Executive Summary

I. Recommendations

A. Recommendation on Approvability

The sponsor submitted a pediatric study report that included 11 patients from an ongoing study in response to the Agency's Written Request for study of argatroban in pediatric patients. The study was planned to include a minimum of 24 pediatric patients with at least 8 patients in the birth to <6 months age range and at least 8 patients in the ≥8 years to <17 years age range. The study was designed as a pharmacokinetic/pharmacodynamic and safety study to provide appropriate dose recommendation and safety information in pediatric patients. This study was also conducted to fulfill the phase 4 commitment that was requested by the Agency in the Approval Letter dated in June 30, 2000 to provide appropriate dosing instructions in pediatric population.

In the submitted study report, only 11 pediatric patients were studied. These patients included 6 patients in the birth to <6 months age group, 4 patients in the ≥8 years to <17 years age group and 1 patient in the 6 months to <8 years age group. Among the 11 patients, 4 were diagnosed with HIT, 4 had suspicion of HIT, and 3 had underlying conditions that required alternative anticoagulation. There were 2 patients who were diagnosed with HIT in the birth to <6 months group who discontinued study prematurely due to serious adverse events, which lead to death. One patient had intracranial hemorrhage on Day 5 that was considered to be possibly related to the study drug treatment and subsequently died on Day 6.

From a clinical perspective, Argatroban should be approvable for the proposed indication for the prophylaxis or treatment of thrombosis in pediatric patients with heparin-induced thrombocytopenia (HIT) with recommendation to the sponsor to complete the ongoing pediatric study to fulfil Phase 4 commitment and to provide sufficient safety information and to allow appropriate dose instruction in pediatric population. The sponsor should encourage enrollment of more patients with objectively diagnosed HIT/HITTS in the ongoing study.

The sponsor should also provide the following information in the complete study report:

1. The sponsor should clarify 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 information.
2. The sponsor should include 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.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

No new recommendations on Phase 4 study. The sponsor should complete Phase 4 commitments specified in Approval Letter dated June 30, 2000. This submission is also in response to the Phase 4 commitment #1 listed below:

1. To conduct pharmacokinetic and safety studies in pediatric subjects to allow for appropriate dosing instructions in this population.

This submission included 11 currently enrolled patients of planned 24 patients in the study protocol. The sponsor should complete the study as planned to fulfil this phase 4 commitment.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Product name: Argatroban

Drug class: Direct thrombin inhibitor

In response to the Agency's Written Request, one pediatric study (SKF105043/013) was conducted in pediatric patients for the indication for prophylaxis and/or treatment of thrombosis in pediatric patients who 1) have a diagnosis of heparin-induced thrombocytopenia (HIT) and thrombosis syndrome (HITTS), or 2) require anticoagulation and have documented histories of positive HIT antibody test in the absence of thrombocytopenia or heparin challenge (patients with latent disease), or 3) require alternative anticoagulation (i.e., not heparin) due to an underlying condition, including patients with anti-thrombin 3 deficiency or hypercoagulable states. A minimum of 24 patients were requested in the study to include at least 8 patients in the birth to <6 months age range and at least 8 patients in the ≥8 years to <17 years age range. The current submission included 11 patients in the ongoing study. This study was also conducted to fulfil the phase 4 commitment that was requested by the Agency in the Approval Letter in 2000.

B. Study SKF105043/013

One open-label, pharmacokinetic/pharmacodynamic and safety study was conducted in pediatric patients. Eleven of the planned 24 patients enrolled in the study. Among the 11 patients, six patients were <6 months old (range from 2.7 weeks to 21.0 weeks), 1 patient was 6.8 years old, and 4 patients were between the ages of 8 and 16 years (range from 10.9 years to 16.1 years). There were 8 males and 3 females. Seven patients were white, 2 patients were black, and 2 patients were Hispanic. Four were diagnosed with heparin-induced thrombocytopenia (HIT), 4 had suspicion of HIT, and 3 had underlying condition that required alternative anticoagulation. All 4 patients who were diagnosed with HIT were in the <6 months of age group.

Among the 11 patients, 9 (82%) patients completed the study and 2 patients discontinued study prematurely due to serious adverse events which lead to death. One patient, a 16-week-old white male who was diagnosed with HIT, had intracranial hemorrhage during argatroban treatment and subsequently died due to this event. The other patient, a 19-week-old black male who was also diagnosed with HIT, died of sepsis/worsening disseminated intravascular coagulation.

Two patients received initial 1 or more boluses of Argatroban at a total dose of 250µg/kg and all 11 patients received Argatroban by continuous infusion. Of the 11 patients, 6 (55%) patients had ≥5 Argatroban infusions during the study. The mean infusion dose was 3.3 ± 3.7 µg/kg/min, and ranged from 0.54 to 13.0 µg/kg/min. Among 9 patients who received Argatroban solely as a continuous infusion, 8 patients initiated Argatroban at 1.0 mcg/kg/min and one initiated at 5.4 mcg/kg/min. The median treatment duration was 118 hours with a range from 1.3 hours to 319 hours.

The study was not designed to evaluate the efficacy of argatroban. However, occurrence/recurrence of thrombosis information was collected in the study. Among 11 enrolled patients, one patient (9%) experienced thrombosis during administration of argatroban. The patient had a superior vena caval occlusion on Day 2, intracranial hemorrhage and extensive infarction on Day 5. Two additional patients (18.2%) experienced thrombosis within the 30-day follow-up period. The first patient had an intrahepatic inferior vena caval venous thrombosis on Day 28 and the argatroban dosing was completed on Day 11. The second patient had a superior vena caval occlusion on Day 23 and had completed Argatroban dosing on Day 15.

There were a total of 107 reports of Treatment-Emergent Adverse Events **(**TEAEs) during the study. Ten (91%) patients (5 patients aged <6 months, 1 patient aged 6 months through <8 years, and 4 patients aged 8 years through 16 years) had at least 1 TEAE.

Two patients, both <6 months of age and diagnosed with HIT, had SAEs that resulted in

death during the study. One patient had intracranial hemorrhage that was considered possibly related to Argatroban and the other had sepsis and worsening disseminated intravascular coagulation that was considered unrelated to Argatroban. One case of nonfatal SAEs was reported in a patient as subdural hematomas on a post-study head CT.

Among the 11 patients, the most frequently reported TEAE was hypotension (36%), reported by 4 patients (3 patients <6 months of age and 1 patient ≥8 years of age), followed by hypernatremia (3 patients, 27%), hypokalemia (3 patients, 27%), and agitation (3 patients, 27%). Four patients (36%) had TEAEs that were considered by the investigator to be severe. These TEAEs were respiratory distress (2 cases), superior vena cava occlusion, renal failure, abnormal hepatic function, hyperbilirubinemia and cerebral hemorrhage (one case), and worsening disseminated intravascular coagulation (one case). Only abnormal hepatic function, hyperbilirubinemia, and intracranial hemorrhage in one case were considered to be possibly related to study drug by investigator.

Overall, the number of pediatric patients studied in the reported trial is insufficient to provide adequate safety information and appropriate dose recommendation in pediatric population. In the submitted safety data there was one case of intracranial hemorrhage which was considered to be possibly related to Argatroban treatment. The ongoing pediatric study should complete as planned to provide sufficient safety information and appropriate dosing instructions in pediatric population as requested by the Agency in the Approval Letter in 2000.

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/s/

Kathy Robie-Suh

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