from Applicant's submission)

Table 4 Teva's proposed drug substance specifications for argatroban (adopted from DMF [redacted])

Related Substances by LC Method I	[redacted]
Related Substances by LC Method II	[redacted]

(Excerpted from Applicant's submission)

Table 5 Comparison of impurity profiles after storage at shelf-life conditions

Tests	Teva Lot K1151012[redacted]	Teva Lot K2871112[redacted]	Teva Lot K2881112[redacted]	RLD Lot CC2823[redacted]
Related [redacted] %	[redacted]			
Any unknown impurity, %				
Total impurities, %				

(Excerpted from Applicant's submission)

Table 6 Teva's drug product impurity specifications and justifications

Tests	Specifications	Justification of Specifications
Related Substances by LC, %		
A) Related [redacted]	[redacted]	
B) Any unknown impurity	[redacted]	
C) Total impurities	[redacted]	

(Excerpted from Applicant's submission)

Leachables

The CMC team asked Pharmacology/Toxicology to review the Toxicological Qualification of Leachables in Argatroban document provided by Teva (located in eCTD module 3.2.P.2). From the Pharmacology/Toxicology perspective, the levels of leachables identified in the Argatroban infusion bags were toxicologically justified.

2.6 Proposed Clinical Population and Dosing Regimen

Teva proposed dosing recommendations consistent with the current label of the LD (Argatroban Injection in 0.9% Sodium Chloride, for intravenous infusion only); for prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT) or as an anticoagulant in adults patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI). The dose for HIT without hepatic impairment is 2 µg/kg/min administered as a continuous infusion. The dose for patients with or at risk for HIT undergoing PCI is started at 25 µg/kg/min and a bolus of 350 µg/kg administered via a large bore intravenous line over 3 to 5 minutes. Refer to Sandoz's approved label for Argatroban Injection for detailed dosage and administration information. The maximum daily dose of Teva's Argatroban Injection is 1008 mg/day (i.e., 10 µg/kg/min × 60 min × 24 hours × 70 kg = 1008 mg/day).

2.7 Regulatory Background

A pre-NDA meeting request (IND [redacted] was submitted in, 2013 and the Agency provided responses to the questions posed by Teva.

3 Studies Submitted

3.1 Studies Reviewed

N/A

3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

None

4 Pharmacology

N/A

5 Pharmacokinetics

N/A

6 General Toxicology

N/A

7 Genetic Toxicology

N/A

8 Carcinogenicity

N/A

9 Reproductive and Developmental Toxicology

N/A

10 Special Toxicology Studies

N/A

11 Integrated Summary and Safety Evaluation

See Executive Summary

12 Appendix/Attachments

None

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/s/

CHRISTOPHER M SHETH
05/23/2014

HALEH SABER
05/25/2014