

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**201811Orig1s000**

**OTHER REVIEW(S)**

**Selected Requirements of Prescribing Information  
REGULATORY PROJECT MANAGER  
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW  
OF THE PRESCRIBING INFORMATION**

**Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements**

**Application:** NDA 201811

**Application Type:** Class 1 505(b)(2) NDA resubmission

**Name of Drug/Dosage Form:** Argatroban Injection, 100 mg/mL

**Applicant:** Fresenius Kabi USA, LLC

**Receipt Date:** January 23, 2015

**Goal Date:** March 23, 2015

### **1. Regulatory History and Applicant's Main Proposals**

This is a Class 1 resubmission for a 505(b)(2) application by Fresenius Kabi USA, LLC, in response to the complete response (CR) letter issued on February 24, 2014. This is the fifth review cycle for this application.

DHP issued a complete response letter in the previous cycle due to the Fresenius drug product manufacturing and testing site located in Grand Island, NY was found to be unacceptable and received a Withhold recommendation by the Office of Compliance. PDUFA goal date for this submission is March 23, 2015.

### **2. Review of the Prescribing Information**

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

### **3. Conclusions/Recommendations**

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant during labeling negotiations. The resubmitted PI will be used for further labeling review.

# Selected Requirements of Prescribing Information

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## Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

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## Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

### HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.
- Comment:*
- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.
- Comment:*
- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.
- Comment:*
- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.
- Comment:*
- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.
- Comment:*
- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.
- Comment:*

## Selected Requirements of Prescribing Information

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a BOXED WARNING is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state "None.")
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

*Comment:*

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

*Comment:*

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

*Comment:*

#### Product Title in Highlights

- YES** 10. Product title must be **bolded**.

*Comment:*

#### Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

*Comment:*

## Selected Requirements of Prescribing Information

### Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.  
Comment:
- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.  
Comment:
- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.  
Comment:
- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).  
Comment:

### Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.  
Comment:
- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.  
Comment:
- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).  
Comment:

### Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.  
Comment:

## Selected Requirements of Prescribing Information

### Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

***Comment:*** *Since there is only one dosage form, it is not necessary to use bullet.*

### Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

***Comment:***

### Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

***Comment:***

### Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

***Comment:***

### Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

***Comment:***

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.  
*Comment:*
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.  
*Comment:*
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- NO** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].  
*Comment: The preposition “with” in the subsection headings should not be capitalized. The subsection headings in the Full Prescribing Information section will also need to be revised to reflect this change.*
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:*
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
*Comment:*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

**Comment:**

## Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

#### BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

#### CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

Comment:

#### ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

## Selected Requirements of Prescribing Information

### PATIENT COUNSELING INFORMATION Section in the FPI

- N/A** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:**

- N/A** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:**

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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BEATRICE A KALLUNGAL  
03/18/2015

PATRICIA N GARVEY  
03/18/2015

505(b)(2) ASSESSMENT

Application Information		
NDA # 201811	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: <b>Argatroban Injection</b> Established/Proper Name: <b>Argatroban Injection</b> Dosage Form: <b>Injection</b> Strengths: <b>100 mg/mL (2.5mL in a <sup>(b) (4)</sup> vial)</b>		
Applicant: <b>Fresenius Kabi USA, LLC</b>		
Date of Receipt: <b>January 23, 2015</b>		
PDUFA Goal Date: <b>March 23, 2015</b>		Action Goal Date (if different):
RPM: <b>Beatrice Kallungal</b>		
Proposed Indication(s): <b>Anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia and in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI).</b>		

**GENERAL INFORMATION**

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES  NO

*If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
<b>Acova (ARGATROBAN Injection) N020883</b>	<b>Clinical findings of safety and efficacy; findings from animal studies for reproductive toxicity and mutagenesis</b>
<b>Published literature</b>	<b>Safety findings</b>

\*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature<sup>1</sup>. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

**No clinical or bioequivalence studies were conducted by the Applicant to bridge their product with the reference listed product. In support of a waiver of in vivo bioequivalence (BE), the applicant conducted an in vitro bridging study to assess in vitro equivalence of the anticoagulant pharmacodynamic (PD) activity between Fresenius Kabi's product and the RLD. PD effects were measured by determining the prothrombin time (PT), the activated partial thromboplastin time (aPTT), and the thrombin time (TT) in pooled donor human plasma spiked with clinically relevant concentrations of Fresenius Kabi's or Pfizer's argatroban product. The results of the data analyses indicate that an acceptable in vitro bridge between Fresenius Kabi's product and Pfizer's RLD product was established.**

**A waiver for the CFR's requirement to provide in vivo bioequivalence (BE) data was granted for the proposed Argatroban Injection product (refer to Dr. Angelica Dorantes-Biopharmaceutics review dated 4/24/12 in DARRTS). Approval of the NDA was recommended from the standpoint of Biopharmaceutics. The current fifth resubmission of this NDA does not contain any new biopharmaceutics information for review.**

**RELIANCE ON PUBLISHED LITERATURE**

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES  NO   
 If "NO," proceed to question #5.

