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 Memorandum

Date: June 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, NDAs 22-359, 22-485, and 201-743

Subject: 505(b)(2) Applications 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 these 505(b)(2) applications.

BACKGROUND

The Division of Hematology Products (DHP) consulted the Pediatric and Maternal Health Staff (PMHS) - Pediatric Team to review pediatric use information in labeling for three 505(b)(2) applications submitted for Argatroban Injection (NDAs 22-359, 22-485, and 201-743). The referenced product is Pfizer's Argatroban Injection, NDA 20-883. None of the 505(b)(2) applicants submitted labeling that contains the complete pediatric use information which appears throughout Pfizer's Argatroban Injection labeling. One 505(b)(2) applicant included no pediatric use information (22-359), and instead, directed clinicians to use other Argatroban products with pediatric data in labeling.

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 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, Pediatric Exclusivity was not granted because the terms of the PWR were not adequately met (inadequate enrollment). However, three years of Waxman-Hatch (WH) Exclusivity was granted to Encysive Pharmaceuticals, Inc. (now Pfizer) for revisions to labeling based on data submitted in response to the Pediatric Written Request. The WH Exclusivity expires May 5, 2011.

A pediatric indication was not approved for Argatroban Injection because the limited data submitted did not support safe and effective use in pediatric patients. 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

Reviewer Comments:

1. *All of the pediatric use information added to Pfizer's Argatroban Injection labeling on May 5, 2008, is "protected" information.*

2. *The innovator Argatroban labeling is in the old labeling format and the 505(b)(2) Argatroban labeling is in the Physicians Labeling Rule (PLR) format. The Pediatric Use subsection is located in USE IN SPECIAL POPULATIONS section of labeling (a new section) in the PLR format.*

Best Pharmaceuticals for Children Act of 2007

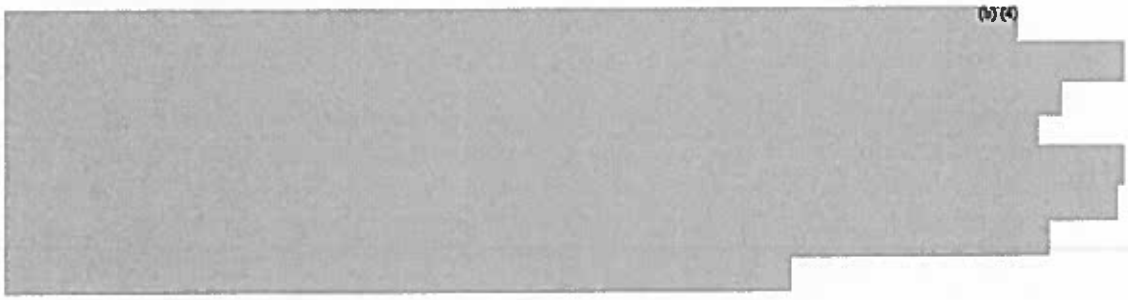
The Best Pharmaceuticals for Children Act (BPCA) (section 505A of the Food, Drug and Cosmetic Act) addresses the approval of drugs under 505(j) when pediatric information protected by exclusivity [either six-month pediatric exclusivity (BPCA) or three-year new clinical studies exclusivity (Waxman-Hatch)] has been added to the labeling.

505A(l)(2) states:
PEDIATRIC INFORMATION IS ADDED TO LABELING.—''(1) GENERAL RULE.—A drug for which an application has been submitted or approved under section 505(j) shall not be considered ineligible for approval under that section or misbranded under section 502 on the basis that the labeling of the drug omits a pediatric indication or any other aspect of labeling pertaining to pediatric use when the omitted indication or other aspect is protected by patent or by exclusivity under clause (iii) or (iv) of section 505(j)(5)(F).
''(2) LABELING.— Notwithstanding clauses (iii) and (iv) of section 505(j)(5)(F), the Secretary may require that the labeling of a drug approved under section 505(j) that omits a pediatric indication or other aspect of labeling as described in paragraph (1) include —
''(A) a statement that, because of marketing exclusivity for a manufacturer — ''(i) the drug is not labeled for pediatric use; or ''(ii) in the case of a drug for which there is an additional

pediatric use not referred to in paragraph (1), the drug is not labeled for the pediatric use under paragraph (1); and "(B) a statement of any appropriate pediatric contraindications, warnings, or precautions that the Secretary considers necessary."

