CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

203049Orig1s004

Trade Name:	**Argatroban injection**
Generic Name:	**Argatroban injection for intravenous administration**
Sponsor:	**Hikma Pharmaceuticals Co. Ltd.**
Approval Date:	09/30/2016
Indications:	Argatroban is a direct thrombin inhibitor indicated: • For prohphylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT) • As an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203049Orig1s004

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203049Orig1s004

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203049/S-004

SUPPLEMENT APPROVAL

Exela Pharma Sciences, LLC
Attention: Jonathon E. Sterling
US Agent for Hikma Pharmaceuticals Co. Ltd.
PO Box 818
1245 Blowing Rock Blvd
Lenoir, NC 28645

Dear Mr. Sterling:

Please refer to your Supplemental New Drug Application (sNDA) dated April 24, 2015, received April 27, 2015 and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Argatroban Injection, 250 mg Vial (100 mg/mL) and 50 mg Vial (1 mg/mL).

We acknowledge receipt of your amendment dated, March 31, 2016, received April 1, 2016, which constituted a complete response to our October 26, 2015, action letter.

This Prior Approval supplemental new drug application provides for:

1. The addition of a ready to use dilution presentation of the current drug product.
2. Subsequent revisions to the US Prescribing Information, including revisions to the Highlights, Dosage and Administration, Dosage Forms and Strengths, How Supplied, Use in Specific Populations, Clinical Pharmacology, and Patient Counseling Information sections.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate-container labels submitted on September 19, 2016, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 203049/S-004**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROPRIETARY NAME

If you intend to have a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit a request for a proposed proprietary name review. (See the guidance for industry titled, "Contents of a Complete Submission for the Evaluation of Proprietary Names", at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012").

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory

comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Alice Kacuba, Chief, Project Management Staff, at (301) 796-1381 or email at alice.kacuba@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ann Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labels

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

/s/

ANN T FARRELL
09/30/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203049Orig1s004

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203049/S-004

COMPLETE RESPONSE

Hikma Pharmaceuticals Co. Ltd.
c/o Exela Pharma Sciences, LLC.
Attention: Jonathan E. Sterling
Vice President of Quality and Regulatory
P.O. Box 818
1245 Blowing Rock Blvd.
Lenoir, NC 28645

Dear Mr. Sterling:

Please refer to your Supplemental New Drug Application (sNDA) dated April 24, 2015, received April 27, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Argatroban injection 250mg/2.5mL and 50mg/50mL.

We acknowledge receipt of your amendment dated October 21, 2015, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

This "Prior Approval" labeling supplement to your application proposes the addition of a ready to use dilution presentation of the current drug product.

We have completed our review of this application and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

1. The analytical method QCTM-047-04 for the proposed lower strength product, Ready to Use Argatroban Injection (1 mg/mL), is not acceptable due to its inadequate method validation report, (b) (4)

    - Provide a complete validation report for the revised analytical methods QCTM-047-04, for the proposed lower strength product, Ready to Use Argatroban Injection (1 mg/mL), including specificity, linearity, range, accuracy (with recovery), precision, detection limit, quantitation limit, robustness, and system suitability testing. Refer to ICH Q2A Text on *"Validation of Analytical Procedures and ICH Q2B Validation of Analytical Procedures: Methodology."*

- The above validation report should include raw experimental data, calculation results, and acceptance criteria for each validation parameter along with acceptable chromatograms (i.e. there should be a baseline separation between peaks). For method validation report format, refer to the earlier method validation reports by (b) (4) for test method number: CO-AN-013-R1 submitted in NDA 203049/S-000 and NDA/S-002 for Determination of Impurities in Argatroban Injection (100 mg/mL) by HPLC.

- In addition, provide justification with comparative supporting data for the changes made to the method QCTM-047-02 (refer to #CCR/QC/2014/029) as summarized in P.9 of QCTM-047-04 for testing samples for drug product in 100 mg/mL strength and the proposed drug product in 1 mg/mL strength. Confirm when the changes were submitted to the Agency for review (refer to #CCR/QC/2014/029).

2. The three-month stability data generated under 40°C/75% RH and 25°C/60% RH storage conditions (for batches XLNH425, XLNH1426, and XLNH1427) do not support the proposed twenty-four (24) months expiration dating period for the proposed lower strength product, Ready to Use Argatroban Injection (1 mg/mL), refer to ICH Q1A(R2), Section 2.2.7.

    - Provide a minimum of 12-month stability data under the long term storage condition (25°C/60% RH) and 6-month stability data under the accelerated storage condition (40°C/75% RH) for three primary batches of the proposed product (1 mg/mL). You may also provide supporting data from batches in 1 mg/mL strength if available.

3. Provide updated batch records based on an adequately validated method as required in Comments No. 1 and No. 2.

4. Submit a side-by-side tabular comparison of the physicochemical properties (such as concentration/amount, pH and osmolality) of the proposed drug product and the listed drug, before and after dilution or reconstitution.

5. Submit a side-by-side tabular comparison of the qualitative and quantitative composition of the proposed product and the reference product.

6. Include a biowaiver request with supporting data/information in your resubmission; in particular, submit data demonstrating that the physiologic disposition of Argatroban is similar between the proposed and the reference product.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65**.** You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, please call Amy Baird, Chief, Project Management Staff at 301-796-4969.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

ANN T FARRELL
10/26/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203049Orig1s004

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use for ARGATROBAN INJECTION safely and effectively. See full prescribing information for ARGATROBAN INJECTION.