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO   
 If "NO", proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES  NO

**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO   
 If "NO," proceed to question #10.

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
<b>Acova (ARGATROBAN Injection)</b>	<b>020883</b>	<b>Y</b>

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A  YES  NO

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES  NO

*If "YES", please list which drug(s) and answer question d) i. below.*

*If "NO", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

*(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)*

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

**The RLD is a sterile solution and available in 250 mg in 2.5 mL (100 mg/mL) single-use vials. The injection solution (100 mg/mL) needs to be diluted in 0.9% Sodium Chloride for Injection, 5% Dextrose for Injection, or Lactated Ringer's for Injection to a final concentration of 1 mg/mL prior to infusion.**

**Fresenius Kabi's argatroban product is also a concentrated solution at a concentration of 100 mg/mL (250 mg of argatroban in 2.5 mL single-use vials). The solution should be diluted in 0.9% Sodium Chloride Injection, 5% Dextrose Injection, or Lactated Ringer's Injection to a final concentration of 1 mg/mL prior to infusion. The difference between the two products is that the inactive ingredients (D-Sorbitol and dehydrated alcohol) of the RLD used to dissolve argatroban, are replaced by propylene glycol in Fresenius Kabi's product.**

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES  NO

If "**NO**" to (a) proceed to question #11.  
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A  YES  NO

*If this application relies only on non product-specific published literature, answer "N/A"  
If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s): **NDA 203049, Argatroban Injection, 250mg per 2.5ml (100mg per ml), Hikma Pharmaceuticals Company, LTD.**

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO

*If "NO", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A  YES  NO

*If this application relies only on non product-specific published literature, answer "N/A"  
If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*

*If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

#### PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): **Argatroban/5,214,052**

No patents listed  *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

*If "NO", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): **Patent# 5,214,052**

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES  NO

*If "NO", please contact the applicant and request the signed certification.*

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES  NO

*If "NO", please contact the applicant and request the documentation.*

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): **Paragraph IV notification to the NDA Holder was received by Pfizer, Inc. on July 16, 2010, by Encysive Pharmaceuticals, Inc. on July 21, 2010, and by the US Patent Holder, Mitsubishi Chemical Corporation, on July 20, 2010**

*Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

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/s/  
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BEATRICE A KALLUNGAL  
03/18/2015

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

---

**Date of This Memorandum:** March 4, 2015  
**Requesting Office or Division:** Division of Hematology Products (DHP)  
**Application Type and Number:** NDA 201811  
**Product Name and Strength:** Argatroban injection, 250 mg/2.5 mL (100 mg/mL)  
**Submission Date:** January 23, 2015  
**Applicant/Sponsor Name:** Fresenius Kabi USA  
**OSE RCM #:** 2012-2764  
**DMEPA Primary Reviewer:** Mishale Mistry, PharmD, MPH  
**DMEPA Team Leader:** Yelena Maslov, PharmD

---

#### 1 PURPOSE OF MEMO

The Division of Hematology Products requested that we review the revised container label, carton labeling, and Prescribing Information labeling (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>1</sup>

#### 2 CONCLUSIONS

The revised container label, carton labeling, and Prescribing Information labeling is acceptable from a medication error perspective.

---

<sup>1</sup> Maslov Y. Label and Labeling Review for Argatroban (NDA 201811). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2010 Dec 13. 10 p. OSE RCM No.: 2010-1531.

