CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022434Orig1s000

MEDICAL REVIEW(S)

FILE MEMORANDUM

MEMO DATE:	6/16/2011 PM: Ebla Ali-Ibrahim
TO NDA:	22434 (Class 2 resubmission based on CMC deficiencies)
Submission Date:	01/10/2011
FDA Received Date:	01/12/2011
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Other reviewers:	Clinical Pharmacology: Zhang, Hua Non-Clinical: Lee, Shwu Luan Product Quality: Chen, Xiao H.
FROM:	Firoozeh Alvandi, MD, Medical Reviewer; Division of Hematology Products
SUBJECT:	Argatroban
Via:	Virginia Kwitkowski, MS, RN, ACNP-BC Clinical Team Leader, DHP, OODP

ISSUE: NDA 22434

ACTIONS RECOMMENDED: The recommended regulatory action is 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. Review of the label submitted found the format acceptable; however, the applicant must add pediatric information from the innovator which contains important safety information (see below). For details and recommendations regarding this NDA submission, refer to reviews by other disciplines.

Background:

Eagle has developed an argatroban formulation that differs from the reference listed drug (RLD) in its inert ingredient and in that it is a ready to use formulation. The inert ingredient in the Eagle argatroban is 2 mg lactobionic acid, 2 mg L-methionine, 8 mg sodium chloride (the inert ingredients in the RLD are 750 mg D-sorbitol, 1,000 mg dehydrated alcohol).

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 *in vitro* studies including a pilot and a pivotal study and hemolytic potential testing

1. The pivotal clotting study (EGL-ARG-10-CLOT) demonstrated the pharmacodynamic equivalence of the Argatroban Injection RTU (1 mg/mL) and Argatroban Injection (100 mg/mL) formulations (diluted according to label instructions to 1 mg/mL).
Study EGL-ARG-10-CLOT compared the two formulations in vitro at the anticipated range of plasma concentration in patients, by measuring the activated partial thromboplastin time (aPTT), prothrombin time (PT), and thrombin time (TT) in male and female human plasma. The statistical analyses clearly demonstrated that the Argatroban Injection RTU (1 mg/mL) is pharmacodynamically equivalent to Argatroban Injection (100 mg/mL) in terms of anticoagulant activity as measured by aPTT, PT, and TT at all concentrations tested spanning the therapeutic range, using equivalence criteria of 90% to 110% for aPTT and PT, and 85% to 115% for TT. While the protocol specified that the equivalence criterion for TT was 85% to 115%, this parameter also met the more strict equivalence criterion of 90% to 110%.

See CMC review and Clinical Pharmacology review.

2. Study EGL-ARG-10-PILOT was an in vitro pilot study conducted to compare the anticoagulant activity of the two formulations as measured by aPTT, PT and TT over the therapeutic plasma concentration range in pooled male and pooled female human plasma. The goal of the study was to determine if the plasma concentrations of argatroban selected for the assays are appropriate for comparing the two formulations in the pivotal study, and to provide an estimated standard deviation for sample size calculations for the pivotal study. The TT assay did not yield reliable quantifiable results at the highest concentration tested (1 µg/mL), and, therefore, only this highest dose for TT was not used in the main clotting study.

See CMC review and Clinical Pharmacology review.

Below is a table summarizing the pilot and pivotal studies.

Study	Plasma Pools	Objectives and Plasma Concentrations	Conclusions
EGL-ARG-10-PILOT	6 (3 male, 3 female)	To measure the effects of plasma concentrations of two argatroban formulations on clotting tests (aPTT, PT, and TT) over possible therapeutic ranges in pooled male and pooled female human plasma. The goals of the study were to: 1. determine if the plasma concentrations of argatroban selected for the assays are appropriate for comparing the two formulations to be used in the pivotal study, and 2. provide an estimated standard deviation for sample size calculations for the pivotal study. **Concentrations:** aPTT (0.25, 0.50, 1.0, 2.0, 3.0, 5.0, and 8.0 µg/mL), PT (1.0, 3.0, 5.0, and 8.0 µg/mL) and TT (0.1, 0.25, 0.50, 0.75, and 1.0 µg/mL). Blank (plasma only) and control (0.9% saline vehicle, no argatroban) samples were also tested. Actual plasma argatroban concentrations in spiked plasma samples were quantified by a new validated LC/MS/MS assay.	**Suitability of Test Concentrations:** The results showed that the argatroban concentrations selected and used in this pilot study were appropriate for use in the main clotting study, with one exception. The TT assay at the highest concentration (1.0 µg/mL) did not achieve measurable coagulation in several samples; as a result, five out of six pools were not evaluable at this concentration. Therefore this highest concentration was not used for the TT assay in the pivotal clotting study. **Comparison of the Test and Reference Formulations:** The data show that the two formulations of argatroban are comparable in terms of anticoagulant activity as demonstrated by the aPTT, PT, and TT assays. The ratios of the geometric means for the adjusted responses between the test and reference formulations were generally close to 100%. **Determination of the Sample Size for the Pivotal Study:** Assuming the standard deviation is less than or equal to 0.135 for PT and aPTT on the logarithmic scale, a sample size of 25 subjects would have at least 90% power to establish equivalence using the equivalence limit of 0.90 to 1.10 at the 0.05 significance level. Assuming the standard deviation is less than or equal to 0.239 for TT on the logarithmic scale, a sample size of 34 subjects would have at least 90% power to establish equivalence using the equivalence limit of 0.85 to 1.15 at the 0.05 significance level. To adjust for the potential loss of plasma samples, a total sample size of 40 subjects was planned for the pivotal study based on this analysis.
EGL-ARG-10-CLOT	40 (19 male, 21 female)	To establish the equivalence of two argatroban formulations by measuring the effects of plasma concentrations of argatroban on clotting tests aPTT, PT, and TT over the therapeutic range in pooled male and pooled female human plasma. **Concentrations:** aPTT (0.25, 0.50, 1.0, 2.0, 3.0, 5.0, and 8.0 µg/mL), PT (1.0, 3.0, 5.0, and 8.0 µg/mL) and TT (0.1, 0.25, 0.50, and 0.75 µg/mL). Blank (plasma only) and control (0.9% saline vehicle, no argatroban) samples were also tested. Actual plasma argatroban concentrations in spiked plasma samples were quantified by a new validated LC/MS/MS assay.	The statistical analyses indicate that the two formulations of argatroban are equivalent using the criteria of 90% - 110% for aPTT and PT. While the protocol specified that the equivalence criterion for TT was 85% - 115%, this parameter also met the more strict equivalence criterion of 90% - 110%.

