DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Pediatric and Maternal Health Staff – Pediatric Labeling Review

Date: February 28, 2011 **Date Consulted:** February 8, 2011

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To: Division of Hematology Products (DHP)

Drug: Argatroban Injection, NDA 22-434

Subject: 505(b)(2) Application and Pediatric Exclusivity

Materials Reviewed:

- Draft argatroban labeling, NDA 22-434, submitted January 12, 2011
- Current approved Argatroban labeling – pediatric labeling changes approved for Argatroban Injection – S-014 (May 5, 2008)
- Patent and Exclusivity data for NDA 20-883
- PeRC Meeting Minutes, January 30, 2008
- Medical Officer Review of the Pediatric Exclusivity Studies, NDA 20-883/S-014, February 15, 2008
- Medical Team Leader Review of the Pediatric Labeling Supplement Resubmission, February 22, 2008
- Clinical Pharmacology Review Summary of the pharmacokinetics study in pediatric patients NDA 20-883/S-014, February 13, 2008
- PMHS Office of Generics Pediatric Carve-out Review, September 9, 2009

Consult Question: Please review and update pediatric use information in labeling for this 505(b)(2) application.

INTRODUCTION

Eagle Pharmaceuticals, Inc. submitted a 505(b)(2) application for Argatroban Injection (b) (4) (b) (4) on September 28, 2008, and FDA issued a Complete Response Letter on January 29, 2010 for CMC deficiencies. Eagle Pharmaceuticals, Inc. submitted a Complete Response submission on January 12, 2011, addressing the CMC deficiencies. The referenced drug product is Pfizer's Argatroban Injection, NDA 20-883. Pfizer has three years of Waxman–Hatch (W-H) Exclusivity (expires May 5, 2011) for revisions to Argatroban Injection labeling based on data submitted in response to the Pediatric Written Request. The pediatric use information that was added to Pfizer's Argatroban Injection labeling is considered protected pediatric use information because of the W-H Exclusivity.

(b) (4) carved-out all pediatric use information from their proposed Argatroban Injection labeling, including the subsection header 8.4 Pediatric Use, as well as all protected pediatric use information

The Division of Hematology Products (DHP) consulted the Pediatric and Maternal Health Staff (PMHS) - Pediatric Team to review and comment on pediatric use information for this 505(b)(2) argatroban injection labeling.

BACKGROUND

Argatroban

Argatroban is a synthetic thrombin inhibitor derived from L-arginine that reversibly binds to the thrombin active site. Argatroban Injection was initially approved on June 30, 2000, as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia. An additional indication was approved on April 3, 2002, for use as an anticoagulant in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI).

Pediatric Argatroban Studies

Pediatric studies were required for Argatroban under the Pediatric Research Equity Act (PREA), as well as a postmarketing commitment for pediatric pharmacokinetic and safety studies to allow for appropriate dosing and safety. In addition, Encysive Pharmaceuticals, Inc. (now Pfizer, Inc.) submitted a Proposed Pediatric Study Request (PPSR) on April 26, 2002, and in response, FDA issued a Pediatric Written Request (PWR) on April 2, 2003, (amended on February 13, 2004 and April 7, 2005) requesting information from studies in pediatric patients birth to < 16 years of age for the prophylaxis and/or treatment of thrombosis in patients who: 1) have a diagnosis of heparin-induced thrombocytopenia and thrombosis syndrome (HIT/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. The PWR requested safety, clinical outcomes data, and pharmacokinetic/pharmacodynamic parameters on a minimum of 24 patients.

Although these studies were considered sufficient to fulfill the PREA pediatric study requirement (b) (4) However, three years of Waxman-Hatch (W-H) Exclusivity was

granted to Encysive Pharmaceuticals, Inc. (now Pfizer). The W-H Exclusivity expires May 5, 2011.

(b) (4)

Much internal discussion occurred around the placement of the pediatric study information in labeling because the product is used in critically ill pediatric patients and the differences in pediatric and adult pharmacokinetic parameters are clinically significant. Argatroban has lower clearance in pediatric patients compared to healthy adult patients, and also lower clearance in pediatric patients with increased bilirubin levels; thus, recommended starting doses based on PK are lower than those customarily used in adult practice. Since efficacy was not established in pediatric patients, the Pediatric Review Committee (PeRC) recommended that all information from this pediatric study be placed only in the Pediatric Use subsection of labeling. Due to the difference and variability in drug clearance in children and pediatric dosing safety concerns, the Division of Medical Imaging and Hematology Products (DMIHP) decided to place the pediatric PK/PD information in the CLINICAL PHARMACOLOGY/Special Populations section of Argatroban labeling, rather than in the Pediatric Use subsection (cross-referencing used), and included a statement in the DOSAGE AND ADMINISTRATION/ Dosing in Special Populations section directing the physician to the PRECAUTIONS/Pediatric Use subsection section for information on pediatric dosing. The following sections of Argatroban labeling were revised on May 5, 2008, to include the clinical data from the study conducted in pediatric patients with Heparin-Induced Thrombocytopenia (HIT) or Heparin-Induced Thrombocytopenia with Thrombosis (HITTS):