Vee S. Label and Labeling Review via email communication dated May 18, 2012. OSE RCM No.: 2012-1122

**APPENDIX A. LABEL AND LABELING SUBMITTED ON JANUARY 23, 2015**

**Container Label**

(b) (4)



**Carton Labeling**

(b) (4)



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/s/  
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MISHALE P MISTRY  
03/04/2015

YELENA L MASLOV  
03/04/2015

# **REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION**

**To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements**

**Application:** NDA 201811

**Application Type:** New NDA – 505(b)2

**Name of Drug:** Argatroban Injection

**Applicant:** APP Pharmaceuticals

**Submission Date:** January 31, 2012

**Receipt Date:** January 31, 2012

## **1.0 Regulatory History and Applicant's Main Proposals**

This submission contains a response to the complete response (CR) letter that was issued on February 24, 2011. The main issue was regarding a manufacturing site deficiency. In this submission, APP is transferring the manufacture of the drug product to Grand Island, New York manufacturing facility. PDUFA Goal Date is **July 31, 2012**.

## **2.0 Review of the Prescribing Information (PI)**

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

## **3.0 Conclusions/Recommendations**

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by June 15, 2012. The resubmitted PI will be used for further labeling review.

## 5.0 Appendix

---

### Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

---

### Highlights (HL)

#### GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

**Comment:**

- YES** 2. HL is one-half page or less than one-half page (the HL Boxed Warning does not count against the one-half page requirement). If longer than one-half page:
- Filing Period (Regulatory Project Manager Physicians' Labeling Rule (PLR) Format Review): RPM has notified the Cross-Discipline Team Leader (CDTL).
  - End-of Cycle Period: A waiver has been or will be granted by the review division.

**Comment:**

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

**Comment:**

- NO** 4. White space must be present before each major heading in HL.

**Comment:** *No white space present before Dosage and Administration*

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

**Comment:**

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a Boxed Warning is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state "None.")
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present**

## Selected Requirements of Prescribing Information (SRPI)

• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* See Recent Major Changes section below.

\*\* Virtually all product labeling should include at least one Warning and Precaution.

**Comment:**

**YES**

7. A horizontal line must separate HL and Table of Contents (TOC).

**Comment:**

### HIGHLIGHT DETAILS

#### Highlights Heading

**YES**

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

**Comment:**

#### Highlights Limitation Statement

**NO**

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

**Comment:** *Name Of Drug Product - Not In Upper Case*

#### Product Title

**YES**

10. Product title in HL must be **bolded**.

**Comment:**

#### Initial U.S. Approval

**YES**

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

**Comment:**

#### Boxed Warning

**N/A**

12. All text must be **bolded**.

**Comment:**

**N/A**

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

**Comment:**

**N/A**

14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

**Comment:**

**N/A**

## Selected Requirements of Prescribing Information (SRPI)

15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

N/A

16. Should use sentence case for summary (combination of uppercase and lowercase letters typical in a sentence).

Comment:

### Recent Major Changes (RMC)

N/A

17. Other than these five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions, there are no other sections noted in RMC.

Comment:

N/A

18. Must be listed in same order in HL as they appear in FPI.

Comment:

N/A

19. Includes heading(s) and if appropriate subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010”.

Comment:

N/A

20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

### Indications and Usage

YES

21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

### Dosage Forms and Strengths

YES

22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

### Contraindications

YES

23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

YES

24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

## Selected Requirements of Prescribing Information (SRPI)

### Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”. Only includes a U.S. phone number.

Comment:

### Patient Counseling Information Statement

- YES** 26. Must include one of the following **bolded** verbatim statements:

Product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

Product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

### Revision Date

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: *revision date is not in MM/YYYY format*

---

## Contents: Table of Contents (TOC)

### GENERAL FORMAT

- NO** 28. A horizontal line must separate TOC from the FPI.

Comment: *Horizontal line is currently in FPI section and not at the end of TOC*

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded and in title case.

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

## Selected Requirements of Prescribing Information (SRPI)

### Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

### Comment:

---

## Full Prescribing Information (FPI)

### GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

### Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

### Comment:

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

<b>Boxed Warning</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>

## Selected Requirements of Prescribing Information (SRPI)

14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

### Comment:

- N/A** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI at approval.

### Comment:

- NO** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.1)*].

### Comment: *Outer Bracket Was In Italics*

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

### Comment:

## FULL PRESCRIBING INFORMATION DETAILS

### Boxed Warning

- N/A** 42. All text is **bolded**.

### Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

### Comment:

- N/A** 44. Should use sentence case (combination of uppercase and lowercase letters typical in a sentence) for the information in the Boxed Warning.

