CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022434Orig1s000

OTHER REVIEW(S)

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:	May 3, 2011
Application Type/Number:	NDA 022434
To:	Ann Farrell, MD, Director Division of Hematology Products
Through:	Melina Griffis, R.Ph., Team Leader Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis
From:	Anne C. Tobenkin, Pharm.D., Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name and Strength:	Argatroban Injection 50 mg/50 mL (1 mg/mL)
Applicant/sponsor:	Eagle Pharmaceuticals
OSE RCM #:	2011-323

1 INTRODUCTION

This review evaluates the container labels, as well as carton and package insert labeling for NDA #022434, Argatroban Injections 50 mg/50 mL (1 mg/mL) in response to a request from the Division of Hematology Products dated February 11, 2011. There is no proposed proprietary name for this product at this time.

1.1 REGULATORY HISTORY

Argatroban Injection 50 mg/50 mL (1 mg/mL) is the subject of a 505 (b)(2) application submitted on January 12, 2011, 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 50 mg/50 mL (1 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 identified medication error 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[1] (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 March 21, 2011 used the following MedDRA High Level Group Terms (HLGT) "Medication Errors" and "Product Quality Issues" along with active ingredient names of "Argatroban" and the verbatim name "Argatro%" with a date limitation of July 3, 2010 when the most recent Argatroban AERS search was run.

2.2 LABELS AND LABELING RISK ASSESSMENT

For Argatroban Injection 50 mg/50 mL, the Applicant submitted the following container label and carton labeling as well as package insert labeling on January 12, 2011 (See Appendix A for container label and carton labeling images):

- Container Label and Carton Labeling: 50 mg/50 mL (1 mg/mL)

3 RESULTS AND DISCUSSION

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

[1] 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 retrieved one (n=1) case of medication error involving Argatroban, however the error was related to pump confusion, rather then label or labeling confusion and was therefore not considered relevant to the review.

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, the package insert labeling contains dangerous abbreviations and the principal display panels of the carton labeling and container label contain ambiguous information which can lead to confusion.

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 50 mg/50 mL (100 mg/mL) and have the following recommendations for the revision of the insert labeling.

1. Highlights of Prescribing Information.

a. *Dosage Forms and Strengths* Section: The sentence, Solution for injection, ready to use single dose vials, 50 mg/50 mL, does not state the concentration, 1 mg/mL. Revise the statement to include the concentration after the total drug content statement.

b. *Dosage and Administration*: We note the use of dangerous abbreviations and symbols in the insert labeling. The abbreviation 'IV' is on the dangerous abbreviations, List of Error-Prone Abbreviations, Symbols, and Dose Designations[2] because the abbreviation has been confused with the abbreviations 'IM' (intramuscular), 'IU' (international units), and 'IN' (intranasal). Thus, we request the abbreviation 'IV' be replaced with the word "intravenously."

c. *Adverse Reactions*: The symbols '<' and '>' utilized in this section of the labeling 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. Replace all instances of the symbol '<' with phrase "less than" and symbol '>' with phrase "greater than."

[2] Institute for Safe Medication Practices, "List of Error-Prone Abbreviations, Symbols, and Dose Designations. www.ismp.org.

2. Full Prescribing Information

a. *Dosage and Administration:* see 1b and 1c in highlights and revise accordingly.

b. In the *Storage* or in the *Dosage and Administration section*, state how long the vial can be outside of the carton before it must be discarded.

4.2 COMMENTS TO THE APPLICANT

1. All Container Labels and Carton Labeling for Argatroban Injection"

a. Center or left align the name, dosage form, and strength.

b. 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[3] because the abbreviation 'IV' has been confused with the abbreviations 'IM' (intramuscular), 'IU' (international units), and 'IN' (intranasal). Revise this statement accordingly.

c. Remove the color box that is used for the name, total drug content, and concentration and instead only box or highlight the total drug content, 50 mg per 50 mL.

d. Remove the redundant (b) (4) statement that appears before the 'Single Use Only' statement. Additionally, add the statement 'Discard Unused Portion' so that it appears in conjunction with the 'Single Use Vial', on the principle display panel.

e. Remove the box that surrounds the 'Ready to Use' statement and revise the ambiguous statement so that it reads, 'Do not dilute prior to administration' as this better communicates the proper preparation, or lack thereof.

f. Include a statement on the side panel that instructs to protect from light.

