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*APPLICATION NUMBER:*

**201743Orig1s000**

**STATISTICAL REVIEW(S)**

FILE MEMORANDUM

MEMO DATE: 10/26/2010 PM: Ebla Ali-Ibrahim

TO NDA: 201743  
Submission Date: 4/13/2010  
FDA Received Date: 4/14/2010  
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Other reviewers: Biometrics: Lee, Kyung Y.  
Clinical Pharmacology: Zhang, Hua  
Non-Clinical: Lee, Shwu Luan  
Product Quality: Leutzinger, Eldon E.  
Product Quality Microbiology: Langille, Stephen E.

FROM: Firoozeh Alvandi, MD, Medical Reviewer; Division of Hematology Products

SUBJECT: Argatroban

Via: Virginia Kwitkowski, MS, RN, ACNP-BC  
Acting Clinical Team Leader, DHP, OODP

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ISSUE: NA

ACTIONS RECOMMENDED: Tentative approval

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. Review of the label submitted in the PLR format found the label to be acceptable. For details and recommendations regarding this NDA submission, refer to reviews by other disciplines.

Background:

Sandoz Canada has developed an argatroban formulation that differs from the current marketed product in that it does not contain any alcohol and does not require reconstitution.

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 studies:

1. A comparative physico-characteristics including impurity profile between Sandoz's argatroban and Encysive's argatroban (module 3; 3.2). See CMC review.

2. An *in vitro* study to evaluate and compare the results of aPTT, TT, PT and ACT in plasma containing different concentrations of argatroban from 3 different batches of 2 formulations of argatroban (Reference and Test formulations) and 2 different placebos (module 5; 5.3). This *in vitro* study was performed using plasma from 48 healthy adult, non-smoking subjects comparing the effect of argatroban of three batches by Sandoz Canada Inc. (Test formulation) to 3 batches by Encysive Pharmaceuticals (Reference formulation), using pooled human plasma. Five different plasma concentrations of argatroban were used for the test and the reference formulations - 0.25, 0.5, 1, 3 and 5 mcg/mL. At each of these concentrations, the test and reference solutions were diluted in dextrose (and separately in saline [NDA 22485]). Samples of plasma spiked with the test and reference placebo solutions, a sample of plasma only (Blank) and samples spiked with the saline vehicle (Control Dextrose) (and separately in Control Saline [NDA 22485]) were also tested using the aPTT, PT and TT coagulation tests. There were ultimately 6 pools of 8 subjects each and each pool was comprised of plasma from 4 males and 4 females. See Clinical Pharmacology review.

The applicant submitted a literature search from recent literature published in 2008 (module 5, 5.4). Review of this and additional review of more recent publications, did not raise additional safety concerns. Among the more recently published literature, one reference (Jonathan R. Genzen et al. Prolonged elevation of plasma argatroban in a cardiac transplant patient with a suspected history of heparin-induced thrombocytopenia with thrombosis. *Transfusion*. 2010;50:801-807), in a first report to measure plasma argatroban concentration in the context of cardiopulmonary bypass (CPB), suggested that prolonged elevated levels of plasma argatroban may have contributed to the extended coagulopathy observed in a 65-year-old critically ill male patient with history of heparin induced thrombocytopenia with thrombosis (HITT) undergoing CPBs. The article concluded that because direct thrombin inhibitors (DTIs) do not have reversal agents, surgical teams and transfusion services should be aware and vigilant of the possibility of need for massive transfusion events during anticoagulation with these agents.

The proposed label format appears acceptable from the clinical perspective. We recommend that information on pediatric experience and dosing of argatroban be 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 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" should also be retained. Given a 3-year Waxman-Hatch (WH) Exclusivity granted to the innovator (Encysive, now Pfizer), approval of the applicant's NDA 201743 will be tentative until the May 5, 2011 date of expiration of the HW Exclusivity (see PMHS memorandum of June 15, 2010).

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/s/  
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FIROOZEH ALVANDI  
01/26/2011

VIRGINIA E KWITKOWSKI  
01/26/2011