### Comment:

### Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

### Comment:

### Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

## Selected Requirements of Prescribing Information (SRPI)

*“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”*

**Comment:**

**N/A**

47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”*

**Comment:**

### **Patient Counseling Information**

**N/A**

48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

**Comment:**

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/s/  
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MONSURAT O AKINSANYA  
06/05/2012

JANET K JAMISON  
06/05/2012

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: December 13, 2010  
Application Type/Number: NDA 201811  
To: Ann Farrell, MD, Director  
Division of Hematology Products  
Through: Zachary Oleszczuk, Pharm.D., Team Leader  
Carol Holquist, R.Ph., Director  
Division of Medication Error Prevention and Analysis  
From: Yelena Maslov, Pharm.D., Safety Evaluator  
Division of Medication Error Prevention and Analysis  
Subject: Label and Labeling Review  
Drug Name(s): Argatroban Injection (100 mg/mL)  
Applicant/sponsor: APP Pharmaceuticals  
OSE RCM #: 2010-1531

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## **1 INTRODUCTION**

This review responds to a request from the Division of Hematology Products dated July 12, 2010, for DMEPA to evaluate the container labels, as well as carton and package insert labeling for APP Pharmaceuticals' Argatroban Injections 250 mg/2.5 mL (100 mg/mL). There is no proposed proprietary name for this product at this time.

### **1.1 REGULATORY HISTORY**

Argatroban Injection 250 mg/2.5 mL (100 mg/mL) is the subject of a 505 (b)(2) application submitted on April 5, 2010, that references Argatroban Injection 250 mg/2.5 mL (100 mg/mL) sponsored by Pfizer. Argatroban Injection 250 mg/2.5 mL by Pfizer is a concentrated solution for injection that was approved on June 30, 2000 under NDA 020883.

## **2 METHODS AND MATERIALS**

Since the referenced listed product, Argatroban Injection 250 mg/2.5 mL (100 mg/mL), has been marketed since 2000, DMEPA conducted a search for medication errors involving Argatroban using FDA Adverse Event Reporting System (AERS) database. Identification of these errors may be indicative of potential issues with the proposed 505 (b)(2) Argatroban Injection 250 mg/2.5 mL (100 mg/mL). We eliminated reports not pertaining to medication errors (e.g. medication errors due to another drug product or adverse events related to the use of the drug) and grouped duplicate reports into cases. The cases were further grouped by the type of error and evaluated for the root cause.

Additionally, DMEPA evaluated the proposed labels and labeling for Argatroban using Failure Mode and Effects Analysis<sup>1</sup> (FMEA), principles of human factors, and lessons learned from the post marketing experience to identify areas that can contribute to medication errors.

### **2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE SEARCH CRITERIA**

The AERS search conducted on July 2, 2010, used the following MedDRA High Level Group Terms (HLGT) "Medication Errors" and "Product Quality Issues" along with active ingredient names of "Argatroban," the trade name "Argatroban," and the verbatim name "Argatro%" without dates limitations.

### **2.2 LABELS AND LABELING RISK ASSESSMENT**

For Argatroban Injection 250 mg/2.5 mL, the Applicant submitted the following container label and carton labeling as well as package insert labeling on April 5, 2010 (See Appendix A for container label and carton labeling images):

- Container Label and Carton Labeling: 250 mg/2.5 mL (100 mg/mL)

## **3 RESULTS AND DISCUSSION**

The following sections describe the results of the DMEPA's medication error searches and label and labeling evaluation.

---

<sup>1</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

### 3.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE CASES

In total DMEPA evaluated twenty five (n=25) cases of medication errors involving Argatroban, twenty cases (n=20) from the United States and five (n=5) foreign. The errors included overdose (n=16), wrong dose (n=4), wrong dilution technique (n=3), and the drug name confusion (n=2). Table 1 describes the breakdown of these cases by type and cause.

*Table 1: Total Number of Errors (n=25) By Type and Cause*

Type of Error	Subtype of Error	United States (N=20)	Foreign (N=5)
Overdose (N=16)			
	<i>Monitoring Error</i>	None	N=2
	<i>Infusion Pump</i>	N=5	None
	<i>Wrong Rate of Administration</i>	N=2	None
	<i>No contributing Factors</i>	N=4	N=2
	<i>Wrong Drug</i>	None	N=1
Wrong Dose (N=4)	<i>Lack of Total Drug Content on the container label</i>	N=4	None
Wrong Dilution (N=3)		N = 3	None
Drug Confusion (N=2)		N=2	None

The following sections discuss these errors in detail.