3. Hemolytic Potential Testing of Argatroban Injection. An in vitro hemolytic potential test was conducted using Argatroban Injection (Eagle Pharmaceuticals, Inc.) incubated with human whole blood. For comparison, the hemolytic properties of Argatroban (argatroban injection; SmithKline Beecham Corporation) was similarly assessed. Following incubation and centrifugation, hemolysis was evaluated by spectrophotometric analysis for hemoglobin concentration in the supernatant. No hemolysis was noted in 0.5 mL human whole blood when incubated with up to 0.4 mL of Argatroban Injection.

See CMC review and Clinical Pharmacology review.

The label is in the PLR format. The information on pediatric experience and dosing of argatroban must 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.

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/s/

FIROOZEH ALVANDI
06/16/2011

VIRGINIA E KWITKOWSKI
06/16/2011

Summary Review for Regulatory Action

Date	January 28, 2010
From	Dwaine Rieves, MD
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	22-434
Applicant Name	Eagle Pharmaceuticals, Inc.
Date of Submission	March 27, 2009
PDUFA Goal Date	January 30, 2010
Proprietary Name / **Established (USAN) Name**	Argatroban Injection RTU (Ready To Use) Argatroban
Dosage Forms / Strength	50 mL solution in single-use, piggyback vial at a concentration of 1 mg/mL
Proposed Indication(s)	For prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT); As an anticoagulant for patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI)
Action/Recommended Action	Complete Response/CMC-based

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Firoozeh Alvandi, MD
Statistical Review	Not applicable
Pharmacology Toxicology Review	Ron Honchel, PhD
CMC Review/OBP Review	Mark Sassaman, PhD
Microbiology Review	Stephen Langille, PhD
Clinical Pharmacology Review	Joseph Grillo, PhD
DDMAC	Not applicable
DSI	Not applicable (no inspection)
CDTL Review	Kathy Robie Suh, MD, PhD
OSE/DMEPA	Not applicable
OSE/DDRE	Not applicable
OSE/DRISK	Not applicable
Other	Not applicable

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

Argatroban is a direct thrombin inhibitor previously approved for use among patients with heparin-induced thrombocytopenia (HIT). Additionally, the approved indication includes the drug's use among patients undergoing percutaneous coronary intervention (PCI) with or at risk for HIT.

The current NDA is a 505b2 application that relies, for clinical verification of safety and efficacy, entirely upon the previous findings for argatroban. The applicant (Eagle Pharmaceuticals) provided an *in vitro* "bridging" study in which the Eagle argatroban was compared to the currently approved product. In this study, human plasma was spiked with the drugs and anticoagulation parameters (PT/APTT/TT) compared. This study showed the same (consistent with acceptability for "sameness") anticoagulation results for the two drugs.

This was a first cycle review. The NDA was logged into our system as a "resubmission" following a prior Refusal to File determination. The applicant had submitted an original NDA (22-434) on September 26, 2008. Preliminary review (prior to the filing date) disclosed an important data deficiency pertaining to the "bridging study" and the applicant was informed of the Refusal to File the application in a letter dated November 21, 2009. The applicant submitted the current "resubmission" on March 27, 2009.

The main findings from this first cycle were deficiencies in manufacturing information. Although not evident prior to the filing meeting, the subsequent review disclosed numerous manufacturing deficiencies exemplified by: inadequacies within a Drug Master File's description of the manufacturing process and process controls, inadequate characterization of impurities, particularly impurities from forced degradation studies; unacceptable specification for total impurities; unacceptable analytical procedures for detection of heavy metals and isomer characterization; lack of an accuracy determination during the analytical assay validation; unsatisfactory container-closure and stability data as well as numerous other deficiencies. Together, these deficiencies largely precluded identification and characterization of the drug proposed for marketing.

The extent of the manufacturing deficiencies were described to the applicant in telephone conversations (May 14 and 20, 2009 and October 13 and 20, 2009). Overall, the manufacturing deficiencies were so extensive that they also precluded verification of the sufficiency of nonclinical data and the proposed labeling. The clinical pharmacology review determined that the "bridging study" data were sufficient to establish acceptable pharmacologic similarity between the Eagle argatroban and the currently marketed argatroban.

However, even this conclusion is predicated upon verification of the manufacturing process for the tested drug.

Labeling was not addressed during this review cycle. The labeling will ultimately need to include pediatric dosing information even though this was, interpreted as “protected” under exclusivity; the pediatric dosing information represents important safety information. PREA does apply to this application and this issue will need to be addressed in the subsequent review cycle. In general, the review team anticipates waiver of pediatric studies, as has been done for other argatroban 505b2 applications.

2. Background

The currently marketed argatroban is a concentrated solution that requires dilution. Eagle's argatroban is a new formulation that is supplied in a "ready to use" format of 1 mg/mL in a total volume of 50 mL. The formulation contains different excipients from the marketed drug (lactobionic acid and methionine are unique to the Eagle formulation/it does not contain the sorbitol and alcohol found in the currently marketed product).

3. CMC/Device

I concur with the chemistry reviewer’s observation that the sponsor failed to supply acceptable manufacturing and drug characterization data. The extent of deficiencies is large and beyond an item by item description. The reviewer has recommended a complete resubmission of the manufacturing/drug characterization data. The review was also complicated by important deficiencies within a Drug Master File held by another sponsor.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that manufacturing information needs to be complete before all non-clinical aspects can be resolved.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

I concur with the reviewer's finding that final microbiology acceptance is contingent upon resolution of manufacturing deficiencies.

7. Clinical/Statistical-Efficacy

I concur with the review teams' conclusions that sufficient safety and efficacy data exist to support the safety and efficacy of the Baxter argatroban, if the review of manufacturing data verify the acceptablity of the "bridging study" data. This finding is based on the observations for the currently marketed argatroban, the bioavailability comparability between the two drugs (both for intravenous administration) and the bridging study findings.

8. Safety

No new safety considerations were detected in the supplied safety summary. The overall pattern of adverse reactions maintained consistency with the approved labeling.

9. Advisory Committee Meeting

This supplement was not presented to an advisory committee.

10. Pediatrics

Pediatric study aspects will need to be reviewed in the subsequent cycle; as noted above, the review team anticipates waiver of pediatric studies.

11. Other Relevant Regulatory Issues

The original supplement involved a transformation of the argatroban label to conform to the physicians labeling rule.

12. Labeling

Labeling will need finalization once the manufacturing issues are resolved.

