

## M E M O R A N D U M

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

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Subject: NDA 20-883/SE8-014 Argatroban Injection  
Pediatric labeling supplement, re-submission dated August 16, 2007

To: NDA 20-883

Argatroban is a synthetic, direct thrombin inhibitor derived from L-arginine. It is approved for anticoagulation for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia and as an anticoagulant in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI).

This is the second review cycle for this pediatric supplement. The supplement was originally submitted on June 29, 2005 to obtain approval and labeling for use of argatroban in pediatric patients with heparin induced thrombocytopenia and thrombosis syndrome (HIT/HITTS) and to be considered for pediatric exclusivity. The submission consisted of results of a single, ongoing pharmacokinetic/pharmacodynamic (PK/PD) and safety study undertaken by the sponsor in response to a Written Request (WR) for pediatric studies. Pediatric exclusivity was denied because of insufficient study sample size to characterize safety and efficacy of argatroban (only 11 of requested minimum 24 patients studied) and the study did not provide interpretable PK/PD data to meet the study objective. The first cycle review of the supplement concluded that the data submitted were inadequate to support labeling of argatroban for pediatric use. The supplement was found to be approvable and the following recommendations were made to address the deficiencies (approvable letter, 12/21/05):

1. Continue the study (SKF105043/013) of argatroban in pediatric patients with HIT/HITTS to completion and submit the full report, including safety, PK/PD analyses, datasets and supporting information for review.
2. Add liver function testing including bilirubin (direct and indirect), ALT and AST with related reference laboratory values at baseline and during argatroban treatment for all additional patients to be studied in the trial.
3. Clarify the use of heparin and other anticoagulants as a concomitant medication in 9 of 11 patients studied, including reason for use, dose and treatment timing and duration.

4. Evaluate and address need for dose adjustment in pediatric patients with abnormal hepatic function.
5. Explore more thoroughly through further analyses the relationship between age and dose and weight and dose, particularly in infants.
6. Provide revised labeling incorporating safety and PK/PD information based on the results of the completed study.

The resubmission has been reviewed by the clinical reviewer (M. Lu, M.D., review completed 2/12/08, signed 2/15/08) and by the Clinical Pharmacology/Pharmacometrics reviewer (R. Madabushi, Ph.D., signed 2/13/08). In the current submission the sponsor has provided PK/PD and safety data from an additional 7 pediatric patients enrolled and studied in their pediatric study. The study has been discontinued with completion of these patients. Thus, a total of 18 pediatric patients (8 patients less than 6 months of age, 6 patients 6 months up to 8 years of age, and 4 patients 8 years and older) have been studied. Safety findings in the study included a total of 4 deaths (one (5.5 year old) due to massive intracranial bleeding in a patient with dilated cardiomyopathy who underwent extracorporeal membrane oxygenation (ECMO); one (2.6 year old) due to cardiac dysfunction and acidosis; one (16.4 week old) following superior vena caval thrombosis and infarction and one (19.4 week old) due to worsening disseminated intravascular coagulation. (See also clinical review by M. Lu, M.D., signed 12/16/05). From the clinical and laboratory data available, the relationship between degree of anticoagulation and death in these patients was not clear. The clinical review concluded, "The overall safety information is very limited due to the small number of patients enrolled in the study and the complicated medical conditions in all patients at baseline. It is difficult to make a dose recommendation for pediatric patients based on the available clinical outcome and safety from the submitted study." The Clinical Pharmacology review should be consulted for additional comments and recommendations regarding dosing. The Clinical Pharmacology/Pharmacometrics Review had the following major findings and conclusions.

- In the present study, plasma samples corresponding to steady-state levels of argatroban were collected over a range of doses in seriously ill pediatric patients (N=15, 166 data points). The concentration - time data was adequate to characterize systemic clearance.
- The clearance in pediatric patients was found to be different from healthy adults. The clearance in pediatric patients was approximately 50% of healthy adults.
- The estimated clearance in a typical 20 kg pediatric patient was 3.1 L/hr with 95% confidence intervals ranging from 2.2 L/hr to 4.0 L/hr. Body weight was a significant predictor of clearance.
- The mean clearance in four patients with elevated serum bilirubin levels secondary to cardiac complications was 0.6 L/hr.