#### **3.1.1 Overdoses (n=16)**

##### **Foreign Cases (n=5)**

Five of sixteen cases that resulted in Argatroban overdose, were foreign cases from Japan (n=3), Germany (n=1), and Austria (n=1). Two cases (ISR #5960863-5 and ISR #6779016-6) reported overdoses due to failure to monitor coagulation parameters; and thus, the dose was not reduced after anticoagulation occurred. One case (ISR #4943357-5) reported the overdose of Argatroban occurred as a result of confusion with Vancomycin. The case did not report any additional details regarding these medication errors. Since no further details were provided, we could not determine the root cause of these errors. The remaining two cases (n=2, ISR #4730332-9 and ISR #6158031-X) did not provide any contributing factors to the overdose; thus, we are unable to determine why this error occurred.

##### **United States Cases (n=11)**

Eleven of the 16 overdose cases were reported in the United States. These cases involved infusion pumps errors and wrong rate of administration errors.

##### **Infusion Pump Cases (n=5)**

Five of the US overdose cases were practice related and not caused by the labels and labeling. These cases include infusion pump failure (n=2) and incorrect infusion pump programming (n=3). One of the cases (ISR #5146803-X) that reported incorrect infusion pump programming reported that that the error resulted from misinterpretation of a total dose of Argatroban. Although the physician ordered the medication correctly as 5 mcg/min, the dose was misinterpreted at some point in the medication process as 5 mcg/kg/min. No additional details

regarding contributing factors were provided. This type of medication error does not seem to be related to the Argatroban labeling since the medication was ordered correctly.

#### *Wrong Rate of Administration Cases (n=2)*

Two medication error cases of overdose resulted from infusion of Argatroban at a rate that was too fast. These cases did not specifically state that an infusion pump was involved. Only one case (ISR #5066934-2,) provided the actual rate of infusion and reported that the patient was administered Argatroban at the rate of 250 mL/2 hours, although the medication was prescribed correctly as 1.2 mL/hour (2.4 mL/2 hours). No additional details regarding contributing factors were provided. This type of medication error does not seem to be related to the Argatroban labeling since the medication was ordered correctly. The case reported patient outcome of no harm.

The remaining case (ISR #5168208-8) reported that patient was administered Argatroban at the correct rate of 2 mcg/kg/minute. However, at some point the administration process patient was inadvertently administered 50 mg bolus over 30 minutes. No additional details regarding the case were provided. The patient experienced an increase in activated partial thromboplastin time (aPTT) and INR levels. However, we note that the package insert labeling for Argatroban Injection 250 mg/2.5 mL presents complete information regarding the correct administration and monitoring of patients receiving the product.

#### *Unspecified Overdose (n=4)*

The remaining four medication error cases resulting in overdose did not report the reason for the overdose. Three (n=3) of the four cases reported a patient outcome as a temporary increase in activated partial thromboplastin time (aPTT), which normalized. The remaining case (n=1) did not report patient outcome. Since there are no details regarding the errors, we are unable to evaluate these four cases further.

#### **3.1.2 Wrong Dose (n=4)**

Four cases (n=4) reported an unspecified incorrect dose of Argatroban. These errors are due to the lack of expressing how much drug per total volume is contained in each vial (i.e., total drug content) on the labeling. All four cases reported the excessive dose withdrawal. One of the four cases (ISR #4157136-2) stated that the error reached the patient and required monitoring to preclude patient harm. Another case (ISR #4035778-2) described patient outcome of no harm because the error was quickly discovered after the product was dispensed. In the remaining two cases (ISR #3783566-4 and ISR #4363879-7), the error occurred, but did not reach the patient.

#### **3.1.3 Wrong Dilution (n=3)**

Three cases were categorized as wrong dilution technique.

Two cases (ISR #3853326-3 and ISR # 5367276-8) were associated with previously marketed labels that included the inaccurate term “Reconstitution” on Argatroban’s container label and carton labeling. Argatroban does not require reconstitution; however the word “Reconstitution” appeared on older labels. In both cases, technicians attempted to reconstitute Argatroban after reading this term, and the product precipitated. Additionally, in both cases, this type of error was intercepted by the pharmacists and did not reach patients.

