FILE MEMORANDUM

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FROM:	Firoozeh Alvandi, MD, Medical Reviewer; Division of Hematology Products	
SUBJECT:	Argatroban	
Via:	Virginia Kwitkowski, MS, RN, ACNP-BC Clinical Team Leader, DHP, OHOP	

ISSUE: NA

ACTIONS RECOMMENDED: Approval, from the clinical perspective.

SUMMARY OF REVIEWER FINDINGS: No new safety concerns arise from review of recent literature. No clinical efficacy or safety data were submitted in this NDA application. Information on pediatric experience and dosing of argatroban must be retained in the label as appears in the reference listed drug. For details and recommendations regarding this NDA submission, refer to reviews by other disciplines.

Background:

Hikma Pharma Sciences (Exela) has developed an argatroban formulation that differs from the current marketed product with respect to inactive ingredients, specifically in the identity of one of the [redacted] (Hikma's Argatroban contains propylene glycol, USP and the RLD contains D-Sorbitol USP) [redacted] the drug substance (Hikma's Argatroban contains 800 mg dehydrated alcohol, USP and the RLD contains 1000 mg dehydrated alcohol, USP).

This is a 505(b)(2) because the applicant is relying on reference product (Argatroban by Pfizer [originally by Encysive]; NDA 20-883) to provide pharmacological equivalence. There were no clinical efficacy/safety data submitted for review. The applicant completed the following study:

1. An *in-vitro* pharmacokinetic study conducted to establish "bridge" data between the applicant's proposed drug product, Hikma's Argatroban Injection and the reference listed drug, Pfizer's Argatroban Injection. The applicant conducted "An in vitro coagulation study of a new formulation of Argatroban, Reference listed drug, and propylene glycol" to evaluate the effects of a new formulation of argatroban injection (argatroban NF), of the reference listed drug (argatroban RLD), and of propylene glycol (excipient) on activated partial thromboplastin time (APTT), prothrombin time (PT), and thrombin time (TT) in human plasma.

Plasma was collected from 40 humans ≥ 18 years of age (20 male and 20 female donors) using sodium citrate as the anticoagulant, and frozen in 50-mL aliquots. One 50-mL aliquot of plasma from each donor was thawed, and the aliquots were pooled on each day of the study. 1-mg/mL solution of argatroban was prepared and propylene glycol was diluted in 0.9% saline for injection for a solution to contain 5.2 mg of excipient/mL. The 1-mg/mL dose solutions of argatroban NF and argatroban RLD, or the excipient were added to the plasma in quadruplicate and mixed gently. For samples treated with argatroban, the concentrations of argatroban ranged from 0.05 µg/mL to 8 µg/mL. The plasma samples were loaded into the autoanalyzer for analysis. Each replicate was analyzed for prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time (TT) using the Amax Destiny Plus autoanalyzer. Aliquots (1 mL) of the human plasma samples were placed in amber containers and analyzed for argatroban using a validated LC-MS/MS method. See review from other disciplines for details.

The applicant submitted a literature search pertaining to the safety of propylene glycol (module 4). See review from other disciplines for additional details as to the acceptability of the amount of propylene glycol in the applicant's new formulation of Argatroban.

Review of recently published literature pertaining to Argatroban, did not raise additional safety concerns. Information resulting from the search is consistent with the established safety profile of argatroban.

The proposed label was submitted in a non-PLR format. Upon request, the sponsor provided a label in the required PLR format, subsequent to the initial submission. 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.

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/s/

FIROOZEH ALVANDI
12/01/2011

VIRGINIA E KWITKOWSKI
12/02/2011
Concur.