2. Container Label (50 mg/50 mL)

a. Invert the name, total drug content, and all statements which pertain to proper administration of Argatroban which appear at the bottom of the label so that they can be read while the drug is hanging upside down during infusion.

3. Carton Labeling (50 mg/50 mL)

a. Remove the redundant statement 'Each mL contains 1 mg of Argatroban', as this is stated in the concentration statement (1 mg/mL) which follows the total drug content statement.

[3] Institute for Safe Medication Practices, "List of Error-Prone Abbreviations, Symbols, and Dose Designations. www.ismp.org.

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

ISR # 7347154-5

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/s/

MELINA N GRIFFIS
05/03/2011

CAROL A HOLQUIST
05/03/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
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Silver Spring, MD 20993
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Maternal Health Team Label Review

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

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

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

Lisa Mathis, MD
Associate Director, Office of New Drugs

To: The Division of Hematology Products (DHP)

Drug: Argatroban Injection, NDA 22-434

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 March 27, 2009, Eagle Pharmaceuticals, Inc. submitted a 505 (b)(2) new drug application (NDA 22-434) to the Division of Hematology Products (DHP) (formerly the Division of Medical Imaging and Hematology Products) for Argatroban Injection. 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). A Complete Response letter was issued to the sponsor on January 29, 2010, stating that the application could not be approved in its present form, citing product quality issues. On January 10, 2011, the sponsor submitted an amendment in response to the January 29, 2010, Complete Response letter, which included proposed product labeling.

On February 8, 2011, DHP consulted the Pediatric and Maternal Health Staff's (PMHS) 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

(b) (4)

(b) (4)

DISCUSSION AND CONCLUSIONS

The Pregnancy and Nursing Mothers section of labeling should describe available animal and human data in a manner that allows clinicians, who are prescribing medication for pregnant patients and female patients of reproductive potential, to balance the benefits of treating the patient with the potential risks to the mother, fetus and/or infant. PMHS- maternal health labeling recommendations comply with current regulations but incorporate "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). Usually the first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. 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 MHT is working with the review division to ensure consistency among the pregnancy subsection labeling for all 505(b)(2) argatroban products, as appropriate, based on the data reviewed in each submission.

This review provides the Maternal Health Team's recommended revisions to the highlights, pregnancy and nursing mothers sections of the sponsor's proposed labeling. Appendix A of this review provides a tracked-changes version of labeling that highlights the recommended MHT revisions.

MHT LABELING RECOMMENDATIONS

MHT's recommended language for the Highlights, Pregnancy, and Nursing Mothers sections of Argatroban labeling:

(b) (4)

(b) (4)

8.3 (b) (4)

Appendix A-
Track Changes Version of Labeling

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/s/

TAMMIE B BRENT HOWARD
03/29/2011

Karen B FEIBUS
03/29/2011
I concur with the labeling recommendations presented in this review.

LISA L MATHIS
03/31/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Pediatric and Maternal Health Staff – Pediatric Labeling Review

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

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 22-434

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

Materials Reviewed:

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

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

INTRODUCTION

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

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

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

BACKGROUND

Argatroban

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

Pediatric Argatroban Studies

Pediatric studies were required for Argatroban under the Pediatric Research Equity Act (PREA), as well as a postmarketing commitment for pediatric pharmacokinetic and safety studies to allow for appropriate dosing and safety. In addition, Encysive Pharmaceuticals, Inc. (now Pfizer, Inc.) submitted a Proposed Pediatric Study Request (PPSR) on April 26, 2002, and in response, FDA issued a Pediatric Written Request (PWR) on April 2, 2003, (amended on February 13, 2004 and April 7, 2005) requesting information from studies in pediatric patients birth to < 16 years of age for the prophylaxis and/or treatment of thrombosis in patients who: 1) have a diagnosis of heparin-induced thrombocytopenia and thrombosis syndrome (HIT/HITTS), or 2) require anticoagulation and have documented histories of positive HIT antibody test in the absence of thrombocytopenia or heparin challenge (patients with latent disease), or 3) require alternative anticoagulation (i.e., not heparin) due to an underlying condition, including patients with anti-thrombin 3 deficiency or hypercoagulable states. The PWR requested safety, clinical outcomes data, and pharmacokinetic/pharmacodynamic parameters on a minimum of 24 patients.