13. Decision/Action/Risk Benefit Assessment

The review team has recommended a Complete Response focused upon the unresolved manufacturing deficiencies. I concur with this conclusion.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22434	ORIG-1	EAGLE PHARMACEUTICALS INC	ARGATROBAN INJECTION

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/s/

RAFEL D RIEVES
01/28/2010

Cross-Discipline Team Leader Review

Date	January 27, 2010
From	Kathy M. Robie Suh, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	22-434
Applicant	Eagle Pharmaceuticals, Inc.
Date of Submission	March 27, 2009
PDUFA Goal Date	January 30, 2010
Proprietary Name / Established (USAN) names	Argatroban Injection RTU
Dosage forms / Strength	Injection, (50 mg/50 mL; 100 mg/100 mL)
Proposed Indication(s)	1. for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT). 2. as an anticoagulant in patients with or at risk for heparin-induced thrombocytopenia (HIT) undergoing percutaneous coronary intervention (PCI)
Recommended:	Complete Response

1. Introduction

Argatroban is a small molecule, synthetic direct thrombin inhibitor derived from L-arginine and approved for intravenous administration for treatment and prevention of thrombosis in patients with heparin-induced thrombocytopenia (HIT) and for anticoagulation in patients with HIT who are undergoing percutaneous coronary interventions (PCI). The current application for Argatroban Injection RTU 50 mg/50 mL (b) (4) (Eagle argatroban) is submitted as a 505(b)(2) NDA. The innovator product (Argatroban Injection, 250 mg/2.5 mL, GlaxoSmithKline) is a concentrated solution which must be diluted for use. In the current application the sponsor has developed a ready to use (RTU) formulation of Argatroban.

The proposed package insert for the Eagle argatroban is essentially the same in content as that of the innovator RLD product, except for the Description section and that the sponsor has carved out (deleted) the information in the RLD argatroban package insert describing the pediatric experience with argatroban. Also, the formatting of the sponsor's proposed labeling has been constructed to comply with the requirements of the Physician's Labeling Rule (PLR). (The RLD package insert is still in the old format).

2. Background

The subject of the current NDA application is a new formulation of approved argatroban.

This NDA application was originally submitted on September 26, 2008 (received September 29, 2008). The initial submission was deemed insufficiently complete to permit a substantive review and a Refusal to File letter was sent to the sponsor on November 21, 2008. The letter cited data omissions related to the *in vitro* studies essential to assess the sponsor's drug's similarity to the reference listed drug (RLD). Specific reference was made to numerous deficiencies in the "bridging" study, including omissions of: data sets that identify the actual Argatroban concentrations in stock and spiked solutions; detailed information regarding the assay procedure and validation (including raw data) for methodologies including Argatroban concentrations in the stock and spiked solutions, prothrombin time (PT), activated partial thromboplastin time (aPTT), and thrombin generation assay; datasets that permit duplication of the submitted analyses; datasets to allow verification of the plot of thrombin generation in platelet poor plasma spiked with GSK-argatroban; and data definition and supportive information for the submitted (electronic) datasets. The Refusal to File letter was discussed with the sponsor in a meeting on January 29, 2009 (IND 102,622 meeting minutes).

The NDA was resubmitted on letter date March 27, 2009 (received March 30, 2009). The application was filed, however, major Clinical Pharmacology and Chemistry, Manufacturing and Controls (CMC) deficiencies were identified and were communicated to the sponsor in a filing communications letter on May 19, 2009. Additional information was provided by the sponsor in multiple amendments over the next several months. Teleconferences were held with the sponsor on May 14 and 20, 2009 and October 13 and 20, 2009,

Because the sponsor for this new argatroban product is different from the sponsor of the already approved product, the sponsor for this new application is relying upon information in the public domain (labeling for approved argatroban product and published studies and information about argatroban) to support the safety and efficacy of the new product. No clinical primary data are submitted to support the application. An *in vitro* clinical pharmacology bridging study was conducted.

3. CMC/Device

The CMC information in the response to the CR was reviewed by Mark Sassaman, Ph.D. (November 23, 2009). The review found numerous deficiencies and stated the following:

> The application has numerous deficiencies. There are very few areas that can be adequately reviewed. Under normal circumstances, CMC reviewers would itemize deficiencies and expect the applicant to provide complete responses. In this case, that policy would be counterproductive. If a list of deficiencies were assembled, the applicant would be obligated to respond only to items on that list. Due to the large volume of missing and/or unsatisfactory information, the most prudent recommendation is to begin afresh. On several occasions, FDA communicated interim assessments of problems with the application, informed Eagle that the application could neither be approved nor reviewed, and recommended withdrawal and resubmission under a new NDA number. The Office of Regulatory Policy assured the company that no new PDUFA fees would be assessed. Still, Eagle decided in favor of not withdrawing, possibly in hope of being able to respond to deficiencies after only a brief delay.
>
> The application is not reviewable; had Eagle been forthcoming with correct establishment information, the application would not have been filed.
>
> CMC reviewers remain open to the possibility of discussing deficiencies and a path forward with the applicant during a face-to-face meeting or telephone conference but do not plan on issuing an itemized list.

The review concluded that the application cannot be approved in its current form. Among the many deficiencies were: the drug product has never be made at the facility intended for commercial production, no available stability data, and a recent change in presentation, "such that the originally submitted application is, by definition, for a different drug product".

4. Nonclinical Pharmacology/Toxicology

For this 505(b)(2) application the sponsor relies on the Agency's previous findings of safety and efficacy for Argatroban extablished in preclinical toxicity studies conducted by the innovator. No Pharmacology/Toxicology studies were provided in this application. The Pharmacology/Toxicology Review (Ronald Honschel, Ph.D., December 22, 2009) concluded the following:

1. The Sponsor failed to provide adequate information in regards to impurities and degradation products. Therefore, from a preclinical standpoint, we cannot recommend approval at this time.

2. Nonclinical studies could potentially be required to qualify impurities or degradation products if qualification thresholds are exceeded as described in ICH Guidance Q3A and Q3B.

5. Clinical Pharmacology/Biopharmaceutics

For this application in support of a waiver of *in vivo* bioequivalence data the sponsor provided an *in vitro* "bridging" study to assess the equivalence of the anticoagulant activity between Eagle's argatroban product (RTU solution 50 mg/50 mL (b) (4) and the admixed innovator formulation. The study was reviewed by FDA Clinical Pharmacology (Joseph A. Grillo, Pharm.D., January 20, 2010). The reviewer found that the sponsor's adjustments of observed coagulation parameters when argatroban concentrations exceeded (b) (4) were statistically inappropriate. However, a reviewer generated proper analysis of the raw unadjusted data found the results to be within the acceptable equivalence range between 0.9 and 1.11 defined by the sponsor. The review concluded that the analysis is acceptable, but is limited by technical error in the accurate and precise preparation of the stock and spiking solutions. The review concluded that the application was acceptable from a Clinical Pharmacology perspective provided agreement is reached on wording in the package insert.