ARGATROBAN Injection, for intravenous use
Initial US Approval: 2000

----------RECENT MAJOR CHANGES----------
Dosing and Administration, Dosing in Patients Undergoing Percutaneous Coronary Intervention (2.3) 5/2016

----------INDICATIONS AND USAGE----------
Argatroban is a direct thrombin inhibitor indicated:

- For prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT) (1.1)
- As an anticoagulant in adults patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI) (1.2)

----------DOSAGE AND ADMINISTRATION----------
- Argatroban Injection 250 mg/2.5 mL (100 mg/mL) must be diluted 100-fold by mixing with 0.9% Sodium Chloride Injection, 5% Dextrose Injection, or Lactated Ringer's Injection to a final concentration of 1 mg/mL. (2.1)
- Argatroban Injection 50 mg/mL (1 mg/mL) is ready for intravenous infusion. Dilution is not required (2.1). Argatroban dosage may be adjusted by mixing with 0.9% Sodium Chloride Injection, 5% Dextrose Injection. (2.1)

Heparin-Induced Thrombocytopenia

The dose for heparin-induced thrombocytopenia without hepatic impairment is 2 mcg/kg/min administered as a continuous infusion. (2.2)

Percutaneous Coronary Intervention

The dose for patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention is started at 25 mcg/kg/min and a bolus of 350 mcg/kg administered via a large bore intravenous line over 3 to 5 minutes. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
- Injection: 250 mg/2.5 mL (100 mg/mL) single-dose vial. (3)
- Injection: 50 mg/50 mL (1 mg/mL) ready for intravenous infusion single-dose vial. (3)

----------CONTRAINDICATIONS----------
- Major bleeding (4)
- History of hypersensitivity to this product(4)

----------WARNINGS AND PRECAUTIONS----------
- Hemorrhage can occur. Unexplained fall in hematocrit or blood pressure may indicate hemorrhage (5.1)
- Hepatic impairment: Adjust starting dose and titrate carefully in patients with HIT who have moderate or severe hepatic impairment. Avoid use in PCI in patients with clinically significant hepatic impairment (5.2)

----------ADVERSE REACTIONS----------
- HIT patients: The most common (>5%) adverse reactions were dyspnea, hypotension, fever, diarrhea, sepsis, and cardiac arrest (6.1)
- PCI patients: The most common (>5%) adverse reactions were chest pain, hypotension, back pain, nausea, vomiting and headache (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact West-Ward Pharmaceuticals Corp. at 1-877-2332001 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- Heparin: Allow sufficient time for heparin's effect on aPTT to decrease before initiating Argatroban Injection therapy. (7.1)
- Warfarin: Concomitant use results in increased prolongation of PT and INR. (7.2)
- Thrombolytic agents or glycoprotein IIb/IIIa antagonists: Safety and effectiveness of concomitant use with argatroban have not been established. (7.4,7.5)

----------USE IN SPECIFIC POPULATIONS----------
- Nursing Mothers: Discontinue nursing or drug, taking into account the importance of the drug to the mother. (8.3)
- Pediatric use: Safety and effectiveness have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised 09/2016

FULL PRESCRIBING INFORMATION: CONTENTS *

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Heparin-Induced Thrombocytopenia

Argatroban Injection is indicated for prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT).

1.2 Percutaneous Coronary Intervention

Argatroban Injection is indicated as an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI).

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Intravenous Administration:

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

Dilution is not required for Argatroban Injection 50 mg/50 mL (1 mg/mL).

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

Argatroban 250 mg/2.5 mL (100 mg/mL) 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. The contents of each 2.5-mL vial should be diluted 100-fold by mixing with 250 mL of diluent. Use 250 mg (2.5 mL) per 250 mL of diluent or 500 mg (5 mL) per 500 mL of diluent.

The constituted solution must be mixed by repeated inversion of the diluent bag for 1 minute. Upon preparation, the solution may show slight but brief haziness due to the formation of microprecipitates that rapidly dissolve upon mixing. Use of diluent at room temperature is recommended. The final solution must be clear before use. The pH of the intravenous solution prepared as recommended is 3.2 to 7.5. Solutions prepared as recommended are stable at controlled room temperature, 20º to 25ºC (68º to 77ºF) (see USP) in ambient indoor light for 24 hours; therefore, light-resistant measure such as foil protection for intravenous lines are unnecessary. Solutions are physically and chemically stable for up to 96 hours when protected from light and stored at controlled room temperature, 20º to 25ºC (68º to 77ºF) (see USP) or at refrigerated conditions, 5º±3ºC (41º±5ºF). Prepared solutions should not be exposed to direct sunlight. No significant potency losses have been noted following simulated delivery of the solution through intravenous tubing.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Argatroban Injection 50 mg/50 mL (1 mg/mL)

Each 50 mL glass vial contains 50 mg argatroban (1 mg/mL); and, as supplied, is ready for intravenous infusion. Dilution is not required. Argatroban Injection is a clear, colorless to pale yellow solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if solution is cloudy, contains precipitates, or if the flip top cap is not intact.

Vial may be inverted for use with a medical infusion set.

2.2 Dosing in Patients with Heparin- Induced Thrombocytopenia

Initial Dosage

Before administering argatroban, discontinue heparin therapy and obtain a baseline aPTT. The recommended initial dose of argatroban for adult patients without hepatic impairment is 2 mcg/kg/min, administered as a continuous infusion (see Table 1).

Table 1.
Recommended Doses and Infusion Rates for 2 mcg/kg/min Dose of Argatroban for Patients With HIT* and Without Hepatic Impairment (1 mg/mL Final Concentration)

Body Weight (kg)	Dose (mcg/min)	Infusion Rate (mL/hr)
50	100	6
60	120	7
70	140	8
80	160	10
90	180	11
100	200	12
110	220	13
120	240	14
130	260	16
140	280	17

*with or without thrombosis

Monitoring Therapy
For use in HIT, therapy with Argatroban Injection is monitored using the aPTT with a target range of 1.5 to 3 times the initial baseline value (not to exceed 100 seconds). Tests of anticoagulant effects (including the aPTT) typically attain steady-state levels within 1 to 3 hours following initiation of Argatroban Injection. Check the aPTT 2 hours after initiation of therapy and after any dose change to confirm that the patient has attained the desired therapeutic range.

Dosage Adjustment
After the initiation of Argatroban Injection, adjust the dose (not to exceed 10 mcg/kg/min) as necessary to obtain a steady-state aPTT in the target range [see *Clinical Studies (14.1)*].

2.3 Dosing in Patients Undergoing Percutaneous Coronary Intervention

Initial Dosage
Initiate an infusion of Argatroban Injection at 25 mcg/kg/min and administer a bolus of 350 mcg/kg via a large bore intravenous line over 3 to 5 minutes (see Table 2). Check an activated clotting time (ACT) 5 to 10 minutes after the bolus dose is completed. The PCI procedure may proceed if the ACT is greater than 300 seconds.