In addition, FDA added a provision on pediatric risk information in § 201.56(d)(5) of the January 24, 2006, Final Rule: Requirements on Content and Format of Labeling for Human Prescription Drugs and Biological Products to avoid any possible confusion as to what information the agency may require in generic labeling that otherwise omits a pediatric indication or other aspect of labeling pertaining to pediatric use protected by patent or exclusivity.

§ 201.56(d)(5) states:
"Any risk information that is required under § 201.57(c)(9)(iv) is considered appropriate pediatric contraindications, warnings, or precautions within the meaning of 505A(1)(2) of the Federal Food Drug and Cosmetic Act (the act) (21 U.S.C. 355A(1)(2)), whether such information appears in the Contraindications, Warnings and Precautions, or Use in Specific Populations section of labeling."
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.



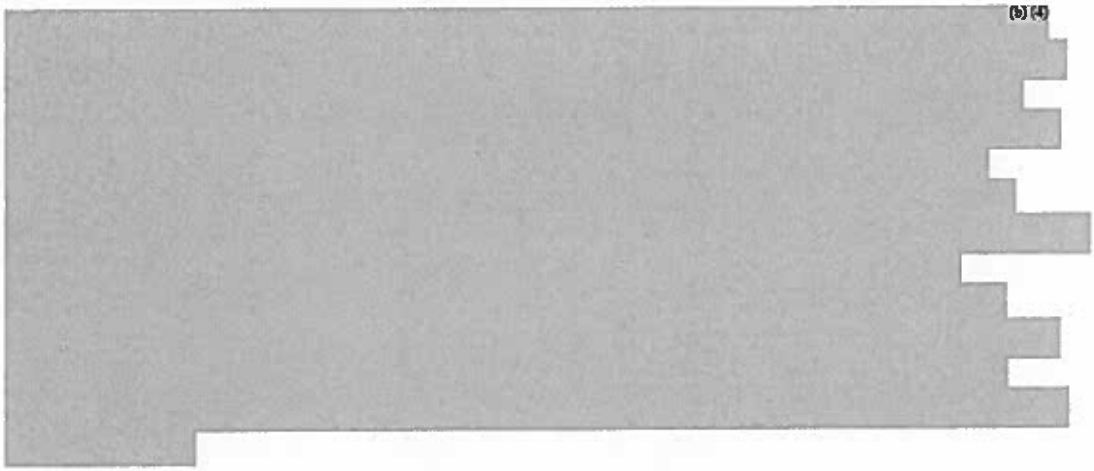
RECOMMENDATIONS
PMHS-Pediatric Team has the following recommendations for Argatroban Injection 505(b)(2) labeling:

1. Retain all protected pediatric use information (added to Pfizer's Argatroban Injection labeling on May 5, 2008) for safe use reasons in all 505(b)(2) Argatroban Injection labeling. Clinicians using Argatroban 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. Protected pediatric use information appears in the following sections of Pfizer's Argatroban Injection labeling:

    - CLINICAL PHARMACOLOGY/ SPECIAL POPULATIONS/Age: Pediatric
    - PRECAUTIONS /Pediatric Use

- DOSAGE AND ADMINISTRTION/Dosing in Special Populations/Pediatric HIT/HITTS Patients

2. Request all 505(b)(2) Argatroban Injection applicants to submit revised labeling that incorporates all of the pediatric use information that appears in Pfizer's 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 any 505(b)(2) Argatroban Injection labeling submitted in the PLR format.

3. 

4. DHP can ensure that all 505(b)(2) Argatroban Injection labeling, when resubmitted, contain the identical pediatric use information throughout labeling, which appears in Pfizer's Argatroban Injection labeling.