6. Clinical Microbiology

Product Quality Microbiology Review (Stephen E. Langille, Ph.D., January 21, 2010) for the first cycle described the manufacturing aspects related to product quality microbiology as follows:

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -
The drug product will be (b) (4)
Cipla manufacturing facility in Verna Goa, India.

The review commented that the sponsor did not provide updated manufacturing process control information, validation information, and stability data for the manufacture of Argatroban Injection in (b) (4) of the Cipla manufacturing facility and that these deficiencies could result in microbial and/or endotoxin contamination of the drug product.

7. Clinical/Statistical- Efficacy

This application is submitted as a 505(b)(2) NDA relying on previous determination of efficacy and safety of RLD argatroban for its labeled indications. Argatroban is indicated as an anticoagulant:

- for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia.
- in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI).

No clinical studies have been conducted with Eagle's argatroban product. The Eagle product is a ready to use formulation to be used for the same indications and with the same dosing as the already approved RLD. The Eagle product will be used "as is" while the RLD requires dilution prior to its use.

Statistical review was not required for the application.

8. Safety

Argatroban is contraindicated in patients with overt major bleeding, or in patients hypersensitive to this product or any of its components (see WARNINGS). Its major safety concerns include hemorrhage. Because argatroban is metabolized mainly in the liver, caution must be exercised when using argatroban in patients with hepatic impairment. Based on information in the Argatroban RLD label, in clinical studies in HIT/HITTS patients hypotension, fever and diarrhea appeared to be the most common adverse reactions with argatroban relative to control. In HIT patients undergoing PCI chest pain was a common event. Other notable adverse reactions include intracranial bleeding among patients with acute myocardial infarction receiving argatroban and thrombolytics and allergic reactions.

The Clinical Review of the CR response submission (Firoozeh Alvandi, M.D. , January 25, 2010) found that a review of the literature revealed no new safety signals and findings were consistent with the safety sections of Eagle's proposed labeling.

The formulations differ in their excipients.

Based on Pharmacology/Toxicology review the impurities in the Eagle product may not have been adequately qualified..

9. Advisory Committee Meeting

There was no Advisory Committee meeting held for this application.

10. Pediatrics

The labeling for the RLD contains information under Special Populations and in the Pediatric Use sections of the package insert based upon a study conducted by the RLD sponsor. As such, some exclusivity provisions may apply. The sponsor has deleted the information about pediatric experience from the Pediatric Use section of the package insert, retaining only the statement that, "Safety and efficacy of argatroban in pediatric patients have not been demonstrated." However, placement in the label of the pediatric information was based on concerns for safety should the product be used off label in pediatric patients and not on

findings of efficacy and safety from the study. The pediatric information in the RLD labeling is as follows:

Under **SPECIAL POPULATIONS**:

"Pediatric: Argatroban clearance is decreased in seriously ill pediatric patients. Pharmacokinetic parameters of Argatroban were characterized in a population pharmacokinetic/pharmacodynamic analysis with sparse data from 15 seriously ill pediatric patients. Clearance in pediatric patients
(0.16 L/hr/kg) was 50% lower compared to healthy adults (0.31 L/hr/kg). Four pediatric patients with elevated bilirubin (secondary to cardiac complications or hepatic impairment) had, on average, 80% lower clearance (0.03 L/hr/kg) when compared to pediatric patients with normal bilirubin levels. (See **PRECAUTIONS, Pediatric Use.**)"

Under **PRECAUTIONS:**

"Pediatric Use: The safety and effectiveness of Argatroban, including the appropriate anticoagulation goals and duration of therapy, have not been established among pediatric patients. Argatroban was studied among 18 seriously ill pediatric patients who required an alternative to heparin anticoagulation. Most patients were diagnosed with HIT or suspected HIT. Age ranges of patients were <6 months, n = 8; six months to <8 years, n = 6; 8 to 16 years, n = 4. All patients had serious underlying conditions and were receiving multiple concomitant medications. Thirteen patients received Argatroban solely as a continuous infusion (no bolus dose). Dosing was initiated in the majority of these 13 patients at 1 mcg/kg/min. Dosing was titrated as needed to achieve and maintain an aPTT of 1.5 to 3 times the baseline value. Most patients required multiple dose adjustments to maintain anticoagulation parameters within the desired range. During the 30-day study period, thrombotic events occurred during Argatroban administration to two patients and following Argatroban discontinuation in three other patients. Major bleeding occurred among two patients; one patient experienced an intracranial hemorrhage after 4 days of Argatroban therapy in the setting of sepsis and thrombocytopenia. Another patient completed 14 days of Argatroban treatment in the study, but experienced an intracranial hemorrhage while receiving Argatroban following completion of the study treatment period.
When Argatroban is used among seriously ill pediatric patients with HIT/HITTS who require an alternative to heparin and who have normal hepatic function, initiate a continuous infusion of Argatroban at a dose of 0.75 mcg/kg/min. Initiate the infusion at a dose of 0.2 mcg/kg/min among seriously ill pediatric patients with impaired hepatic function (see **CLINICAL PHARMACOLOGY**, **Pharmacokinetics**). Check the aPTT two hours after the initiation of the Argatroban infusion and adjust the dose to achieve the target aPTT. These dose recommendations are based upon a goal of aPTT prolongation of 1.5 to 3 times the baseline value and avoidance of an aPTT >100 seconds. Increments of 0.1 to 0.25 mcg/kg/min for pediatric patients with normal hepatic function and increments of 0.05 mcg/kg/min or lower for pediatric patients with impaired hepatic function may be considered but dose selection must take into account multiple factors including the current Argatroban dose, the current aPTT, target aPTT, and the clinical status of the patient. These dose recommendations are based upon a goal of aPTT prolongation of 1.5 to 3 times the baseline value and avoidance of an aPTT >100 seconds."

The Clinical Review for the application (Firoozeh Alvandi, M. D., January 27, 2010) states the following:

> Reviewer comment: *The proposed label for Eagle's argatroban does not contain the information on pediatric experience with argatroban as given in the RLD label. Although, as stated in the current RLD label "The safety and effectiveness of Argatroban, including the appropriate anticoagulation goals and duration of therapy, have not been established in pediatric patients", in medical practice Argatroban may be used for treatment of pediatric patients with HIT/HITTS in the clinical setting. For this reason it is important that all known safety information to improve the safe use of the drug, given the lower clearance of argatroban in the pediatric population, particularly in association with elevated bilirubin levels, be available for physicians. As such, due to safety reasons, the protected information should be retained in Eagle's Argatroban labels. The dose adjustment information included in the Pediatric Use section of the RLD label should be included in the labels of any 505(b)(2) or generic argatroban products as well in order to reduce the risk of overdose and consequent serious adverse events such as bleeding and intracranial hemorrhage associated with Argatroban therapy in pediatric patients.*
>
> *The pediatric information in the RLD label provides important safety precautions, and given the safety concerns associated with Argatroban Injection use in pediatric patients, protected pediatric information should be retained in Eagle's Argatroban drug label in the CLINICAL PHARMACOLOGY/SPECIAL POPULATIONS/Pediatric Use, PRECAUTIONS/Pediatric Use, and DOSAGE AND ADMINISTRATION/Dosing in Special Populations/Pediatric HIT/HITTS sections, 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, as should 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". (Eagle's proposed labeling currently does not include this pediatric information).*

Pediatric waiver for the Baxter argatroban product was granted on May 15, 2009 based on the determination that the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and the unlikelihood of its use in a substantial number of pediatric patients.