The Sponsor (Pfizer) of Argatroban reported in these cases that they revised the label and labeling to include the total drug content and replaced the term “reconstitution” with the term “dilution” on container label and carton labeling in January of 2003. Since these revisions, no additional medication error cases involving wrong dilution technique pertaining to the lack of total drug content or incorrect infusion preparation terms have been reported. Although a lack of reported

errors can not guarantee that errors are not occurring, it does provide some reassurance that the revisions may have minimized the errors.

The remaining medication error case (n=1) occurred because the physician diluted Argatroban Injection 250 mg/2.5 mL incorrectly. The patient outcome was reported as fluid overload. Although the case did not report the contributing factors for incorrect product dilution, we note that the package insert labeling for Argatroban Injection 250 mg/2.5 mL presents complete information regarding the correct product preparation for administration.

In comparison to the reference listed drug product, Argatroban Injection 250 mg/2.5 mL, the proposed product contains the total drug content as well as the statement “Dilute prior to (b) (4)” on the container label and carton labeling. Thus, DMEPA believes that incorrect dilution errors will be minimized with the proposed product.

#### **3.1.4 Drug Name Confusion (n=2)**

Two cases of drug name confusion were reported in the US. One case (ISR #3855407-8) occurred in 2002, and involves confusion between Argatroban Injection and Orgaran Injection due to phonetic similarities. Although the wrong product (Orgaran) was prepared and delivered to patient’s room, the error did not reach the patient. Subsequently, Orgaran Injection was discontinued and there are no available generics currently on the market. As a result, no additional errors pertaining to mix-up between Argatroban and Orgaran were identified.

The second medication error case (ISR #3971285-0) involved a complaint regarding the look-alike and sound-alike names between Argatroban and Aggrastat. A student asked a pharmacist whether Argatroban and Aggrastat were different names for the same product due to their phonetic and orthographic similarity. The case of confusion between two products was reported in 2002 and does not appear to be an ongoing problem. Although these two names do have some orthographic similarity (both start with the letter ‘A’ and contain 3 upstrokes and 1 down stroke in the approximately same position), the name Argatroban is longer than Aggrastat and does not contain a wide down stroke (two lower case letters ‘gg’ together). Additionally, the two medications have different product characteristics such as strength and concentration (Aggrastat 12.5 mg/250 mL (50 mcg/mL) vs. Argatroban Injection 250 mg/2.5 mL or Argatroban Injection 125 mg/125 mL as well as dose (Aggrastat 0.4 mcg/kg for 30 minutes followed up 0.1 mcg/kg/min vs. Argatroban 25 mcg/kg/min bolus, if needed; followed by infusion of 2 mcg/kg/min-30 mcg/kg/min depending on indication). Thus, we believe that drug confusion between Argatroban and Aggrastat will be minimized by the orthographic and phonetic differences in addition to the different product characteristics. Additionally, this error is not related to the information provided on the labels and labeling.

### **3.1 LABELS AND LABELING**

Our evaluation of the proposed container labels as well as carton and package insert labeling noted areas of needed improvement in order to minimize the potential for medication errors. Specifically, package insert labeling contains dangerous abbreviations. Additionally, the side panel of the carton labeling and container label contains incorrect information regarding the amount of argatroban per each milliliter of solution.

## **4 RECOMMENDATIONS**

Our evaluation of the proposed container labels as well as carton and package insert labeling noted areas of needed improvement in order to minimize the potential for medication errors. Section 4.1 *Comments to the Division* contains our recommendations regarding package insert labeling. Section 4.2 *Comments to the Applicant* contains our recommendations for the container

labels and the carton labeling. We request the recommendations in Section 4.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager Sue Kang at 301-796-4216.

#### 4.1 COMMENTS TO THE DIVISION

We evaluated the insert labeling for Agratroban Injection 250 mg/2.5 mL (100 mg/mL) sponsored by APP Pharmaceuticals and have the following recommendations for the revision of the insert labeling.

1. Highlights of Prescribing Information, *Dosage Forms and Strengths* Section

The sentence, (b) (4) does not state the total concentration contained in the vial. Revise the statement to read, “250 mg/2.5 mL (100 mg/mL) single (b) (4) vial.”

2. Full Prescribing Information, Section 2 *Dosage and Administration*

We note the use of dangerous abbreviations and symbols in your insert labeling. The first dangerous abbreviation is “IV”. The abbreviation ‘IV’ is on the dangerous abbreviations, List of Error-Prone Abbreviations, Symbols, and Dose Designations<sup>2</sup> because the abbreviation has been confused with the abbreviations ‘IM’ (intramuscular), ‘IU’ (international units), and ‘IN’ (intranasal). Thus, we request you replace all instances of the abbreviation ‘IV’ with the word “intravenously.”