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
06/15/2010

HARI C SACHS
06/15/2010
I agree with the recommendations contained in this consult

FILE MEMORANDUM

MEMO DATE:	10/26/2010	PM: Ebla Ali-Ibrahim
TO NDA:	201743	
Submission Date:	4/13/2010	
FDA Received Date:	4/14/2010	
SDN / SN:	1	
eCTD number:	noneCTD	
Network path in edr:	\\FDSWA150\NONECTD\N201743\N_000\2010-04-13 (submission)	
Other reviewers:	Biometrics: Lee, Kyung Y. Clinical Pharmacology: Zhang, Hua Non-Clinical: Lee, Shwu Luan Product Quality: Leutzinger, Eldon E. Product Quality Microbiology: Langille, Stephen E.	
FROM:	Firoozeh Alvandi, MD, Medical Reviewer; Division of Hematology Products	
SUBJECT:	Argatroban	
Via:	Virginia Kwitkowski, MS, RN, ACNP-BC Acting Clinical Team Leader, DHP, OODP	

ISSUE: NA

ACTIONS RECOMMENDED: Tentative approval

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 in the PLR format found the label to be acceptable. For details and recommendations regarding this NDA submission, refer to reviews by other disciplines.

Background:

Sandoz Canada has developed an argatroban formulation that differs from the current marketed product in that it does not contain any alcohol and does not require reconstitution.

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 the following studies:
1. A comparative physico-characterisitics including impurity profile between Sandoz's argatroban and Encysive's argatroban (module 3; 3.2). See CMC review.

2. An *in vitro* study to evaluate and compare the results of aPTT, TT, PT and ACT in plasma containing different concentrations of argatroban from 3 different batches of 2 formulations of argatroban (Reference and Test formulations) and 2 different placebos (module 5; 5.3). This in vitro study was performed using plasma from 48 healthy adult, non-smoking subjects comparing the effect of argatroban of three batches by Sandoz Canada Inc. (Test formulation) to 3 batches by Encysive Pharmaceuticals (Reference formulation), using pooled human plasma. Five different plasma concentrations of argatroban were used for the test and the reference formulations - 0.25, 0.5, 1, 3 and 5 mcg/mL. At each of these concentrations, the test and reference solutions were diluted in dextrose (and separately in saline [NDA 22485]). Samples of plasma spiked with the test and reference placebo solutions, a sample of plasma only (Blank) and samples spiked with the saline vehicle (Control Dextrose) (and separately in Control Saline [NDA 22485]) were also tested using the aPTT, PT and TT coagulation tests. There were ultimately 6 pools of 8 subjects each and each pool was comprised of plasma from 4 males and 4 females. See Clinical Pharmacology review.

The applicant submitted a literature search from recent literature published in 2008 (module 5, 5.4). Review of this and additional review of more recent publications, did not raise additional safety concerns. Among the more recently published literature, one reference (Jonathan R. Genzen et al. Prolonged elevation of plasma argatroban in a cardiac transplant patient with a suspected history of heparin-induced thrombocytopenia with thrombosis. *Transfusion*. 2010;50:801-807), in a first report to measure plasma argatroban concentration in the context of cardiopulmonary bypass (CPB), suggested that prolonged elevated levels of plasma argatroban may have contributed to the extended coagulopathy observed in a 65-year-old critically ill male patient with history of heparin induced thrombocytopenia with thrombosis (HITT) undergoing CPBs. The article concluded that because direct thrombin inhibitors (DTIs) do not have reversal agents, surgical teams and transfusion services should be aware and vigilant of the possibility of need for massive transfusion events during anticoagulation with these agents.

The proposed label format appears acceptable from the clinical perspective. We recommend that information on pediatric experience and dosing of argatroban 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. Given a 3-year Waxman-Hatch (WH) Exclusivity granted to the innovator (Encysive, now Pfizer), approval of the applicant's NDA 201743 will be tentative until the May 5, 2011 date of expiration of the HW Exclusivity (see PMHS memorandum of June 15, 2010).

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

/s/

FIROOZEH ALVANDI
01/26/2011

VIRGINIA E KWITKOWSKI
01/26/2011