11. Other Relevant Regulatory Issues

No Division of Scientific Investigations (DSI) audits were conducted for this application.

12. Labeling

The sponsor's proposed labeling for Eagle's argatroban is essentially the same in content as that of the innovator RLD product, except for the Description section of the labeling and the deletion of the information about pediatric experience with argatroban. However, the formatting of the sponsor's proposed labeling has been constructed to comply with the requirements of the Physician's Labeling Rule (PLR). (The RLD label is still in the old format).

In the original submission (September 26, 2008) the sponsor's exclusivity statement (1.3.5.3) indicated that Eagle's proposed labeling "retains the associated contraindications, warnings, precautions, or similar risk information that would not be eligible for exclusivity" and furthermore, once the innovator exclusivity expires on May 5, 2011, Eagle intends to include the full labeling for this use. As discussed in the Clinical Review (Firoozeh Alvandi, M.D., January 27, 2010) the pediatric experience information included in the label was added due to safety concerns and should be retained as described under 10 above. Exact wording of the labeling in the PLR format will need to be negotiated with the sponsor.

13. Recommendations/Risk Benefit Assessment

Based on findings of the CMC review and the Pharmacology/Toxicology review a Complete Response letter should be issued for this application with deficiencies as identified in those reviews.

In their resubmission Eagle should include revised labeling that includes the information about pediatric experience with argatroban as described in the RLD package insert, since this information is essential to safety should the product be used off-label in pediatric patients.

When approved, the labeling for the Eagle argatroban should be essentially the same in content as for the RLD, except for the sections related to the description of the product. Particularly, the information in the Pediatric Use section of the RLD should be retained in the Eagle argatroban product labeling, as it provides information important for safety, should the product be used in pediatric patients. Approved labeling for the new product should be in PLR format.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22434	ORIG-1	EAGLE PHARMACEUTICALS INC	ARGATROBAN INJECTION

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/s/

KATHY M ROBIE SUH
01/27/2010

CLINICAL REVIEW

Application Type	NDA 505(b)(2) Application
Application Number(s)	NDA 22-434
Priority or Standard	Standard
Submit Date(s)	March 27, 2009
Received Date(s)	March 30, 2009
PDUFA Goal Date	January 30, 2010
Reviewer Name(s)	Firoozeh Alvandi, MD
Review Completion Date	January 25, 2010
Established Name	Argatroban Injection
(Proposed) Trade Name	Argatroban Injection Ready to Use (RTU)
Therapeutic Class	Direct Thrombin Inhibitor
Applicant	Eagle Pharmaceuticals, Inc.
Formulation(s)	Argatroban 1mg/mL Pre-Mixed
Dosing Regimen	Intravenous
Indication(s)	Prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT), patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI)
Intended Population(s)	Patients with or at risk for HIT

TABLE OF CONTENTS

1. RECOMMENDATIONS/RISK BENEFIT ANALYSIS 3

1.1 RECOMMENDATION ON REGULATORY ACTION 3
1.2 RISK BENEFIT ANALYSIS 3
1.3 RECOMMENDATIONS FOR POSTMARKET RISK MANAGEMENT ACTIVITIES 4
1.4 RECOMMENDATIONS FOR POSTMARKET STUDIES/CLINICAL TRIALS 4

2. INTRODUCTION AND REGULATORY BACKGROUND 4

2.1 PRODUCT INFORMATION 5

2.2 TABLE(S) OF CURRENTLY AVAILABLE TREATMENT(S) FOR PROPOSED INDICATION(S) 5
2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES 5
2.4 IMPORTANT SAFETY ISSUES WITH CONSIDERATION TO RELATED DRUGS 5
2.6 OTHER RELEVANT BACKGROUND INFORMATION 6

3. ETHICS AND GOOD CLINICAL PRACTICES 6

3.1 SUBMISSION QUALITY AND INTEGRITY 6
3.2 COMPLIANCE WITH GOOD CLINICAL PRACTICES 6
3.3 FINANCIAL DISCLOSURES 6

4. SIGNIFICANT EFFICACY OR SAFETY FINDINGS RELATED TO OTHER REVIEW DISCIPLINES 6

4.1 CHEMISTRY MANUFACTURING AND CONTROLS 6
4.2 CLINICAL MICROBIOLOGY 7
4.3 PRECLINICAL PHARMACOLOGY/TOXICOLOGY 7
4.4 CLINICAL PHARMACOLOGY 7

5. SOURCES OF CLINICAL DATA 7

5.1 TABLES OF STUDIES /CLINICAL TRIALS 7
5.1.2 PEDIATRIC SAFETY INFORMATION 7
5.2 REVIEW STRATEGY 10

6. REVIEW OF EFFICACY 10

7. REVIEW OF SAFETY 10

8. POSTMARKET EXPERIENCE 11

9. APPENDICES 11

9.1 LITERATURE REVIEW /REFERENCES 11
9.2 LABELING RECOMMENDATIONS 11
9.3 ADVISORY COMMITTEE MEETING 12

1. RECOMMENDATIONS/RISK BENEFIT ANALYSIS

1.1 Recommendation on Regulatory Action

From a clinical perspective Eagle's Argatroban Injection RTU is acceptable for approval, pending approval by other review disciplines, for the following indications:

- Prophylaxis and treatment of thrombosis due to Heparin Induced Thrombocytopenia (HIT), and
- Anticoagulation for patients with or at risk of HIT, undergoing Percutaneous Coronary Intervention (PCI).

The conclusions and recommendations should convey at least the following:
Information on pediatric use as reflected in the Reference Listed Drug (RLD) argatroban (NDA 20883) label should also be included in the Eagle Argatroban label, as it conveys important safety information.

1.2 Risk Benefit Analysis

Risk-benefit assessment for Eagle Argatroban Injection is based on the risk-benefit assessment for the Reference Listed Drug (RLD) listed in the Orange Book.

Eagle Argatroban Injection is intended for use for the prophylaxis and treatment of thrombosis in patients with HIT or HIT with thrombosis (HITT) and for patients with or at risk for HIT/HITT or who are undergoing PCI.