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

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

(b) (4)

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

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

Best Pharmaceuticals for Children Act of 2007

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

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

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

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

Pediatric Use Labeling

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

DISCUSSION AND CONCLUSONS

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

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

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

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

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

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

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

Appendix A – Tracked Changes Labeling

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/s/

JEANINE A BEST
02/28/2011

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

LISA L MATHIS
02/28/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 22-434 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: Argatroban Injection Dosage Form: Injection Strengths: 1 mg/mL		
Applicant: Eagle Pharmaceuticals, Inc Agent for Applicant (if applicable):		
Date of Application: March 27, 2009 Date of Receipt: March 30, 2009 Date clock started after UN: N/A		
PDUFA Goal Date: January 30, 2010	Action Goal Date (if different):	
Filing Date: May 26, 2009	Date of Filing Meeting: May 6, 2009	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5 S		
Proposed indication(s)/Proposed change(s): Anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia. Anticoagulant in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary interventions (PCI).		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html*** ***and refer to Appendix A for further information.***		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☒	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device	
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)	

Other:	☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*): N/A

List referenced IND Number(s): 102,622

Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	✓			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	✓			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	✓			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		✓		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	✓			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).*

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		✓		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).		✓		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*		✓		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:	✓			

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
NDA 20-883	Argatroban	M-75	May 5, 2011

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		✓		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		✓		

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		✓		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☒ All paper (except for COL) ☐ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).			✓	
Index: Does the submission contain an accurate comprehensive index?				
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.	✓			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? ***If yes,*** *date consult sent to the Controlled Substance Staff:*				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	✓			
Are all establishments and their registration numbers listed on the form/attached to the form?				
Patent Information **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?		✓		
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	✓			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?		✓		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	✓			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	✓			

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	✓			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		✓		
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	✓			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***	✓			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***		✓		

Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***			✓	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	✓			
Is the PI submitted in PLR format?	✓			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?		✓		
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)		✓		
REMS consulted to OSE/DRISK?		✓		
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?		✓		
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		✓		

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		✓		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** January 29, 2009 ***If yes, distribute minutes before filing meeting***	✓			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***				

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 6, 2009

BLA/NDA/Supp #: 22-434

PROPRIETARY NAME: N/A

ESTABLISHED/PROPER NAME: Argatroban Injection

DOSAGE FORM/STRENGTH: 1 mg/mL

APPLICANT: Eagle Pharmaceuticals, Inc

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

Indicated as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT). It is also proposed for patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI).

BACKGROUND:

Eagle Pharmaceuticals, Inc.'s Argatroban Injection drug product, 1 mg/mL (50 mg in 50 mL and (b) (4) is a ready to use solution indicated as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT). It is also proposed for patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI).

The Reference Listed Drug, ARGATROBAN Injection, was approved in June 30, 2008 under NDA 20-883 (Encysive Pharmaceutical). Baxter's Argatroban has the same indication, route of administration, and dosing regimen (frequency and duration) but differs in the dosage form and formulation composition.

<u>REVIEW TEAM</u>:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Ebla Ali Ibrahim	Y
	CPMS/TL:	Kyong Kang	N
Cross-Discipline Team Leader (CDTL)			
Clinical	Reviewer:	MinH Ha Tran (no longer an employee) Firoozeh Alvandi	Y N

	TL:	Kassa Ayalew (transferred to another division) Kathy Robie Suh	Y Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Joseph Grillo	Y
	TL:	Young Moon Choi	Y
Biostatistics	Reviewer:	Satish Misra	Y
	TL:	Jyoti Zalkikar	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ronald Honchel	Y
	TL:	Adebayo Laniyonu	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Mark Sassman	Y
	TL:	Eldon Leutzinger	Y
Quality Microbiology *(for sterile products)*	Reviewer:	Steve Langille	N
	TL:	James McVey	N
CMC Labeling Review *(for BLAs/BLA supplements)*	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		

Other reviewers		
Other attendees		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues: Clinical Pharm and CMC issues	☐ Not Applicable ☒ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

Comments:	

Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs/BLA supplements only) **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Ebla Ali Ibrahim **21st Century Review Milestones (see attached)** (optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☐	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22434	ORIG-1	EAGLE PHARMACEUTICALS INC	ARGATROBAN INJECTION

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

/s/

EBLA ALI IBRAHIM
01/22/2010