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RESEARCH**

APPLICATION NUMBER:

203049Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 22, 2011
From	Janice Brown for Sarah Pope Miksinski Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 203049
Applicant	Hikma Pharmaceuticals Co. Ltd., U.S. Agent: Exela Pharma Sciences. LLC
Date of Submission	March 18, 2011 (received March 21, 2011)
PDUFA Goal Date	January 28, 2012
Proprietary Name / Established (USAN) names	Argatroban Injection (argatroban)
Dosage forms / Strength	Injection, 100 mg per/mL; Each vial contains 250 mg of Argatroban
Proposed Indication(s)	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)
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.

Introduction

Argatroban is a small molecule, 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 100 mg/mL (b)(4) solution is submitted as a 505(b)(2) NDA. The innovator product (Argatroban Injection, 250 mg/2.5 mL) is a concentrated solution which must be diluted prior to use. In this NDA, the product is also a concentrated solution containing 250 mg of Argatroban/2.5 mL solution and must be diluted prior to infusion. The applicant is seeking approval for all listed drug indications.

1. Background

The subject of the current NDA application is a new formulation for argatroban. 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 clinical data was submitted to support the application. In support of a waiver of *in vivo* bioequivalence (BE), Exela performed an *in vitro* bridging study to assess *in vitro* equivalence of the anticoagulant pharmacodynamic activity between Exela's and Pfizer's products.

2. 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.

Exela's drug product has the same active ingredient, dosage form, strength, route of administration, and conditions of use as Pfizer's Argatroban Injection. The difference is Exela's drug product contains a different excipient than Pfizer's approved Argatroban Injection. Exela's formulation propylene glycol replaces D-sorbitol (b)(4). Another change to Exela's drug product is the quantity of dehydrated alcohol used in the product. Exela's product contains (b)(4) of dehydrated alcohol and the listed product (Pfizer's Argatroban Injection) contains (b)(4). A comparison of the ingredients in Exela's Argatroban Injection, 250 mg/vial with Pfizer's Argatroban Injection is presented in table 1.

Table 1: Comparison of Exela's and Pfizer's Argatroban Injection Formulation

Ingredients	Exela's Formulation	Pfizer's Formulation
Each vial contains: (in mg)		
Argatroban	250	250
Dehydrated Alcohol, USP	800	1000
D-Sorbitol USP	--	750
Propylene Glycol, USP	1300	--
(b)(4)	(b)(4)	(b)(4)

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. 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.

The manufacturing process for Argatroban injection utilizes standard methods of compounding, filtration, (b) (4). Sufficient stability data have been provided to support an expiry period of 24 months for the drug product stored at the recommended room temperature conditions. Argatroban injection is light sensitive and should not be frozen.

Biopharmaceutics: The ONDQA biopharmaceutics review completed by Deepika Arora Lakhani, Ph.D. (signed November 21, 2011) granted a BA/BE waiver for the proposed Argatroban Injection and recommended approval of the NDA.

Microbiology: The product quality microbiology review completed by Denise A. Miller, Ph.D. (signed November 29, 2011) found the drug product (b) (4) information acceptable and recommended approval of the NDA from a quality microbiology standpoint.

3. Nonclinical Pharmacology/Toxicology

The safety of propylene glycol (PG) in the drug product, i.e., (b) (4) w/v (or (b) (4) v/v), was assessed by a single dose study in dogs (summary of a published reference) and clinical study data (including an article by Wilson *et al.*, 2005). The content of PG is within the range of the PG content (up to 80% v/v) in other FDA approved drugs and was found acceptable. No pharmacology/toxicology issues which preclude approval were found and the Pharmacology/Toxicology Review (Shwu-Luan Lee, Ph.D., final signature December 1, 2011) recommended approval of the NDA.

4. Clinical Pharmacology/Biopharmaceutics

Exela submitted an *in vitro* bridging study to assess *in vitro* equivalence of the anticoagulant pharmacodynamic activity between Exela's Argatroban injection and the listed drug, Pfizer's Argatroban Injection, in support of a waiver of *in vivo* bioequivalence (BE). The results of the data analyses of the current study indicate that an acceptable *in vitro* bridge between Exela's product and Pfizer's product was established. The Clinical Pharmacology reviewer, Young Jin Moon, Ph.D. recommended approval (signed October 31, 2011) of the NDA from a clinical pharmacology perspective.

5. Clinical Microbiology

No Clinical Microbiology review was required for this NDA.

6. Clinical/Statistical- Efficacy

No efficacy information is included in the NDA. No Statistical Review was done for this NDA.

7. Safety

Clinical Review of the NDA was completed by Firoozeh Alvandi, M.D. (December 1, 2011). The reviewer found no new safety concerns from review of the recent literature and recommended approval of the NDA from a clinical perspective.

8. Advisory Committee Meeting

There was no Advisory Committee meeting held for this application.

9. Pediatrics

The labeling for the LD contains information in the Pediatric Use section based upon a study conducted by the LD applicant. Information from the study regarding pediatric experience was placed into the label based on safety concerns that could arise should the product be used off label in pediatric patients. Consequently, this information was retained in the label for the new Exela argatroban product.

10. Other Relevant Regulatory Issues

Manufacturing Facilities: All drug substance and drug product manufacturing, packaging and control facilities were given an acceptable recommendation by the Office of Compliance on November 3, 2011.

11. Labeling

The proposed labeling for the Exela Argatroban injection is essentially the same in content as that of the innovator RLD product. . The formatting of the applicant's proposed labeling has been constructed to comply with the requirements of the Physician's Labeling Rule (PLR).

According to the clinical review, the information on pediatric experience and dosing of argatroban, including the pediatric use summary statement "The safety and effectiveness of Argatroban, including the appropriate anticoagulation goals and duration of therapy, have not been established among pediatric patients" was retained in accordance with 505A(o)

(1)(2)(A)(B), allowing protected information as pertains to Contraindications, Warnings, and Precautions, or Use in Specific Populations/Pediatric Use portions to be retained in generic drug labels.

The exact wording of the labeling in the PLR format has been reviewed and comments from all disciplines (including DMEPA) were conveyed to the applicant. The applicant submitted revised labeling incorporating the Division's recommendations on December 13, 2011.

12. Recommendations/Risk Benefit Assessment

CMC, pharmacology/toxicology, and clinical pharmacology recommend approval. Clinical review finds the application adequate.

This application may be approved.

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/s/

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01/04/2012

SARAH P MIKSINSKI
01/04/2012