HIT is associated with formation of an immunoglobulin G (IgG) antibody directed against a neo-epitope in the Heparin-Platelet Factor 4 complex, which upon binding to platelets and endothelial cells results in thrombocytopenia and a thrombosis.

There is an approximately 20-40 fold increased risk of thrombosis in HIT patients as compared to those without HIT. There is a 25-50% risk of development of thrombosis, (with venous thrombosis more prevalent than arterial thrombosis, although, when present, arterial thrombosis may result in limb amputation), when heparin treatment is stopped, with or without Warfarin substitution (Warkentin et al. Chest 133:suppl 340S-380(2008)). HIT is associated with significant mortality.

Heparin (unfractionated or low molecular weight) is contraindicated in HIT and HITT due to cross-reactivity with the causative antibody. There are currently three direct thrombin inhibitors approved for use in patients with HIT (Argatroban, lepirudin, bivalirudin), with two indicated for use in non-PCI settings (Argatroban, lepirudin). Compared to Lepirudin, Argatroban has not been associated with anti-drug antibody formation and can be used in patients with renal insufficiency.

The Eagle argatroban product is a ready-to-use (RTU) formulation of argatroban that does not require dilution prior to use as does the RLD. The safety and efficacy profile of Eagle Argatroban is anticipated to be the same as that of the RLD.

The Reference Listed Drug (NDA 20-883), was approved based on trials (ARG-911 and ARG-915) which examined the outcomes of 722 patients with clinical diagnosis of HIT or HITT who were treated with Argatroban from 5 to 7 days with outcomes compared to those of 193 historical controls (Lewis et al. Circulation 103:1838-43 (2001); Lewis et al. Arch Int Med 163:1849-56 (2003)). ARG-911 was a prospective, historically controlled efficacy and safety study and ARG-915 was a follow-on efficacy and safety study using the same historical control group from ARG-911 as comparator. A summary of the salient results can be found in the clinical reviews for other 505(b)(2) argatroban product, NDA 22-359, Min Ha Tran, D.O., 2/18/09 and Firoozeh Alvandi, M.D., completed 12/17/2009, entered into DARRTS 1/6/2010).

The pediatric information in the RLD label provides important safety precautions, and given the safety concerns (bleeding, intracranial hemorrhage) associated with Argatroban Injection use in pediatric patients, protected pediatric information should be retained in Eagle's Argatroban drug label in the CLINICAL PHARMACOLOGY/SPECIAL POPULATIONS/Pediatric Use, PRECAUTIONS/Pediatric Use, and DOSAGE AND ADMINISTRATION/Dosing in Special Populations/Pediatric HIT/HITTS sections, 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, as should 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."

1.3 Recommendations for Postmarket Risk Management Activities

Safety should be monitored by usual postmarket surveillance and reporting as per 21 CFR 314.80 and 314.81.

1.4 Recommendations for Postmarket Studies/Clinical Trials

Not applicable

2. INTRODUCTION AND REGULATORY BACKGROUND

The sponsor has submitted a 505(b)(2) application for argatroban for the currently approved indications for the RLD drug. These indications are for use for the prophylaxis and treatment of thrombosis in patients with HIT or HIT with thrombosis (HITT) and for patients with or at risk for HIT/HITT or who are undergoing PCI. This is the second review cycle for this NDA application.

2.1 PRODUCT INFORMATION

2.1.1 Argatroban Injection RTU (Eagle Pharmaceuticals Inc., NDA 22-434)

Eagle Argatroban Injection, RTU is an intravenous solution containing argatroban 1 mg/mL, lactobionic acid 2 mg/mL, L-Methionine 2 mg/mL and sodium chloride 8 mg/mL in water for injection. The solution is isotonic with a target pH range of (b) (4) (pH of vehicle is adjusted with sodium hydroxide). It is packaged in a single-use piggyback vial.

Eagle Argatroban Injection is intended for the same indications and route of administration, with the same dosing regimen frequency and duration as the RLD. This application was submitted under Section 505(b)(2) of the Food, Drug, and Cosmetic Act (http://www.fda.gov/cder/guidance/2853dft.pdf.3) given that this product differs from the RLD in its new ready to use formulation and in excipients (sponsor uses term "inactive ingredients").

2.1.2 The Reference Listed Drug (RLD): Argatroban Injection (GlaxoSmithKline, NDA 20-833)

The RLD Argatroban, approved by the FDA on June 30, 2000, is a direct thrombin inhibitor (DTI), available in a parenteral formulation and is indicated for the prophylaxis and treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT) with or without thrombosis and for use as an anticoagulant during percutaneous transluminal intervention (PCI) in patients with or at risk of HIT. RLD Argatroban is provided in 250-mg (in 2.5-mL) single-use vials. Each mL of the solution contains 100 mg Argatroban, 750 mg D-sorbitol, and 1,000 mg dehydrated alcohol. For injection this solution must be diluted 100-fold with 250 mL of 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Lactated Ringers Injection prior to use.

2.2 Table(s) of Currently Available Treatment(s) for Proposed Indication(s)

Currently available treatments for the proposed indications are: Argatroban by Encysive, Bivalirudin (Angiomax®) by Medicines Co, and Lepirudin (Refludan®) by Bayer.

2.3 Availability of Proposed Active Ingredient in the United States

Argatroban is a chemically synthesized drug. RLD Argatroban (NDA 20-883) was first approved June 30, 2000. It is currently marketed in the U.S. by GlaxoSmithKline.

2.4 Important Safety Issues With Consideration to Related Drugs

Safety concerns associated with use of Argatroban include the potential for increased risk of bleeding for which there is no available agent with which to reverse the effects of anticoagulation; the risk of immunogenicity associated with drug accumulation and subsequent prolongation of anticoagulant effect; and drug interaction (adverse drug reaction) with Lepirudin.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

- Teleconference with FDA requested on June 12, 2008
- Preliminary comments sent to sponsor on July 24, 2008
- July 29, 2008 meeting cancelled at sponsor's request, due to no clarification needed for provided responses
- The NDA application was initially submitted September 29, 2008. However it was "refuse to file" due to incomplete and inadequate information pertaining to the study found in section 4.1.2 (the "bridging" study) of the application (letter dated November 21, 2008).
- Jan 29, 2009 meeting with Agency (under sponsor's pre-IND 102622 for argatroban) to discuss bridging study deficiencies.
- March 30, 2009 resubmission of NDA
- The application was filed but a number of Clinical Pharmacology and Chemistry (CMC) deficiencies were identified.

2.6 Other Relevant Background Information

Not applicable.

3. ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

No clinical issues.