- CLINICAL PHARMACOLOGY/ SPECIAL POPULATIONS/Age: Pediatric
- PRECAUTIONS /Pediatric Use
- DOSAGE AND ADMINISTRTION/Dosing in Special Populations/Pediatric HIT/HITTS Patients

Best Pharmaceuticals for Children Act of 2007

The goal of both the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) is to provide pediatric information in drug labeling to encourage the appropriate use of drugs in treating pediatric patients. BPCA [section 505A(o)(2)(A) and 505A(o)(2)(B) the Act] addresses the approval of generic drugs when pediatric information protected by exclusivity [either six-month pediatric exclusivity (BPCA) or three-year new clinical studies exclusivity (Waxman-Hatch)] has been added to the innovator labeling so that when possible, innovator pediatric labeling will not block generics from entering the market. In summary, 1) when new pediatric information in labeling is protected by patent or exclusivity [either six-month pediatric exclusivity (BPCA) or three-year new clinical studies exclusivity (Waxman-Hatch)] and "carved out," a disclaimer is necessary; and, 2) important pediatric safety information, particularly if related to Contraindications, Warnings and Precautions, or Use in Specific Populations (Pediatric Use) may be retained.

BPCA does not address the carve-out of protected pediatric information from 505(b)(2) product labeling; however, approval of a 505(b)(2) application may be delayed because of patent and

exclusivity rights that apply to the listed drug (see 21 CFR 314.50(i), 314.107, 314.108, and section 505(A)(b)(B)(ii) of the Act.[1]

When PMHS-Pediatrics Team recommends that the protected pediatric information is important safety information; and therefore, must be retained in 505(b)(2) product labeling for reasons of safe use, a full approval for the affected 505(b)(2) product cannot be issued until Pediatric and/or Waxman-Hatch Exclusivities have expired.

Pediatric Use Labeling

In 1994, the FDA began the first of several initiatives to improve pediatric use information in drug labeling by issuing a final rule revising the requirements for the *Pediatric Use* subsection of labeling (59 FR 64242, December 13, 1994). This final rule also requires that if there is no substantial evidence to support any pediatric use or use in a particular population, the labeling must state this also. The final rule amending the content and format of labeling for human prescription drugs (71 3922, January 24, 2006) continued the requirement for a Pediatric Use subsection (8.4 Pediatric Use) and requires pediatric use labeling to evidence or a lack of evidence for pediatric use [21 CFR 201.57(c)(9)(iv)]. The Pediatric Use subsection should clearly describe what is known and what is unknown about use of a drug in children, including limitations of use.

DISCUSSION AND CONCLUSONS

Pediatric use information was added to Argatroban Injection (NDA 20-883) labeling on May 5, 2008. Encysive Pharmaceuticals, Inc. (now Pfizer) was awarded three-years of Waxman-Hatch Exclusivity for revisions to labeling based on data submitted in response to the PWR (expires May 5, 2011). (b) (4) Efficacy was not demonstrated in the limited pediatric population studied; however, pediatric dosing safety concerns were seen because of differences and variability in drug clearance in children. PMHS considers the protected Pfizer Argatroban Injection pediatric use information to be important safety information that should be retained in Eagle Pharmaceuticals Inc. 505(b)(2) argatroban injection labeling. Clinicians using Argatroban Injection in critically ill pediatric patients must be informed of the available pediatric use information and related safety concerns, including dosing recommendations due to differences and variability in pediatric PK parameters and the risk of overdosing.

Eagle Pharmaceuticals Inc. failed to include subsection 8.4 Pediatric Use, which is required under [21 CFR 201.57(c)(9)(iv)], and should always clearly describe what is known and what is unknown about use of a drug in children, including any limitations of use.

As mentioned, the protection on pediatric use information expires on May 5, 2011; therefore, if an approval action is taken after May 5, 2011, all pediatric information can and must be retained in Eagle Pharmaceuticals Inc. 505(b)(2) argatroban injection labeling. An approval action taken before May 5, 2011, would have to be a tentative approval, based on the need to retain the protected pediatric use information for safe use reasons.

[1] See Draft Guidance for Industry – Applications Covered by Section 505(b)(2), October 1999

RECOMMENDATIONS

In summary, PMHS-Pediatric Team has the following recommendations for Eagle Pharmaceuticals Inc. 505(b)(2) Argatroban Injection labeling:

- Retain all protected pediatric use information (added to Pfizer's Argatroban Injection labeling on May 5, 2008) for safe use reasons in this Eagle Pharmaceuticals, Inc. 505(b)(2) Argatroban Injection labeling. The pediatric information which appears in PRECAUTIONS/Pediatric Use in Pfizer's Argatroban Injection labeling (old labeling format) should be placed in USE IN SPECIAL POPULATIONS/Pediatric Use in Eagle Pharmaceuticals, Inc. 505(b)(2) Argatroban Injection labeling that was submitted in the PLR format.

- Refer to Appendix A for a tracked-changes version of labeling containing the PMHS recommendations.

Appendix A – Tracked Changes Labeling

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

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02/28/2011

HARI C SACHS
02/28/2011
I agree with the recommendations.

LISA L MATHIS
02/28/2011