Dosage Adjustment
If the ACT is less than 300 seconds, an additional intravenous bolus dose of 150 mcg/kg should be administered, the infusion dose increased to 30 mcg/kg/min, and the ACT checked 5 to 10 minutes later (see Table 2).

If the ACT is greater than 450 seconds, decrease the infusion rate to 15 mcg/kg/min, and check the ACT 5 to 10 minutes later (Table 3).

Continue titrating the dose until a therapeutic ACT (between 300 and 450 seconds) has been achieved; continue the same infusion rate for the duration of the PCI procedure.

In case of dissection, impending abrupt closure, thrombus formation during the procedure, or inability to achieve or maintain an ACT over 300 seconds, additional bolus doses of 150 mcg/kg may be administered and the infusion dose increased to 40 mcg/kg/min. Check the ACT after each additional bolus or change in the rate of infusion.

Table 2.
Recommended Starting and Maintenance Doses (Within the Target ACT Range) of Argatroban Injection in Patients Undergoing PCI Without Hepatic Impairment (1 mg/mL Final Concentration)

Body Weight (kg)	**Starting Bolus Dose (350 mcg/kg)**		**Starting and Maintenance Continuous Infusion Dosing For ACT 300-450 seconds 25 mcg/kg/min**	
	Bolus Dose (mcg)	**Bolus Volume (mL)**	**Continuous Infusion Dose (mcg/min)**	**Continuous Infusion Rate (mL/hr)**
50	17500	18	1250	75
60	21000	21	1500	90
70	24500	25	1750	105
80	28000	28	2000	120
90	31500	32	2250	135
100	35000	35	2500	150
110	38500	39	2750	165
120	42000	42	3000	180
130	45500	46	3250	195
140	49000	49	3500	210

NOTE: 1 mg = 1000mcg; 1 kg = 2.2 lbs

Table 3

Recommended Dose Adjustments of Argatroban Injection for Patients Outside of ACT Target Range Undergoing PCI Without Hepatic Impairment (1 mg/mL Final Concentration)						
Body Weight (kg)	If ACT Less than 300 seconds Dosage Adjustment† 30 mcg/kg/min				If ACT Greater than 450 seconds Dosage Adjustment* 15 mcg/kg/min	
	Additional Bolus Dose (mcg)	Bolus Volume (mL)	Continuous Infusion Dose (mcg/min)	Continuous Infusion Rate (mL/hr)	Continuous Infusion Dose (mcg/min)	Continuous Infusion Rate (mL/hr)
50	7500	8	1500	90	750	45
60	9000	9	1800	108	900	54
70	10500	11	2100	126	1050	63
80	12000	12	2400	144	1200	72
90	13500	14	2700	162	1350	81
100	15000	15	3000	180	1500	90
110	16500	17	3300	198	1650	99
120	18000	18	3600	216	1800	108
130	19500	20	3900	234	1950	117
140	21000	21	4200	252	2100	126

NOTE: 1 mg = 1000 mcg; 1 kg = 2.2 lbs
†Additional intravenous bolus dose of 150 mcg/kg should be administered if ACT less than 300 seconds.
* No bolus dose is given if ACT greater than 450 seconds

Monitoring Therapy
For use in PCI, therapy with Argatroban Injection is monitored using ACT. Obtain ACTs before dosing, 5 to 10 minutes after bolus dosing, following adjustments in the infusion rate, and at the end of the PCI procedure. Obtain additional ACTs every 20 to 30 minutes during prolonged procedure.

Continued Anticoagulation after PCI
If a patient requires anticoagulation after the procedure, Argatroban Injection may be continued, but at a rate of 2 mcg/kg/min and adjusted as needed to maintain the aPTT in the desired range [*see Dosage and Administration (2.1)*].

2.4 Dosing in Patients With Hepatic Impairment

Initial Dosage

For adult patients with HIT and moderate or severe hepatic impairment (based on Child-Pugh classification), an

initial dose of 0.5 mcg/kg/min is recommended, based on the approximately 4-fold decrease in argatroban clearance relative to those with normal hepatic function. Monitor the aPTT closely, and adjust the dosage as clinically indicated.

Monitoring Therapy
Achievement of steady state aPTT levels may take longer and require more dose adjustments in patients with hepatic impairment compared to patients with normal hepatic function.

For patients with hepatic impairment undergoing PCI and who have HIT or are at risk for HIT, carefully titrate argatroban until the desired level of anticoagulation is achieved. Use of Argatroban in PCI patients with clinically significant hepatic disease or AST/ALT levels ≥3 times the upper limit of normal should be avoided [*see Warnings and Precautions (5.2)*].

2.5 Conversion to Oral Anticoagulant Therapy

Initiating Oral Anticoagulant Therapy
When converting patients from Argatroban to oral anticoagulant therapy, consider the potential for combined effects on INR with co-administration of Argatroban and warfarin. A loading dose of warfarin should not be used. Initiate therapy using the expected daily dose of warfarin. To avoid prothrombotic effects and to ensure continuous anticoagulation when initiating warfarin, it is suggested that Argatroban and warfarin therapy be overlapped. There are insufficient data available to recommend the duration of the overlap.

Co-Administration of Warfarin and Argatroban Injection at Doses Up to 2 mcg/kg/min
Measure INR daily while Argatroban Injection and warfarin are co-administered. In general, with doses of Argatroban Injection up to 2 mcg/kg/min, Argatroban Injection can be discontinued when the INR is >4 on combined therapy. After Argatroban Injection is discontinued, repeat the INR measurement in 4 to 6 hours. If the repeat INR is below the desired therapeutic range, resume the infusion of Argatroban Injection and repeat the procedure daily until the desired therapeutic range on warfarin alone is reached.