See also Chemistry, Manufacturing, and Controls (CMC) Review (Mark Sassaman, Ph.D., November 23, 2009) and Clinical Pharmacology Review (Mark Sassaman, Ph.D., November 23, 2009).

3.2 Compliance with Good Clinical Practices

No issues identified.

3.3 Financial Disclosures

No concerns have been identified based on the financial disclosures submitted.

4. SIGNIFICANT EFFICACY OR SAFETY FINDINGS RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry Manufacturing and Controls

See Chemistry, Manufacturing, and Controls (CMC) Review (Mark Sassaman, Ph.D., November 23, 2009).

4.2 Clinical Microbiology

See Microbiology Review (Stephen E. Langille, Ph.D., January 21, 2010).

4.3 Preclinical Pharmacology/Toxicology

See Pharmacology/Toxicology Review (Ronald Honschel, Ph.D., December 22, 2009).

4.4 Clinical Pharmacology

See also Clinical Pharmacology Review (Mark Sassaman, Ph.D., November 23, 2009).

5. SOURCES OF CLINICAL DATA

The sponsor relied on publicly available information (argatroban RLD labeled studies, published literature) to support the efficacy and safety of argatroban.

5.1 Tables of Studies /Clinical Trials

No clinical studies were done.

5.1.1 Updated Safety Information

See 7 below.

5.1.2 Pediatric Safety Information

The approval of the RLD argatroban on June 3, 2000, included a post marketing commitment "to conduct pharmacokinetic and safety studies in pediatric subjects to allow for appropriate dosing instructions in this population". A pediatric study was conducted by the sponsor of the RLD to determine pharmacokinetics and safety of Argatroban Injection in pediatric patients, following issuance of a Pediatric Written Request (PWR) (April 2, 2003 requesting safety, PK/PD, and clinical outcome data on at least 24 patients from ages of 0 (birth) to <16 years with diagnosis of HIT/HITT or requiring anticoagulation for latent disease (documented positive HIT antibody history without thrombocytopenia or heparin challenge), or requiring anticoagulation other than heparin secondary to underlying conditions such anti-thrombin III deficiency. The sponsor (Encysive Pharmaceuticals, Inc.) conducted an "Open-Label Study of Argatroban Injection to Evaluate the Safety and Effectiveness in Pediatric Patients Requiring Anticoagulant Alternatives to Heparin" and a retrospective chart review and submitted a supplement (S-014) with data available on only 11 patients enrolled prospectively. Pediatric Exclusivity was (b) (4) Review of the submission found that the PK/PD data were too scant to be meaningfully interpreted and concluded that the study should be carried to completion (i.e, ≥24 patients enrolled). Other deficiencies also were identified, including need to add liver function testing including bilirubin (direct and indirect), to evaluate and address dose adjustment in pediatric patients with abnormal hepatic function, and to provide revised labeling to include the safety and PK/PD information based on the results of the

completed study. All these deficiencies were communicated to the sponsor in an Approvable Letter for S-014, on December 21, 2005.

A Complete Response (to the December 21, 2005 Approvable Letter) was submitted by the sponsor on August 16, 2007. Data were provided from a total of 18 prospectively enrolled patients. Review of the study results found that, compared to in adults, clearance of argatroban is lower in the pediatric population, especially in the presence of elevated bilirubin levels and concluded that initial continuous infusion Argatroban dose should be lower for pediatric (0.75 mcg/kg/min) than for adult (2.0 mcg/kg/min) patients (02/14/2008 Clinical Pharmacology – Pharmacometrics – Review by Dr. R. Madabushi). Although determination of full therapeutic regimen information could not be made due to the small size of the study and the limited information was not sufficient to support a pediatric indication, important and useful safety information was derived from this study and S-014 was approved on May 5, 2008. The Argatroban labeling was revised to include the following information in the CLINICAL PHARMACOLOGY/SPECIAL POPULATIONS/Pediatric Use, PRECAUTIONS/Pediatric Use, and DOSAGE AND ADMINISTRATION/Dosing in Special Populations/Pediatric HIT/HITTS sections of the RLD Argatroban Injection label:

SPECIAL POPULATIONS, Pediatric:

Pediatric: Argatroban clearance is decreased in seriously ill pediatric patients. Pharmacokinetic parameters of Argatroban were characterized in a population pharmacokinetic/pharmacodynamic analysis with sparse data from 15 seriously ill pediatric patients. Clearance in pediatric patients (0.16 L/hr/kg) was 50% lower compared to healthy adults (0.31 L/hr/kg). Four pediatric patients with elevated bilirubin (secondary to cardiac complications or hepatic impairment) had, on average, 80% lower clearance (0.03 L/hr/kg) when compared to pediatric patients with normal bilirubin levels. (See PRECAUTIONS, Pediatric Use.)

PRECAUTIONS, Pediatric Use:

Pediatric Use: The safety and effectiveness of Argatroban, including the appropriate anticoagulation goals and duration of therapy, have not been established among pediatric patients.

Argatroban was studied among 18 seriously ill pediatric patients who required an alternative to heparin anticoagulation. Most patients were diagnosed with HIT or suspected HIT. Age ranges of patients were <6 months, n = 8; six months to <8 years, n = 6; 8 to 16 years, n = 4. All patients had serious underlying conditions and were receiving multiple concomitant medications. Thirteen patients received Argatroban solely as a continuous infusion (no bolus dose). Dosing was initiated in the majority of these 13 patients at 1 mcg/kg/min. Dosing was titrated as needed to achieve and maintain an aPTT of 1.5 to 3 times the baseline value. Most patients required multiple dose adjustments to maintain anticoagulation parameters within the desired range. During the 30-day study period, thrombotic events occurred during Argatroban administration to two patients and following Argatroban discontinuation in three other patients. Major bleeding occurred among two patients; one patient experienced an intracranial hemorrhage after 4 days of Argatroban therapy in the setting of sepsis and thrombocytopenia.

Another patient completed 14 days of Argatroban treatment in the study, but experienced an intracranial hemorrhage while receiving Argatroban following completion of the study treatment period.

When Argatroban is used among seriously ill pediatric patients with HIT/HITTS who require an alternative to heparin and who have normal hepatic function, initiate a continuous infusion of Argatroban at a dose of 0.75 mcg/kg/min. Initiate the infusion at a dose of 0.2 mcg/kg/min among seriously ill pediatric patients with impaired hepatic function (see CLINICAL PHARMACOLOGY, Pharmacokinetics). Check the aPTT two hours after the initiation of the Argatroban infusion and adjust the dose to achieve the target aPTT. These dose recommendations are based upon a goal of aPTT prolongation of 1.5 to 3 times the baseline value and avoidance of an aPTT >100 seconds. Increments of 0.1 to 0.25 mcg/kg/min for pediatric patients with normal hepatic function and increments of 0.05 mcg/kg/min or lower for pediatric patients with impaired hepatic function may be considered but dose selection must take into account multiple factors including the current Argatroban dose, the current aPTT, target aPTT, and the clinical status of the patient. These dose recommendations are based upon a goal of aPTT prolongation of 1.5 to 3 times the baseline value and avoidance of an aPTT >100 seconds.

