CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203049Orig1s000

OTHER REVIEW(S)

Division of Hematology Products (DHP)

REGULATORY PROJECT MANAGER LABELING REVIEW

Application number: NDA 203049

Name of Drug: Argatroban Injection

Applicant: Hikma Pharmaceuticals, Co. Ltd.

Materials Reviewed: Package Insert (PI)

Submission Date: March 18, 2011
Receipt Date: March 28, 2011

Background and Summary Description

Argatroban Injection was submitted March 18, 2011 (received March 28, 2011) for the indication: as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT/HITTS). NDA 203049 is a 505(b)(2) application. The reference listed drug (RLD) is Argatroban (NDA 20-883) by Encysive Pharmaceuticals, Inc. The labeling for the RLD is in the old labeling format. Hikma Pharmaceuticals' PI version that was submitted on March 18, 2011 was in the old labeling format (just like the RLD) and was asked to send a revised version in the new Physician's Labeling Rule (PLR) format. On May 20, 2011, Hikma Pharmaceuticals submitted a revised PI version in the required PLR format.

Review (PACKAGE INSERT)

The PI for Argatroban Injection submitted in the submission dated May 20, 2011 (received May 25, 2011) follows the PLR format with the exceptions (see attached pages).

Recommendations

1. The comments included regarding the **HIGHLIGHTS and FULL PRESCRIBING INFORMATION** sections should be sent to the sponsor in an information request letter.
2. The entire labeling should be reviewed by the review team including the clinical, chemistry and manufacturing, pharmacology/toxicology, statistical, and clinical pharmacology reviewers for further comments on content.

Regulatory Project Manager Date

Chief, Project Management Staff Date

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/s/

MONSURAT O AKINSANYA
12/23/2011

JANET K JAMISON
12/23/2011

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion, Division of Professional Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 12/20/2011

To: Lara Akinsanya, Regulatory Project Manager
Division of Hematology Products

From: James Dvorsky, Regulatory Reviewer
Office of Prescription Drug Promotion

Subject: Comments on draft labeling (Package Insert) for Argatroban, NDA 203049

In response to your labeling consult request on December 15, 2011, we have reviewed the draft Package Insert for Argatroban and do not have any comments at this time. This review is based upon the December 13, 2011 version of the labeling.

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/s/

JAMES S DVORSKY
12/20/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label and Labeling Review

Date:	November 22, 2011
Reviewer:	Jibril Abdus-Samad, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Todd Bridges, RPh Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name:	Argatroban Injection 250 mg/2.5 mL vial
Application Type/Number:	NDA 203049
Applicant:	Hikma Pharmaceuticals Co. Ltd
OSE RCM #:	2011-2008

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the proposed container labels, carton labeling, and insert labeling for Argatroban (NDA 203049) for areas of vulnerability that can lead to medication errors. Hikma Pharmaceuticals Co. Ltd submitted the proposed labels and labeling on March 18, 2011. The Applicant submitted updated labels on September 27, 2011.

Argatroban Injection 250 mg/2.5 mL is the subject of a 505(b)2 application submitted that notes Argatroban Injection (NDA 020883) as the reference listed drug (RLD), which was originally approved June 30, 2000.

1.1 PRODUCT INFORMATION

The following product information is provided in the March 18, 2011 submission.

- Established Name: Argatroban Injection
- Indication of Use: anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT) and in patients with or at risk for HIT thrombocytopenia undergoing percutaneous coronary intervention (PCI).
- Route of administration: intravenous infusion
- Dosage form: Injection
- Dose: For HIT, the recommended initial dose of Argatroban for adult patients with HIT (b) (4) is 2 mcg/kg/min, administered as a continuous infusion. Therapy with Argatroban is monitored using the aPTT and the dose can be adjusted as clinically indicated. For PCI, the recommended dose is 25 mcg/kg/min and a bolus of 350 mcg/kg administered via a large bore intravenous line over 3 to 5 minutes. Activated clotting time (ACT) is checked to adjust the dosage.
- How Supplied: 250 mg/2.5 mL vial
- Storage: Store the vials in original cartons at room temperature [25°C (77°F), (b) (4) Do not freeze. Retain in the original carton to protect from light.
- Container and Closure System: (b) (4) Amber vial

Both the proposed Argatroban Injection and the RLD require dilution prior to intravenous administration. However, recently the Agency approved Argatroban Injections that are ready-to-use and thus do not require dilution prior to intravenous administration. See Appendix A for the multiple Argatroban Injection products and there respective preparation instructions.

