Office of Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-883 **SUBMISSION DATE**: 29 June 2005
BRAND NAME: Argatroban Injection
REVIEWER: Alfredo R. Sancho, Ph.D.
TEAM LEADER: Young Moon Choi, Ph.D.
OCPB DIVISION: Clinical Pharmacology V
ORM DIVISION: Medical Imaging and Hematology drug products
SPONSOR: Encysive Pharmaceuticals Inc., Houston, TX 77081
SUBMISSION TYPE; CODE: SE8-014
FORMULATION; IV solution (250 mg in 2.5 ml signle use amber vial)
PROPOSED INDICATION: Anticoagulant for prophylaxis or treatment of thrombosis in adults *and pediatric* patients with heparin-induced thrombocytopenia.

EXECUTIVE SUMMARY

Argatroban Injection is an US approved (30 June 2000) anticoagulant for prophylaxis and treatment of thrombosis in adult patients with heparin induced thrombocytopenia (HIT) as well as in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI). Argatroban is a synthetic thrombin inhibitor derived from L-arginine, has a selective inhibitory effect on the actions of thrombin directly, and does not require the presence of a cofactor, such as antithrombin. The recommended initial dose for prophylaxis or treatment of thrombosis in adults with HIT is 2 ug/kg/min, adjusted (not to exceed 10 ug/kg/min) to achieve an activated partial thromboplastin time (aPTT) of 1.5 to 3 times the baseline value (not to exceed 100 seconds). The initial dose should be reduced to 0.5 ug/kg/min in adult patients with hepatic impairment. The management of HIT/HITTS in adults consists of the immediate discontinuation of heparin, and continued anticoagulation with alternative medications such as lepirudin or Argatroban. There are a limited number of anticoagulants available for use in children. HIT/HITTS is less frequently reported in newborns and children as compared to adults. HIT in children mainly occurs in pediatric intensive care with diagnostic features and outcomes similar to those seen in adults.

The present submission is the sponsor's response to the Agency's written request for pediatric data in support of a Pediatric Exclusivity Determination. The sponsor submitted Pharmacokinetic (PK) and Pharmacodynamic (PD) data on 11 pediatric patients included in the approved prospective pediatric study SKF-105043/013 (Study 013). This data was reviewed and re-analyzed as needed. Argatroban plasma concentrations and aPTT measurements in 10 pediatric patients over a wide concentration range of (100 ng/mL – 5000 ng/mL) were available. The key pharmacometrics findings are:

- Pharmacokinetics in pediatric patients was reasonably well characterized. Body weight was found to be a significant predictor of clearance. The estimated clearance in a typical 20 kg pediatric patient was 2.8 L/hr (95% CI: 2.2 L/hr - 3.5 L/hr). The mean clearance in three patients with elevated serum bilirubin levels, most likely secondary to cardiac complications was 0.6 L/hr.
- Effect on aPTT was found to be concentration dependent and the concentration-aPTT relationship was found to be similar in pediatric patients and healthy adults.
- For pediatric patients an initial dose of 0.75 µg/kg/min of Argatroban injection dose as a continuous infusion is recommended. Dosage adjustment as clinically indicated in step sizes of 0.25 µg/kg/min every 2-4 hr is also recommended. The dose of Argatroban in pediatrics is

recommended not to exceed 3.0 µg/kg/min. Pediatric patients with hepatic impairment/elevated bilirubin levels most likely secondary to cardiac complications should be dosed 1/4 of the normals.

Additionally, the sponsor submitted data from a "HIT Registry" in which pediatric patients (n=17) were given intravenous therapy with Argatroban. This HIT Registry contains adult and pediatric patient data. The pediatric data was used in the study "A Retrospective Chart Review to Evaluate the Safety and Effectiveness of Argatroban Injection in Pediatric Patients Requiring Alternative Anticoagulation to Heparin" which took place between 27 February 2002 and 21 November 2003. The Agency's Pediatric Exclusivity Committee met and reviewed this additional data and information. The Agency informed the sponsor on 27 September 2005 that, it had concluded that this additional information would not be acceptable to supplement the data from the approved pediatric study SKF-105043/013 (Study 013).

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Clinical Pharmacology V, has reviewed the information and data included in sNDA 20-883 package submitted on 29 June 2005 and has found that the there is sufficient pediatric information and data to update the package insert of Argatroban Injection.

SIGNATURES

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