DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pediatric and Maternal Health Staff – Pediatric Labeling Review

Date: September 15, 2010

From: Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst
Pediatric and Maternal Health Staff

Through: Hari Cheryl Sachs, MD, Team Leader – Pediatric Team
Pediatric and Maternal Health Staff

Lisa Mathis, M.D., OND Associate Director
Pediatric and Maternal Health Staff

To: Division of Hematology Products (DHP)

Drug: Argatroban Injection, NDA 201-811

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

Materials Reviewed:

- 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
- DMIHP Division Director Pediatric Review Memo, May 2, 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

APP Pharmaceuticals, Inc. submitted a 505(b)(2) application for Argatroban Injection (NDA 201-811 on April 2, 2010. The referenced 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.

APP Pharmaceuticals Inc. carved-out all protected pediatric use information from their proposed Argatroban Injection labeling with the exception of the following pediatric use statement:

> **8 USE IN SPECIFIC POPULATIONS**
> **8.4 Pediatric Use**
> The safety and effectiveness of argatroban, including the appropriate anticoagulation goals and duration of therapy, have not been established among pediatric patients.

The Division of Hematology Products (DHP) consulted the Pediatric and Maternal Health Staff (PMHS) - Pediatric Team to review the pediatric use information in 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)

(b) (4) However, three years of Waxman-Hatch (WH) Exclusivity was granted to Encysive Pharmaceuticals, Inc. (now Pfizer). The WH 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, then a full approval for the affected 505(b)(2) product cannot be issued until Pediatric and/or Waxman-Hatch Exclusivities have expired.

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 APP 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.

The PMHS-Pediatric Team recommended pediatric use labeling revisions for APP Pharmaceuticals Inc. 505(b)(2) Argatroban Injection are provided below. Appendix A of this review also provides a track changes version of labeling containing our recommendations.

RECOMMENDATIONS

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

1. Retain all protected pediatric use information (added to Pfizer's Argatroban Injection labeling on May 5, 2008) for safe use reasons in this APP 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 APP Pharmaceuticals Inc. 505(b)(2) Argatroban Injection labeling that was submitted in the PLR format.

Appendix A – Tracked Changes Labeling

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

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

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEANINE A BEST
09/15/2010

HARI C SACHS
09/15/2010
I agree with the recommnendations.

LISA L MATHIS
09/20/2010