Reference ID: 3048644

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis[1] and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Label submitted September 27, 2011 (Appendix B)
- Carton Labeling submitted September 27, 2011 (Appendix C)
- Insert Labeling submitted September 27, 2011

Additionally, since Argatroban Injection is currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Argatroban. The AERS search conducted on September 16, 2011 used the following search terms: active ingredient "Argatroban", trade name (b) (4), and verbatim term (b) (4). The reaction terms used were the MedDRA High Level Group Terms (HLGT) "Medication Errors" and "Product Quality Issues". The time frame of the search was from 5/5/2011 (date of last DMEPA search from OSE Review 2011-1411) to September 16, 2011. This search yielded zero reports.

3 DISCUSSION OF DEFICIENCIES IDENTIFIED

The following sections discuss deficiencies related to the labeling.

3.1 PREPARATION OF ARGATROBAN INJECTION

The preparation for the proposed Argatroban Injection and the RLD require dilution to a 1 mg/mL concentration prior to intravenous administration. This differs from recently approved Argatroban Injection products which are ready-to-use and thus do not require further dilution prior to administration. Thus, we must clearly label this proposed Argatroban product requires dilution prior to administration to prevent wrong technique errors. See Appendix A for comparison of Argatroban products and their respective preparation instructions.

3.2 CONTAINER LABEL AND CARTON LABELING

The presentation of instructions to dilute Argatroban Injection prior to intravenous administration lacks prominence. The importance of this section is mentioned in section 3.1 of this review. Additionally, the use of the blue color throughout detracts from the important information (dilute prior to use) on the label and labeling that health care practitioners need to know for safe use of the product.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Reference ID: 3048644

3.3 INSERT LABELING

The presentation of the strength in the Dosage Forms and Strengths and the How Supplied sections can be improved by expressing the strength as total drug content per total volume with the concentration in parenthesis [(250 mg/2.5 mL (100 mg/mL)].

4 CONCLUSIONS AND RECOMMENDATIONS

The proposed labels and labeling introduce vulnerability that can lead to medication errors because instructions to dilute this product prior to use lack prominence on the principal display panel. Additionally, the strength presentations within the Dosage Forms, Strengths and How Supplied sections of the insert labeling can be improved by expressing the strength as total drug content per total volume with the concentration in parenthesis.

If you have further questions or need clarifications, please contact Sue Kang, project manager, at 301-796-4216.

4.1 COMMENTS TO THE DIVISION

Insert Labeling

A. Highlights of Prescribing Information, Full Prescribing Information, *Dosage Forms and Strengths*

   Revise the read as follows:

   250 mg/2.5 mL (100 mg/mL) single-use injection vial. Each vial requires dilution prior to infusion.

B. Highlights of Prescribing Information, Dosage and Administration

   Revise the statement, (b) (4)

   (b) (4)

C. Full Prescribing Information, Dosage and Administration – sections 2 and Preparation for Intravenous Administration – section 2.1.

   Revise the preparation instructions to read as follows:

   2. DOSAGE AND ADMINISTRATION

   Argatroban Injection 250 mg/2.5 mL (100 mg/mL) vial must be diluted prior to infusion. Argatroban should not be mixed with other drugs prior to dilution.

   2.1 Preparation for Intraveneous Administration: Withdraw the contents of each Argatroban 250 mg/2.5 mL vial and dilute in 250 mL of 0.9% Sodium Chloride Injection, 5% Dextrose

Reference ID: 3048644

Injection, or Lactated Ringer's Injection to a final concentration of 1 mg/mL. The final solution must be mixed by repeated inversion of the diluent bag for 1 minute. Upon preparation, the final solution may show slight but brief haziness due to the formation of microprecipitates that rapidly dissolve upon mixing. The pH of the intravenous solution prepared as recommended is 3.2 to 7.5.