Co-Administration of Warfarin and Argatroban Injection at Doses Greater than 2 mcg/kg/min

For doses greater than 2 mcg/kg/min, the relationship of INR between warfarin alone to the INR on warfarin plus argatroban is less predictable. In this case, in order to predict the INR on warfarin alone, temporarily reduce the dose of Argatroban Injection to a dose of 2 mcg/kg/min. Repeat the INR on Argatroban Injection and warfarin 4 to 6 hours after reduction of the Argatroban Injection dose and follow the process outlined above for administering Argatroban Injection at doses up to 2 mcg/kg/min.

3 DOSAGE FORMS AND STRENGTHS

• Injection: 250 mg/2.5 mL (100 mg/mL) single-dose vial
• Injection: 50 mg/50 mL (1 mg/mL) ready for intravenous infusion single-dose vial

4 CONTRAINDICATIONS

Argatroban is contraindicated in:

- Patients with major bleeding, *[see Warnings and Precautions (5.1)]*
- Patients with a history of hypersensitivity to argatroban. Airway, skin, and generalized hypersensitivity reactions have been reported *[see Adverse Reactions (6.1)]*

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Hemorrhage

Hemorrhage can occur at any site in the body in patients receiving argatroban. Unexplained fall in hematocrit or

blood pressure may indicate hemorrhage. Intracranial and retroperitoneal hemorrhage [*see Adverse Reactions (6.1)]* have been reported. The risk of hemorrhage with argatroban may be increased in severe hypertension; immediately following lumbar puncture, spinal anesthesia, major surgery (especially involving the brain, spinal cord, or eye), hematologic conditions associated with increased bleeding tendencies such as congenital or acquired bleeding disorders, and gastrointestinal lesions such as ulcerations.

Concomitant use of argatroban with antiplatelet agents, thrombolytics, and other anticoagulants may increase the risk of bleeding.

5.2 Use in Hepatic Impairment

When administering argatroban to patients with hepatic impairment, start with a lower dose and carefully titrate until the desired level of anticoagulation is achieved. Achievement of steady state aPTT levels may take longer and require more argatroban dose adjustments in patients with hepatic impairment compared to patients with normal hepatic function [*see Use in Specific Populations (8.6)*]. Also, upon cessation of argatroban infusion in the hepatically impaired patient, full reversal of anticoagulant effects may require longer than 4 hours due to decreased clearance and increased elimination half-life of argatroban [*see Dosage and Administration (2.3), Clinical Pharmacology (12.3)*]. Avoid the use of high doses of argatroban in patients undergoing PCI who have clinically significant hepatic disease or AST/ALT levels ≥3 times the upper limit of normal.

5.3 Laboratory Tests

Anticoagulation effects associated with Argatroban infusion at doses up to 40 mcg/kg/min correlate with increases of the activated partial thromboplastin time (aPTT). Although other global clot-based tests including prothrombin time (PT), the International Normalized Ratio (INR), and thrombin time (TT) are affected by Argatroban, the therapeutic ranges for these tests have not been identified for argatroban therapy. In clinical trials in PCI, the activated clotting time (ACT) was used for monitoring argatroban anticoagulant activity during the procedure. The concomitant use of argatroban and warfarin results in prolongation of the PT and INR beyond that produced by warfarin alone [*see Dosage and Administration (2.5), Clinical Pharmacology (12.2)*].

6 ADVERSE REACTIONS

The following adverse reaction is also discussed in other sections of the labeling:

- Risk of Hemorrhage [*see Warnings and Precautions (5.1)*].

6.1 Clinical Trials Experience

Adverse Reactions in Patients with HIT (With or Without Thrombosis)

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.

The following safety information is based on all 568 patients treated with argatroban in Study 1 and Study 2. The safety profile of the patients from these studies is compared with that of 193 historical controls in which the adverse reactions were collected retrospectively. Adverse reactions are separated into hemorrhagic and non-hemorrhagic reactions. Major bleeding was defined as bleeding that was overt and associated with a hemoglobin decrease ≥ 2 g/dL, that led to a transfusion of ≥ 2 units, or that was intracranial, retroperitoneal, or into a major prosthetic joint. Minor bleeding was overt bleeding that did not meet the criteria for major bleeding.

Table 4 gives an overview of the most frequently observed hemorrhagic events, presented separately by major and minor bleeding, sorted by decreasing occurrence among argatroban-treated patients with HIT (with or without thrombosis).

Table 4. **Major and Minor Hemorrhagic Adverse Reactions in Patients With HIT***		
Major Hemorrhagic Reactions[a]		
	Argatroban-treated Patients (Study 1 and Study 2) (n = 568) %	**Historical Control[c] (n = 193) %**
Overall bleeding	5.3	6.7
Gastrointestinal	2.3	1.6
Genitourinary and hematuria	0.9	0.5
Decrease in hemoglobin and hematocrit	0.7	0
Multisystem hemorrhage and DIC	0.5	1
Limb and BKA stump	0.5	0
Intracranial hemorrhage	0[b]	0.5
Minor Hemorrhagic Reactions[a]		
	Argatroban-treated Patients (Study 1 and Study 2) (n = 568) %	**Historical Control[c] (n = 193) %**
Gastrointestinal	14.4	18.1
Genitourinary and hematuria	11.6	0.8
Decrease in hemoglobin and hematocrit	10.4	0
Groin	5.4	3.1
Hemoptysis	2.9	0.8
Brachial	2.4	0.8

* with or without thrombosis

a) Patients may have experienced more than 1 adverse reaction.

b) One patient experienced intracranial hemorrhage 4 days after discontinuation of argatroban and following therapy with urokinase and oral anticoagulation.

c) The historical control group consisted of patients with a clinical diagnosis of HIT (with or without thrombosis) that were considered eligible by an independent medical panel.

DIC = disseminated intravascular coagulation.

BKA = below the knee amputation.

Table 5 gives an overview of the most frequently observed non-hemorrhagic reactions sorted by decreasing frequency of occurrence (≥2%) among argatroban-treated HIT/HITTS patients.