The second dangerous abbreviation or symbol is the “<” and “>”. The symbols ‘<’ and ‘>’ are dangerous symbols that appear on the List of Error-Prone Abbreviations, Symbols, and Dose Designations<sup>1</sup>. These symbols are often mistaken and used as opposite of intended. Replace all instances of the symbol ‘<’ with phrase “less than” and symbol ‘>’ with phrase “greater than.”

Please make these revisions in accordance with the agreement FDA made as part of a national campaign to reduce medication errors related to error prone medical abbreviations and dose designations. As part of that campaign the FDA agreed not to approve labels and labeling that included the use of error prone abbreviations.

3. In the Full Prescribing Information, Section 3 *Dosage Forms and Strengths*

The sentence, (b) (4) does not include the total drug content contained in the vial. Revise this sentence to read, “Argatroban Injection is supplied in sterile, single-use vials, containing 250 mg/2.5 mL (100 mg/mL) of argatroban solution for intravenous infusion.”

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<sup>2</sup> Institute for Safe Medication Practices, “List of Error-Prone Abbreviations, Symbols, and Dose Designations. [www.ismp.org](http://www.ismp.org).

## 4.2 COMMENTS TO THE APPLICANT

### All Container Labels and Carton Labeling for Argatroban Injection

1. Revise the amount of argatroban per each mL in the statement, “Each mL contains (b) (4) argatroban and 954 mg propylene glycol” located on the side panel to contain the appropriate amount of argatroban. Each vial contains (b) (4) of Argatroban, not each mL. The revised statement should read, “Each mL contains: 100 mg argatroban and 954 mg propylene glycol.”
2. Revise the dangerous abbreviation ‘IV’ to read “intravenous” that appears on the principle display panels of container and carton labeling. ‘IV’ is a dangerous abbreviation, which appears on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations<sup>3</sup> because the abbreviation ‘IV’ has been confused with the abbreviations ‘IM’ (intramuscular), ‘IU’ (international units), and ‘IN’ (intranasal). Revise this statement accordingly.
3. Add the statement “Single Use Vial, Discard Unused Portion” to the principle display panel. If you need more space, delete the product number “512603” from the principle display panel as this number does not carry any pertinent information regarding the product’s use and occupies space.
4. Revise the phrase (b) (4) to state “Must be Diluted Prior to Administration” in order to emphasize the necessity of this step prior to administration. The FDA received post marketing cases of the wrong dilution of Argatroban, which resulted in patient harm. Therefore, we request you revise this statement accordingly.
5. Revise the font type of the word “Injection” to be in the same type, size, font and color as the word “Argatroban” to emphasize the dosage form in conjunction with the established name of the product.
6. Expand the yellow box around the strength of the product to include the concentration of the product as well.

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<sup>3</sup> Institute for Safe Medication Practices, “List of Error-Prone Abbreviations, Symbols, and Dose Designations. [www.ismp.org](http://www.ismp.org).

**Appendix A: Argatroban Injection 250 mg/2.5 mL (100 mg/mL) Container Label and Carton Labeling**

**Container Label**



**Carton Labeling**



**Appendix B: ISR number of Medication Error Cases from AERS database**

3783566	4157136	5048440	5367276	6375559	6794157
3853326	4276605	5066934	5766141	6446350	6794181
3855407	4366879	5119376	5960863	6679088	6794188
3971285	4730332	5146803	5961123	6752398	
4035778	4789706	5167060	6129453	6779016	
4122159	4943357	5167067	6158031	6793973	

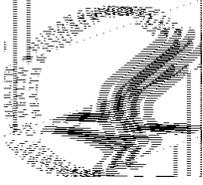
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/s/  
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YELENA L MASLOV  
12/13/2010

ZACHARY A OLESZCZUK  
12/13/2010

CAROL A HOLQUIST  
12/13/2010



**DEPARTMENT OF HEALTH & HUMAN SERVICES**      Public Health Service

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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  
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**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 ADMINISTRATION/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.<sup>1</sup>

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 CONCLUSIONS**

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**

<sup>1</sup> See Draft Guidance for Industry – Applications Covered by Section 505(b)(2), October 1999

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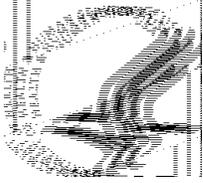
/s/