- Plasma concentration-anticoagulant response (aPTT) data in pediatric patients (N=15, 329 data points) was collected over a wide range of concentrations (100 – 5000 ng/mL).
- After the adjustment for clearance in pediatric patients, the concentration-aPTT relationship was found to be similar in pediatric patients and healthy adults.
- A dose of 0.75 µg/kg/min in pediatric patients is a reasonable and safe starting dose with about ~60% of the subjects reaching a target aPTT of 1.5 to 3 times the baseline and aPTT not exceeding 100 seconds.
- A step size of 0.25 µg/kg/min is most suitable to titrate remaining 39% of the patients not reaching the therapeutic levels with a starting dose of 0.75 µg/kg/min.
- About 1% of patients reach aPTT levels above 100 seconds in the simulations.



The PK/PD results using data from 6 additional patients (one patient had no PK/PD data) were found to be consistent with the results from analysis of the patients previously submitted. Regarding dosing the review stated, “For pediatric patients an initial dose of 0.75 µg/kg/min of argatroban injection 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. Pediatric patients with hepatic impairment/elevated bilirubin levels most likely secondary to cardiac complications should be dosed 1/4<sup>th</sup> of the normals.” The initial argatroban dose of 0.75 µg/kg/min recommended based on Pharmacokinetics review is lower than the more customary dose of 1 µg/kg/min that was used in the study, and may provide safer initiation of anticoagulation in these patients.

The clinical and PK/PD review findings were presented and discussed at a meeting of the Pediatric Review Committee (PeRC, 1/30/08) which recommended that the study information and dose recommendation based on PK/PD review should be included in the Pediatric Use sub-section under PRECAUTIONS section of the labeling and commented that the wording and label placement of the information should encourage the prescribing physician to read the study information as well as dose recommendation in the label. The Clinical Pharmacology/Pharmacometrics review recommended inclusion of PK information for pediatric patients in the CLINICAL PHARMACOLOGY/SPECIAL POPULATION section of the Label and inclusion of dosing information in the DOSAGE AND ADMINISTRATION section of the label.

The Clinical review, Clinical Pharmacology review, and PeRC review all found that the submitted information is sufficient to support labeling statements regarding use of argatroban in pediatric patients with HIT/HITTS. Of particular note is that the pharmacometric analysis suggests that the initial dose for pediatric patients should be lower than that used in the study. Clinical and PeRC review recommend that the dosing information be included in the Pediatric Use sub-section under PRECAUTIONS section of the label along with a description of the study and study results, particularly for safety while Clinical Pharmacology/Pharmacometrics review recommends inclusion of dosing

information for pediatric patients in the DOSAGE AND ADMINISTRATION section of the label.

**Conclusions and Recommendation:**

Based on the available information, this supplement should be approved. Because of the limited safety information and the lack of specific safety and efficacy information for the initial dosing being recommended for pediatric patients, and to provide proper context with regard to actual clinical experience with argatroban in the pediatric study, I recommend that the pediatric dosing information should be included in the Pediatric Use subsection of the PRECAUTIONS section of the label. Additional PK/PD information should be included in the CLINICAL PHARMACOLOGY/SPECIAL POPULATION section of the labeling, as recommended in the Clinical Pharmacology/Pharmacometrics review. The DOSAGE AND ADMINISTRATION section should include a statement directing the physician to the PRECAUTIONS, Pediatric Use section for information on pediatric dosing.

Also, as concluded in the clinical review, this study adequately fulfills the sponsor's phase 4 commitment #1 (approval letter 6/30/2000) "to conduct pharmacokinetic and safety studies in pediatric subjects to allow for appropriate dosing instructions in this population."

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MEDICAL OFFICER