DOSING AND ADMINISTRATION, Dosing in Special Populations, Pediatric HIT/HITTS Patients:

Pediatric HIT/HITTS Patients: Initial Argatroban infusion doses are lower for seriously ill pediatric patients compared to adults with normal hepatic function (see PRECAUTIONS, Pediatric Use).

Reviewer comment: *The proposed label for Eagle's argatroban does not contain the information on pediatric experience with argatroban as given in the RLD label. Although, as stated in the current RLD label "The safety and effectiveness of Argatroban, including the appropriate anticoagulation goals and duration of therapy, have not been established in pediatric patients", in medical practice Argatroban may be used for treatment of pediatric patients with HIT/HITTS in the clinical setting. For this reason it is important that all known safety information to improve the safe use of the drug, given the lower clearance of argatroban in the pediatric population, particularly in association with elevated bilirubin levels, be available for physicians. As such, due to safety reasons, the protected information should be retained in Eagle's Argatroban labels. The dose adjustment information included in the Pediatric Use section of the RLD label should be included in the labels of any 505(b)(2) or generic argatroban products as well in order to reduce the risk of overdose and consequent serious adverse events such as bleeding and intracranial hemorrhage associated with Argatroban therapy in pediatric patients.*

The pediatric information in the RLD label provides important safety precautions, and given the safety concerns associated with Argatroban Injection use in pediatric patients, protected pediatric information should be retained in Eagle's Argatroban drug label in the CLINICAL PHARMACOLOGY/SPECIAL POPULATIONS/Pediatric Use, PRECAUTIONS/Pediatric Use, and DOSAGE AND ADMINISTRATION/Dosing in Special Populations/Pediatric HIT/HITTS sections, 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, as should 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". (Eagle's proposed labeling currently does not include this pediatric information).

5.2 Review Strategy

Eagle's regulatory strategy for its proposed argatroban product relies on the agency's previous findings of safety and efficacy for the RLD (NDA 20-883) as reflected in the approved package insert. The active ingredient, labeled indications, and dosing regimens are identical to those of the RLD. The concentration of the Eagle product to be administered in patients is the same as that for the RLD product as administered. The two products as administered differ only in excipients. No efficacy and safety studies have been done for the Eagle product. Information submitted in both the original NDA submission and in the current resubmission is directed toward demonstrating safety of the excipients and bridging to the RLD. No clinical studies have been conducted.

Important safety and dosing information from results of pediatric studies conducted by the sponsor of the RLD are also reviewed for recommendation to be included in the label of Argatroban Injection RTU.

Other aspects of the review pertain to CMC and Clinical Pharmacology issues. See CMC review and Clinical Pharmacology Review.

5.3 Discussion of Individual Studies/Clinical Trials

Not applicable

6. REVIEW OF EFFICACY

RLD argatroban has been found to be effective previously. Eagle's argatroban application relies on the agency's previous findings of safety and efficacy for the RLD (NDA 20-883) as reflected in the approved package insert. No efficacy studies have been done for the Eagle product.

Reviewer comment: Efficacy for Eagle argatroban can reasonably be concluded from the known efficacy of the RLD. (See also clinical reviews for other 505(b)(2) argatroban product, NDA 22-359, Min Ha Tran, D.O., 2/18/09 and Firoozeh Alvandi, M.D., completed 12/17/2009, entered into DARRTS 1/6/2010).

7. REVIEW OF SAFETY

No clinical safety studies have been conducted for the Eagle argatroban product and its safetyis assessed by consideration of the known toxicities associated with use of RLD argatroban. The major concern for argatroban use per the approved labeling is bleeding.

Information submitted in both the original NDA submission and in the current resubmission is directed toward demonstrating safety of the excipients. In the original submission the sponsor provides references that the concentration and amount of L-

methionine that patients will receive with Eagle argatroban product are well below those that have been used intravenously in humans for nutritional and non-nutritional purposes and are likely to be well-tolerated. The sponsor comments that lactobionic acid is listed in the FDA Inactive Ingredient Guide for use in products for intravenous use. A potency limit is not provided. In the resubmission the sponsor has provided information from in vitro studies intended to demonstrate equivalence of its formulation as compared to the RLD with regard to anticoagulation tests. (See Clinical Pharmacology review by Joseph A. Grillo, January 20, 2010).

The sponsor also provided in the original submission a literature review of publications in English since 2000 for clinical trials, comparative studies or controlled studies in humans. Among 120 articles found, 16 were identified as having relevant safety data. The papers included studies in elderly patients and patients with hepatic or renal impairment and some drug interactions studies. The sponsor concluded that the post-marketing literature confirmed the safety of argatroban that was demonstrated in the pre-marketing safety database and no newly recognized toxicities were identified. The sponsor also concluded based on its *in vitro* studies that the excipients would not be likely to contribute to the risk of argatroban.

Reviewer's comment: Published studies do not reveal new safety concerns for argatroban. Adverse reactions for the Argatroban in the Eagle product would not be expected to differ from those of the RLD. (See also clinical reviews for other 505(b)(2) argatroban product, NDA 22-359, Min Ha Tran, D.O., 2/18/09 and Firoozeh Alvandi, M.D., completed 12/17/2009, entered into DARRTS 1/6/2010).

8. POSTMARKET EXPERIENCE

See Section 7 above.

9. APPENDICES

9.1 Literature Review /References

See Section 7 above.

9.2 Labeling Recommendations

The sponsor has submitted labeling in PLR format with content essentially the same as for the RLD, except for product description and deletion of pediatric use information. (The RLD label has not yet been converted to PLR format).

Based on the results of the pediatric studies conducted by the RLD sponsor, it is recommended that, given that the pediatric information in the RLD label provides important safety precautions and given the safety concerns (bleeding, intracranial hemorrhage) associated with Argatroban Injection use in pediatric patients, protected pediatric information should be retained in the Eagle argatroban drug label in the

CLINICAL PHARMACOLOGY/SPECIAL POPULATIONS/Pediatric Use, PRECAUTIONS/Pediatric Use, and DOSAGE AND ADMINISTRATION/Dosing in Special Populations/Pediatric HIT/HITTS sections, 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. 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 in the Eagle Argatroban Injection labeling.

9.3 Advisory Committee Meeting

Not applicable.

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01/27/2010

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