Table 5.
Non-hemorrhagic Adverse Reactions in Patients[a] With HIT[b]

	Argatroban-treated Patients (Study 1 and Study 2) (n = 568) %	**Historical Control[c] (n = 193) %**
Dyspnea	8.1	8.8
Hypotension	7.2	2.6
Fever	6.9	2.1
Diarrhea	6.2	1.6
Sepsis	6.0	12.4
Cardiac arrest	5.8	3.1
Nausea	4.8	0.5
Ventricular tachycardia	4.8	3.1
Pain	4.6	3.1
Urinary tract infection	4.6	5.2
Vomiting	4.2	0
Infection	3.7	3.6
Pneumonia	3.3	9.3
Atrial fibrillation	3.0	11.4
Coughing	2.8	1.6
Abnormal renal function	2.8	4.7
Abdominal pain	2.6	1.6
Cerebrovascular disorder	2.3	4.1

a) Patients may have experienced more than 1 adverse reaction

b) With or without thrombosis
c) The historical control group consisted of patients with a clinical diagnosis of HIT (with or without thrombosis) that were considered eligible by an independent medical panel.

6.2 Adverse Reactions in Patients with or at Risk for HIT Patients Undergoing PCI

The following safety information is based on 91 patients initially treated with argatroban and 21 patients subsequently re-exposed to argatroban for a total of 112 PCIs with argatroban anticoagulation. Adverse reactions are separated into hemorrhagic (Table 6) and non-hemorrhagic (Table 7) reactions.

Major bleeding was defined as bleeding that was overt and associated with a hemoglobin decrease ≥5 g/dL, that led to a transfusion of ≥2 units, or that was intracranial, retroperitoneal, or into a major prosthetic joint. The rate of major bleeding events in patients treated with argatroban in the PCI trials was 1.8%.

Table 6.
Major and Minor Hemorrhagic Adverse Reactions in Patients With HIT Undergoing PCI

Major Hemorrhagic Reactions[a]	
	Argatroban-treated Patients (n = 112)[b] %
Retroperitoneal	0.9
Gastrointestinal	0.9
Intracranial	0
Minor Hemorrhagic Reactions[a]	
	Argatroban-treated Patients (n = 112)[b] %
Groin (bleeding or hematoma)	3.6
Gastrointestinal (includes hematemesis)	2.6
Genitourinary (includes hematuria)	1.8
Decrease in hemoglobin and/or hematocrit	1.8
CABG (coronary arteries)	1.8
Access site	0.9
Hemoptysis	0.9

Other	0.9

a) Patients may have experienced more than 1 adverse reaction.
b) 91 patients who underwent 112 interventions.
CABG = coronary artery bypass graft.

Table 7 gives an overview of the most frequently observed non-hemorrhagic reactions (>2%), sorted by decreasing frequency of occurrence among argatroban-treated PCI patients.

Table 7.
Non-hemorrhagic Adverse Reactions[a] in Patients With HIT Undergoing PCI

	Argatroban Procedures[a] (n = 112)[b] %
Chest pain	15.2
Hypotension	10.7
Back pain	8.0
Nausea	7.1
Vomiting	6.3
Headache	5.4
Bradycardia	4.5
Abdominal pain	3.6
Fever	3.6
Myocardial infarction	3.6

a) Patients may have experienced more than 1 adverse reaction.
b) 91 patients who underwent 112 interventions.

There were 22 serious adverse reactions in 17 PCI patients (19.6% in 112 interventions). Table 8 lists the serious adverse reactions occurring in argatroban-treated patients with or at risk for HIT undergoing PCI.

Table 8.
Serious Adverse Reactions in Patients With HIT Undergoing PCI[a]

Coded Term	**Argatroban Procedures[b] (n = 112)**

Myocardial infarction	4 (3.5%)
Angina pectoris	2 (1.8%)
Coronary thrombosis	2 (1.8%)
Myocardial ischemia	2 (1.8%)
Occlusion coronary	2 (1.8%)
Chest pain	1 (0.9%)
Fever	1 (0.9%)
Retroperitoneal hemorrhage	1 (0.9%)
Aortic stenosis	1 (0.9%)
Arterial thrombosis	1 (0.9%)
Gastrointestinal hemorrhage	1 (0.9%)
Gastrointestinal disorder (GERD)	1 (0.9%)
Cerebrovascular disorder	1 (0.9%)
Lung edema	1 (0.9%)
Vascular disorder	1 (0.9%)

a) Individual reactions may also have been reported elsewhere (see Table 6 and 7).
b) 91 patients underwent 112 procedures. Some patients may have experienced more than 1 reaction.

Intracranial Bleeding in Other Populations

Increased risks for intracranial bleeding have been observed in investigational studies of argatroban for other uses. In a study of patients with acute myocardial infarction receiving both argatroban and thrombolytic therapy (streptokinase or tissue plasminogen activator), the overall frequency of intracranial bleeding was 1% (8 out of 810 patients). Intracranial bleeding was not observed in 317 subjects or patients who did not receive concomitant thrombolysis [*see Drug Interactions (7.4)*].

The safety and effectiveness of argatroban for cardiac indications other than PCI in patients with HIT have not been established. Intracranial bleeding was also observed in a prospective, placebo-controlled study of argatroban in patients who had onset of acute stroke within 12 hours of study entry. Symptomatic intracranial hemorrhage was reported in 5 of 117 patients (4.3%) who received argatroban at 1 to 3 mcg/kg/min and in none of the 54 patients who received placebo. Asymptomatic intracranial hemorrhage occurred in 5 (4.3%) and 2 (3.7%) of the patients, respectively.

Allergic Reactions

One hundred fifty-six allergic reactions or suspected allergic reactions were observed in 1,127 individuals who were treated with argatroban in clinical pharmacology studies or for various clinical indications. About 95% (148/156) of these reactions occurred in patients who concomitantly received thrombolytic therapy (e.g., streptokinase) or contrast media.

Allergic reactions or suspected allergic reactions in populations other than patients with HIT (with or without thrombosis) include (in descending order of frequency):

- Airway reactions (coughing, dyspnea): 10% or more
- Skin reactions (rash, bullous eruption): 1 to <10%
- General reactions (vasodilation): 1 to 10%

Limited data are available on the potential formation of drug-related antibodies. Plasma from 12 healthy volunteers treated with argatroban over 6 days showed no evidence of neutralizing antibodies. No loss of anticoagulant activity was noted with repeated administration of argatroban to more than 40 patients.