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JEANINE A BEST  
09/15/2010

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

LISA L MATHIS  
09/20/2010



Pediatric and Maternal Health Staff  
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## **Maternal Health Team Label Review**

**Date:** July 13, 2010                      **Date Consulted:** July 12, 2010

**From:** Tammie Howard, RN, MSN  
Regulatory Reviewer, Maternal Health Team  
Pediatric and Maternal Health Staff

**Through:** Karen Feibus, MD  
Team Leader, Maternal Health Team  
Pediatric and Maternal Health Staff

Lisa Mathis, MD  
Associate Director, Office of New Drugs  
Pediatric and Maternal Health Staff

**To:** The Division of Hematology Products (DHP)

**Drug:** Argatroban Injection, NDA 201-811

**Subject:** Labeling Review

**Materials Reviewed:** Pregnancy and Nursing Mothers subsections of Argatroban labeling

**Consult Question:** Please review the Pregnancy and Nursing Mothers subsections of Argatroban labeling.

## BACKGROUND

On April 2, 2010, APP Pharmaceuticals submitted a 505 (b)(2) new drug application (NDA 201-811) to the Division of Hematology Products (DHP) (formerly the Division of Medical Imaging and Hematology Products) for Argatroban Injection 100 mg/mL (2.5 mL in a (b) (4) vial). The sponsor's proposed indication for Argatroban is for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT), and for anticoagulation in patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI).

On July 12, 2010, DHP consulted the Maternal Health Team (MHT) to review the pregnancy and nursing mothers section of the Argatroban labeling. This review provides the MHT recommendations regarding the sponsor's proposed Pregnancy and Nursing Mother's subsections of Argatroban labeling.

## SUBMITTED MATERIAL

### Sponsor's Proposed Pregnancy and Nursing Mothers Labeling

#### Highlights

-----USE IN SPECIFIC POPULATIONS-----

- (b) (4)

#### 8 USE IN SPECIFIC POPULATIONS

##### 8.1 Pregnancy

(b) (4) *Pregnancy Category B.*

(b) (4)  
Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

##### 8.3 Nursing Mothers

(b) (4) It is not known whether (b) (4) is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from argatroban, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

## DISCUSSION AND CONCLUSIONS

In response to the division's consult, the MHT reviewed the Argatroban labeling. The Maternal Health Team (MHT) has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The MHT reviewer ensures that the appropriate regulatory language is present and that available information is organized and presented in a clear and useful manner for healthcare practitioners. Animal data in the pregnancy subsection is presented in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human exposure or dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

The first paragraph of the pregnancy subsection is a summary paragraph that includes the required regulatory language for the designated pregnancy category and statements that briefly describe the outcomes from available human and animal studies. Subsequent paragraphs describe the available data in greater detail.

(b) (4) the MHT is working with the review division to ensure consistency as appropriate based on the data reviewed and relied upon for labeling.

## RECOMMENDATIONS

1. Provided below is the MHT's recommended language for the Highlights, Pregnancy, and Nursing Mothers sections of Argatroban labeling. Appendix A of this review provides a track changes version of the labeling that highlights all changes made.

### Highlights

#### -----USE IN SPECIFIC POPULATIONS -----

- Nursing Mothers: Discontinue nursing or drug, taking into account the importance of the drug to the mother. (8.3).

#### 8.1 Pregnancy:

Pregnancy Category B.

There are no adequate and well-controlled studies of argatroban use in pregnant women. Developmental studies performed in rats with argatroban at intravenous doses up to 27 mg/kg/day (0.3 times the maximum recommended human dose, based on body surface area) and in rabbits at intravenous doses up to 10.8 mg/kg/day (0.2 times the maximum recommended human dose, based on body surface area) have revealed no evidence of (b) (4) harm to the fetus.

Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**8.3 Nursing Mothers:**

It is not known whether argatroban is excreted in human milk. Argatroban is detected in rat milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from argatroban, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Reviewer Comments

Please note that the header (b) (4) under section 8.1 Pregnancy was deleted, (b) (4). The above recommended language should be considered for all Argatroban products that rely on the same non-clinical developmental studies.

Appendix A-  
Track Changes Version of Labeling

30 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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TAMMIE B BRENT HOWARD  
07/27/2010

Karen B FEIBUS  
07/27/2010

I agree with the labeling recommendations contained in this review. I am also signing on behalf of CAPT Lisa Mathis, MD.