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RESEARCH**

APPLICATION NUMBER:
022434Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

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| Date | June 17, 2011 |
| From | Janice Brown for Sarah Pope Miksinski, Ph.D. |
| Subject | Cross-Discipline Team Leader Review |
| NDA/BLA # Supplement# | NDA 22-434 (2 nd review cycle) |
| Applicant | Eagle Pharmaceuticals, Inc. |
| Date of Submission | January 10, 2011 (received January 26, 2011) |
| PDUFA Goal Date | July 12, 2011 |
| Proprietary Name / Established (USAN) names | Argatroban Injection (argatroban) |
| Dosage forms / Strength | Injection, 50 mg per 50 mL |
| Proposed Indication(s) | <ol style="list-style-type: none">1. For prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT).2. As an anticoagulant in adult patients with or at risk for heparin-induced thrombocytopenia (HIT) undergoing percutaneous coronary intervention (PCI) |
| Recommended: | Approval |

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 50 mg/50 mL aqueous solution (Eagle argatroban) is submitted as a 505(b)(2) NDA. The innovator product (Argatroban Injection, 250 mg/2.5 mL, NDA 20-883) is a concentrated solution which must be diluted prior to use. In this NDA, the applicant has developed an aqueous argatroban injectable solution formulated at 1 mg/mL that is ready-to-administer without dilution.

2. Background

The subject of the current NDA application is a new formulation for argatroban. The applicant for this NDA 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.

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 applicant on November 21, 2008.

The NDA was resubmitted on 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 communicated to the applicant in a filing letter on May 19, 2009. Additional information was provided by the applicant in multiple amendments over the next several months. On January 29, 2010 the Division issued a Complete Response letter to the applicant citing unresolved CMC deficiencies and manufacturing facility issues. The manufacturing facility at Verna, Goa 403 722, India was not ready for an inspection.

The applicant submitted a complete response to the CR letter on January 10, 2011 (received January 26, 2011).

3. CMC

Argatroban is a direct thrombin inhibitor synthesized from the naturally occurring amino acid, L-arginine. There are four chiral centers, one of which is not defined (*i.e.*, both stereoisomers are present). Type I (21-*R*) and Type II (21-*S*) isomers are present in a 2:1 molar ratio. The ratio is controlled by the product specification. Eagle's drug product contains lactobionic acid and L-methionine (b)(4) and sodium chloride (b)(4); it is intended to be a ready-to-use formulation for intravenous administration. The argatroban concentration is 1 mg/mL.

CMC: The CMC information for the drug substance was provided in (b) (4) DMF No. (b) (4). Applicant provided adequate reference to their Type II DMF (b) (4) for information pertaining to the drug substance, argatroban. The DMF contains the necessary information related to manufacturing, characterization, physical properties, manufacture, process controls, analytical methods, specifications, validation, container closure system, reference standard and stability data for argatroban. DMF (b) (4) was reviewed and found acceptable to support the NDA.

The manufacturing process for Argatroban injection (b) (4)

The formulated drug product contains 1 mg argatroban, 2 mg lactobionic acid, 2 mg L-methionine USP, 8 mg sodium chloride USP, and sodium hydroxide NF (for pH adjustment) in water for injection USP. Sufficient stability data have been provided to support an expiry period of 24 months for the drug product stored at the recommended room temperature conditions. Argatroban Injection is light sensitive.

BIOPHARMACEUTICS: The ONDQA Biopharmaceutics review (Angelica Dorantes, Ph.D.) granted a waiver for the approval of the proposed Argatroban Premix Injection. To support the BA/BE waiver request, Eagle Pharmaceuticals provided information showing that the proposed Argatroban Injection will be administered at the same dosage level, for the same duration, and for the same indications as the RLD product, Argatroban Injection from Pfizer.

MICROBIOLOGY: The product quality microbiology review completed by Stephen E. Langille, Ph.D. (signed June 09, 2011) found the drug product (b) (4) information in (b) (4) at the Cipla Limited – Goa, India facility acceptable and recommended approval.

4. Nonclinical Pharmacology/Toxicology

Two nonclinical studies were submitted to justify the use of lactobionic acid as an excipient in the drug product. The Pharmacology/Toxicology Review (Shwu-Luan Lee, Ph.D., final signature June 22, 2011) stated, “Based on the results of nonclinical studies and data available on erythromycin lactobionate (an approved FDA drug), the proposed level of lactobionic acid in the drug product is acceptable.” No pharmacology/toxicology issues which preclude approval were found and the review recommended approval.

5. Clinical Pharmacology/Biopharmaceutics

In the re-submission, Eagle submitted another *in vitro* "bridge" study report to compare the anticoagulant activity between Eagle's product and the RLD - Pfizer's ARGATROBAN Injection in support of a waiver of *in vivo* bioequivalence (BE). The results of the data analyses of the current study indicate that an acceptable *in vitro* bridge between Eagle's product and Pfizer's product was established. The Clinical Pharmacology reviewer, Lillian Hua Zhang, Ph.D. (signed June 16, 2011) considers this NDA acceptable from a clinical pharmacology perspective.

6. Clinical Microbiology

There was no Clinical Microbiology review for this cycle.

7. Clinical/Statistical- Efficacy

No new efficacy information is included in the resubmission. No Statistical Review was done for this review cycle.

8. Safety

Clinical Review of the resubmission was completed by Firoozeh Alvandi, M.D. (June 16, 2011). The resubmission included a safety update and a literature search covering the period Aug 1, 2009 through Mar 31, 2010. The reviewer found no new safety concerns from review of the recent literature and recommended approval from a clinical perspective.

9. Advisory Committee Meeting

There was no Advisory Committee meeting held for this application.

10. Pediatrics

As discussed in the previous CDTL Review for this application (Kathy Robie Suh, M.D., Ph.D., January 27, 2010), the labeling for the RLD contains information in the Pediatric Use section based upon a study conducted by the RLD applicant. The study was not sufficient to support an indication for pediatric use. However, information from the study regarding pediatric experience was placed into the label based on concerns for safety should the product be used off label in pediatric patients. Consequently, this information should be retained in the label for the new Eagle argatroban product.

11. Other Relevant Regulatory Issues

Manufacturing Facilities

Initial cGMP recommendation for this NDA dated October 21, 2009 was acceptable. Since the length of time from the initial OC recommendation exceeded two years, a second facility inspection was requested. On June 27, 2011, an overall acceptable cGMP recommendation was given for this NDA.

12. Labeling

The proposed labeling for the Baxter argatroban is essentially the same in content as that of the innovator RLD product, except for the Dosage Forms and Strength, Description and How Supplied sections of the labeling. The formatting of the applicant's proposed labeling has been constructed to comply with the requirements of the Physician's Labeling Rule (PLR).

The Maternal Health Team was consulted to provide comments on the Pregnancy and Nursing Mothers subsections of the proposed labeling. The review provided comments for the labeling (see review by Tammie Howard, signed March 29, 2011).

The exact wording of the labeling in the PLR format has been reviewed and comments from all disciplines were conveyed to the applicant. The applicant submitted revised labeling incorporating the Division's recommendations on June 17, 2011.

13. Recommendations/Risk Benefit Assessment

The applicant has resolved the remaining CMC deficiencies for this 505(b)(2) application for Argatroban Injection 1 mg/mL and CMC recommends approval. No pharmacology/toxicology issues or clinical pharmacology issues have been found to preclude approval. Clinical review finds the application adequate.

This application may be approved.

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/s/

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06/27/2011

SARAH P MIKSINSKI
06/28/2011