7 DRUG INTERACTIONS

7.1 Heparin

If argatroban is to be initiated after cessation of heparin therapy, allow sufficient time for heparin's effect on the aPTT to decrease prior to initiation of argatroban therapy.

7.2 Oral Anticoagulant Agents

Pharmacokinetic drug-drug interactions between argatroban and warfarin (7.5 mg single oral dose) have not been demonstrated. However, the concomitant use of argatroban and warfarin (5 to 7.5 mg initial oral dose, followed by 2.5 to 6 mg/day orally for 6 to 10 days) results in prolongation of the prothrombin time (PT) and International Normalized Ratio (INR) [*see Dosage and Administration (2.5) and Clinical Pharmacology (12.2)*].

7.3 Aspirin/Acetaminophen

No drug-drug interactions have been demonstrated between argatroban and concomitantly administered aspirin or acetaminophen *[see Clinical Pharmacology (12.3)]*.

7.4 Thrombolytic Agents

The safety and effectiveness of argatroban with thrombolytic agents have not been established *[see Adverse Reactions (6.1)]*

7.5 Glycoprotein IIb/IIIa Antagonists

The safety and effectiveness of argatroban with glycoprotein IIb/IIIa antagonists have not been established.

8 USE IN SPECIFIC POPULATIONS

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 impaired fertility

or harm to the fetus. 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

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.

8.4 Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

Argatroban was studied among 18 seriously ill pediatric patients who required an alternative to heparin anticoagulation. Most patients were diagnosed with HIT or suspected HIT. Age ranges of patients were <6 months, n = 8; six months to <8 years, n = 6; 8 to 16 years, n = 4. All patients had serious underlying conditions and were receiving multiple concomitant medications. Thirteen patients received argatroban solely as a continuous infusion (no bolus dose). Dosing was initiated in the majority of these 13 patients at 1 mcg/kg/min and subsequently titrated as needed to achieve and maintain an aPTT of 1.5 to 3 times the baseline value. Most patients required multiple dose adjustments to maintain anticoagulation parameters within the desired range. During the 30-day study period, thrombotic events occurred during argatroban administration to two patients and following argatroban discontinuation in three other patients. Major bleeding occurred among two patients: one patient experienced an intracranial hemorrhage after 4 days of argatroban therapy in the setting of sepsis and thrombocytopenia and another patient experienced an intracranial hemorrhage after receiving argatroban for greater than 14 days. The study findings did not establish the safe and effective use of argatroban in pediatric patients and the dosing of 1 mcg/kg/min was not supported by the pharmacokinetic data described below.

Pediatric Pharmacokinetics (PK) and Pharmacodynamics (PD)

PK parameters of argatroban were characterized in population PK/PD analysis model with sparse data from 15 seriously ill pediatric patients. Argatroban clearance in these seriously ill pediatric patients (0.16 L/hr/kg) was 50% lower compared to argatroban clearance in healthy adults (0.31 L/hr/kg).

These PK/PD analysis models based on a goal of aPTT prolongation of 1.5 to 3 times the baseline value and avoidance of an aPTT >100 seconds for seriously ill pediatric patients with HIT/HITTS who require an alternative to heparin suggested the following:

- For patients with normal hepatic function, a starting infusion rate of 0.75 mcg/kg/min may have comparable aPTT responses as a starting dose of 2 mcg/kg/min in healthy adults. Additionally, based on an evaluation of aPTT every two hours, increasing the dosage by 0.1 to 0.25 mcg/kg/min could achieve additional aPTT responses.
- For patients with hepatic impairment a starting infusion rate of 0.2 mcg/kg/min with increasing dosing by increments of 0.05 mcg/kg/min may have comparable argatroban exposure as expected with adult doses.

The safety and effectiveness of argatroban with the above dosing have not been adequately assessed in pediatric patients and the safety and effectiveness of argatroban is not established in pediatric patients. In addition, the described dosage did not take into account multiple factors that could affect the dosage such as current aPTT, target aPTT, and the clinical status of the patient.

8.5 Geriatric Use

Of the total number of subjects (1340) in clinical studies of argatroban, 35% were 65 and over. In the clinical studies of adult patients with HIT (with or without thrombosis), the effectiveness of argatroban was not affected by age. No trends were observed across age groups for both aPTT and the ACT. The safety analysis did suggest that older

patients had increased underlying conditions, which may predispose them to adverse reactions. The studies were not sized appropriately to detect differences in safety between age groups.

8.6 Hepatic Impairment

Dose reduction and careful titration are required when administering argatroban to patients with hepatic impairment. Reversal of anticoagulation effect may be prolonged in this population *[see Dosage and Administration (2.3), Warning and Precautions (5.2), Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

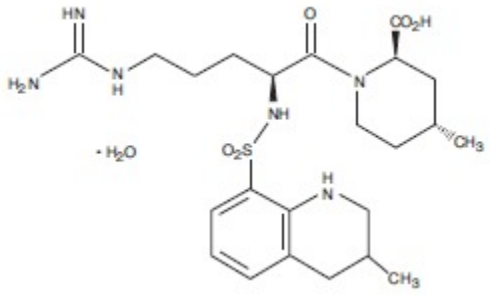
Excessive anticoagulation, with or without bleeding, may be controlled by discontinuing argatroban or by decreasing the argatroban dose. In clinical studies, anticoagulation parameters generally returned from therapeutic levels to baseline within 2 to 4 hours after discontinuation of the drug. Reversal of anticoagulant effect may take longer in patients with hepatic impairment. No specific antidote to argatroban is available; if life-threatening bleeding occurs and excessive plasma levels of argatroban are suspected, discontinue argatroban immediately and measure aPTT and other coagulation parameters. When argatroban was administered as a continuous infusion (2 mcg/kg/min) prior to and during a 4-hour hemodialysis session, approximately 20% of argatroban was cleared through dialysis.

Single intravenous doses of argatroban at 200, 124, 150, and 200 mg/kg were lethal to mice, rats, rabbits, and dogs, respectively. The symptoms of acute toxicity were loss of righting reflex, tremors, clonic convulsions, paralysis of hind limbs, and coma.