D. Full Prescribing Information, Dosage and Administration – section 2

Replace all instances of the symbol < with phrase *less than* and symbol > with phrase *greater than*. The symbols < and > are dangerous symbols that appear on the List of Error-Prone Abbreviations, Symbols, and Dose Designations.[1] These symbols are often mistaken and used as opposite of intended. Additionally, as part of a national campaign to eliminate the use of dangerous abbreviations and symbols in prescribing, the FDA agreed not to allow these symbols in the approved labels and labeling of products.

E. Full Prescribing Information, How Supplied – section 16.1

Revise to read as follows:

Argatroban is supplied as a single-use vial, containing 250 mg/2.5 mL (100 mg/mL).

4.2 COMMENTS TO THE APPLICANT

A. Container Label and Carton Labeling

1. Revise the presentation of the established name from all UPPERCASE letters to Title Case to improve readability and revise the presentation of the strength to read as follows:

   Argatroban Injection
   250 mg/2.5 mL
   (100 mg/mL)

2. Revise the font size and weight of the word *Injection* to match *Argatroban*.
3. Delete the statement, [redacted] (b) (4), from the principal display panel
4. Delete the blue bar that covers a large area and overpowers important information. Consider using the blue color more strategically to highlighting important information on the label, such as the strength expression.
5. Revise the statement, [redacted] (b) (4), to read as follows:

   Dilute Prior to Administration

6. Increase the prominence of the statement, *Dilute Prior to Administration*, by increasing the font size and improving the color contrast between the font color of this statement and the background.

Reference ID: 3048644

7. Revise the dangerous abbreviation, *IV*, to read, *intravenous*. IV is a dangerous abbreviation, which appears on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations[2] because the abbreviation 'IV' has been confused with the abbreviations 'IM' (intramuscular), 'IU' (international units), and 'IN' (intranasal).
8. Increase the prominence of the statement, *For Intravenous Infusion Only*.
9. Add the statement, *Single-Use Vial – Discard Unused Portion*.

B. Carton Labeling

Decrease the prominence of the manufacturer statement, West-Ward Pharmaceuticals, on the side panel by decreasing the font size and relocating the manufacturer statement toward the bottom of the side panel. Currently, West-Ward Pharmaceuticals is as prominent as the established name.

[2] Institute for Safe Medication Practices, "List of Error-Prone Abbreviations, Symbols, and Dose Designations. Last accessed September 16, 2011. http://www.ismp.org/tools/errorproneabbreviations.pdf

Reference ID: 3048644

5 REFERENCES

1. Wilkins-Parker, Jamie. OSE Review 2011-1411: DMEPA Label and Labeling Review for Argatroban Review, May 13, 2011
2. Tobenkin, Anne C. OSE Review 2011-323: DMEPA Label and Labeling Review for Argatroban, May 3, 2011
3. Maslov, Yelena. OSE Review 2010-1010, 2010-1341: DMEPA Label and Labeling Review for Argatroban, December 13, 2010
4. Maslov, Yelena. OSE Review 2010-1531: DMEPA Label and Labeling Review for Argatroban, December 13, 2010

APPENDICES

Appendix A: Argatroban products and preparation instructions

Product	NDA	Strength	Preparation Instructions
Argatroban Injection (proposed product)	203049	250 mg/2.5 mL (100 mg/mL) vial	Dilute in 5% Dextrose, 0.9% Sodium Chloride, or Lactated Ringers to a final concentration of 1 mg/mL
Argatroban Injection (RLD)	020883	250 mg/2.5 mL (100 mg/mL) vial	Dilute in 5% Dextrose, 0.9% Sodium Chloride, or Lactated Ringers to a final concentration of 1 mg/mL
Argatroban Injection	022434	50 mg/50 mL (1 mg/mL) vial	No dilution required. Vial may be inserted for use with a medical infusion set.
Argatroban Injection in 0.9% Sodium Chloride	022485	125 mg/125 mL (1 mg/mL) vial	No dilution required. Vial may be inserted for use with a medical infusion set.
Argatroban Injection in 5% Dextrose	201743	125 mg/125 mL (1 mg/mL) vial	No dilution required. Vial may be inserted for use with a medical infusion set.

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/s/

TODD D BRIDGES
11/22/2011
Also signing for Jibril Abdus-Samad.

CAROL A HOLQUIST
11/22/2011