11 DESCRIPTION

Argatroban is a synthetic direct thrombin inhibitor and the chemical name is 1-[5-[(aminoiminomethyl)amino]-1-oxo-2-[[(1,2,3,4-tetrahydro-3-methyl-8-quinolinyl)sulfonyl]amino]pentyl]-4-methyl-2-piperidinecarboxylic acid, monohydrate. Argatroban has 4 asymmetric carbons. One of the asymmetric carbons has an R configuration (stereoisomer Type I) and an S configuration (stereoisomer Type II). Argatroban consists of a mixture of R and S stereoisomers at a ratio of approximately 65:35.

The molecular formula of Argatroban is C23H36N6O5S•H2O. Its molecular weight is 526.66 g/mol. The structural formula is shown below:



Argatroban is a white, odorless crystalline powder that is freely soluble in glacial acetic acid, slightly soluble in ethanol, and insoluble in acetone, ethyl acetate, and ether. Argatroban Injection 250 mg/2.5 mL (100 mg/mL) is a sterile clear, colorless to pale yellow, slightly viscous solution. Argatroban 250 mg/2.5 mL (100 mg/mL) is available in 250-mg (in 2.5-mL) single-dose amber vials, with white flip-top caps. Each mL of sterile, nonpyrogenic solution contains 100 mg Argatroban. Inert ingredients (per vial): 1300 mg Propylene glycol, 760 mg Dehydrated alcohol. Argatroban Injection 50 mg/50 mL (1 mg/mL) is a sterile clear, colorless to pale yellow, solution. Argatroban 50 mg/50 mL (1 mg/mL) is available in 50-mg (in 50- mL) single-dose amber vials, with white flip-top

caps. Each mL of sterile, nonpyrogenic solution contains 1 mg Argatroban. Inert ingredients (per vial): 260 mg Propylene glycol, 152 mg Dehydrated alcohol, and 450 mg Sodium Chloride.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Argatroban is a direct thrombin inhibitor that reversibly binds to the thrombin active site. Argatroban does not require the co-factor antithrombin III for antithrombotic activity. Argatroban exerts its anticoagulant effects by inhibiting thrombin-catalyzed or -induced reactions, including fibrin formation; activation of coagulation factors V, VIII, and XIII; activation of protein C; and platelet aggregation.

Argatroban inhibits thrombin with an inhibition constant (Ki) of 0.04 μM. At therapeutic concentrations, argatroban has little or no effect on related serine proteases (trypsin, factor Xa, plasmin, and kallikrein).

Argatroban is capable of inhibiting the action of both free and clot-associated thrombin.

12.2 Pharmacodynamics

When argatroban is administered by continuous infusion, anticoagulant effects and plasma concentrations of argatroban follow similar, predictable temporal response profiles, with low intersubject variability. Immediately upon initiation of argatroban infusion, anticoagulant effects are produced as plasma argatroban concentrations begin to rise. Steady-state levels of both drug and anticoagulant effect are typically attained within 1 to 3 hours and are maintained until the infusion is discontinued or the dosage adjusted. Steady-state plasma argatroban concentrations increase proportionally with dose (for infusion doses up to 40 mcg/kg/min in healthy subjects) and are well correlated with steady-state anticoagulant effects. For infusion doses up to 40 mcg/kg/min, argatroban increases in a dose-dependent fashion, the activated partial thromboplastin time (aPTT), the activated clotting time (ACT), the prothrombin time (PT), the International Normalized Ratio (INR), and the thrombin time (TT) in healthy volunteers and cardiac patients. Representative steady-state plasma argatroban concentrations and anticoagulant effects are shown below for argatroban infusion doses up to 10 mcg/kg/min (see Figure 1).

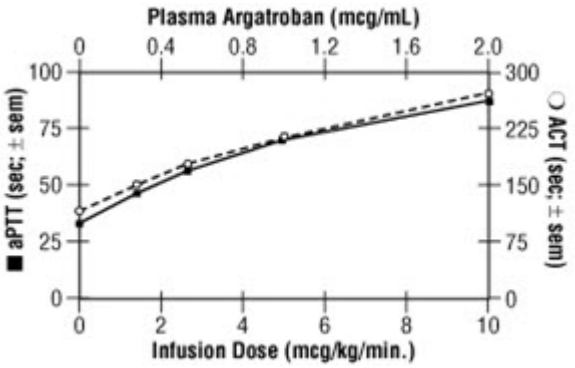


Figure 1. Relationship at Steady State Between Argatroban Dose, Plasma Argatroban Concentration and Anticoagulant Effect

Effect on International Normalized Ratio (INR): Because argatroban is a direct thrombin inhibitor, co-administration of argatroban and warfarin produces a combined effect on the laboratory measurement of the INR. However, concurrent therapy, compared to warfarin monotherapy, exerts no additional effect on vitamin K–dependent factor Xa activity.

The relationship between INR on co-therapy and warfarin alone is dependent on both the dose of argatroban and the thromboplastin reagent used. This relationship is influenced by the International Sensitivity Index (ISI) of the thromboplastin. Data for 2 commonly utilized thromboplastins with ISI values of 0.88 (Innovin, Dade) and 1.78 (Thromboplastin C Plus, Dade) are presented in Figure 2 for an argatroban dose of 2 mcg/kg/min. Thromboplastins with higher ISI values than shown result in higher INRs on combined therapy of warfarin and argatroban. These

data are based on results obtained in normal individuals *[see Dosage and Administration (2.5), Warnings and Precautions (5.3)]*.

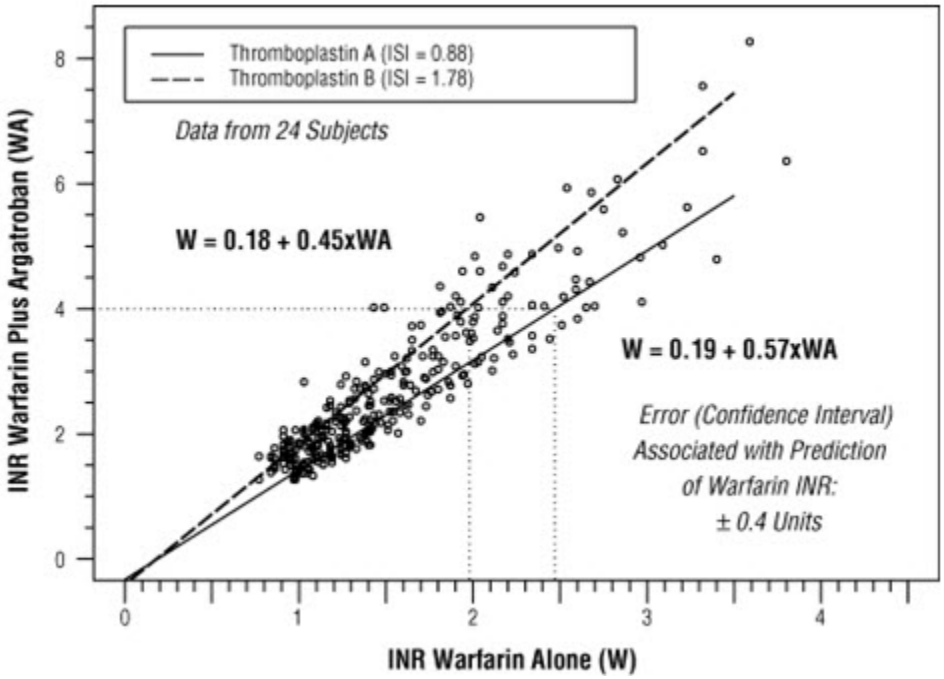


Figure 2. INR Relationship of Argatroban Plus Warfarin Versus Warfarin Alone

Figure 2 demonstrates the relationship between INR for warfarin alone and INR for warfarin co-administered with argatroban at a dose of 2 mcg/kg/min. To calculate INR for warfarin alone (INR_W), based on INR for co-therapy of warfarin and argatroban (INR_{WA}), when the argatroban dose is 2 mcg/kg/min, use the equation next to the appropriate curve. Example: At a dose of 2 mcg/kg/min and an INR performed with Thromboplastin A, the equation 0.19 + 0.57 (INR_{WA}) = INR_W would allow a prediction of the INR on warfarin alone (INR_W). Thus, using an INR_{WA} value of 4.0 obtained on combined therapy: INR_W = 0.19 + 0.57 (4) = 2.47 as the value for INR on warfarin alone. The error (confidence interval) associated with a prediction is ± 0.4 units. Similar linear relationships and prediction errors exist for argatroban at a dose of 1 mcg/kg/min. Thus, for argatroban doses of 1 or 2 mcg/kg/min, INR_W can be predicted from INR_{WA}. For argatroban doses greater than 2 mcg/kg/min, the error associated with predicting INR_W from INR_{WA} is ± 1. Thus, INR_W cannot be reliably predicted from INR_{WA} at doses greater than 2 mcg/kg/min.

12.3 Pharmacokinetics

Distribution
Argatroban distributes mainly in the extracellular fluid as evidenced by an apparent steady-state volume of distribution of 174 mL/kg (12.18 L in a 70-kg adult). Argatroban is 54% bound to human serum proteins, with binding to albumin and α_1-acid glycoprotein being 20% and 34%, respectively.

Metabolism
The main route of argatroban metabolism is hydroxylation and aromatization of the 3-methyltetrahydroquinoline ring in the liver. The formation of each of the 4 known metabolites is catalyzed *in vitro* by the human liver microsomal cytochrome P450 enzymes CYP3A4/5. The primary metabolite (M1) exerts 3- to 5-fold weaker anticoagulant effects than argatroban. Unchanged argatroban is the major component in plasma. The plasma concentrations of M1 range between 0% and 20% of that of the parent drug. The other metabolites (M2 to M4) are found only in very low quantities in the urine and have not been detected in plasma or feces. These data, together with the lack of effect of erythromycin (a potent CYP3A4/5 inhibitor) on argatroban pharmacokinetics, suggest that CYP3A4/5-mediated metabolism is not an important elimination pathway *in vivo*.

Total body clearance is approximately 5.1 mL/kg/min (0.31 L/kg/hr) for infusion doses up to 40 mcg/kg/min. The terminal elimination half-life of argatroban ranges between 39 and 51 minutes.

There is no interconversion of the 21–(R):21–(S) diastereoisomers. The plasma ratio of these diastereoisomers is unchanged by metabolism or hepatic impairment, remaining constant at 65:35 (± 2%).

Excretion
Argatroban is excreted primarily in the feces, presumably through biliary secretion. In a study in which 14C-argatroban (5 mcg/kg/min) was infused for 4 hours into healthy subjects, approximately 65% of the radioactivity was recovered in the feces within 6 days of the start of infusion with little or no radioactivity subsequently detected. Approximately 22% of the radioactivity appeared in the urine within 12 hours of the start of infusion. Little or no additional urinary radioactivity was subsequently detected. Average percent recovery of unchanged drug, relative to total dose, was 16% in urine and at least 14% in feces.

Special Populations
Hepatic Impairment: The dosage of argatroban should be decreased in patients with hepatic impairment *[see Dosage and Administration (2.3), Warnings and Precautions (5.2)]*. Patients with hepatic impairment were not studied in percutaneous coronary intervention (PCI) trials. At a dose of 2.5 mcg/kg/min, hepatic impairment is associated with decreased clearance and increased elimination half-life of argatroban (to 1.9 mL/kg/min and 181 minutes, respectively, for patients with a Child-Pugh score greater than 6).

Renal Impairment: No dosage adjustment is necessary in patients with renal dysfunction. The effect of renal disease on the pharmacokinetics of argatroban was studied in 6 subjects with normal renal function (mean Clcr = 95 ± 16 mL/min) and in 18 subjects with mild (mean Clcr = 64 ± 10 mL/min), moderate (mean Clcr = 41 ± 5.8 mL/min), and severe (mean Clcr = 5 ± 7 mL/min) renal impairment. The pharmacokinetics and pharmacodynamics of argatroban at dosages up to 5 mcg/kg/min were not significantly affected by renal dysfunction.

Use of argatroban was evaluated in a study of 12 patients with stable end-stage renal disease undergoing chronic intermittent hemodialysis. Argatroban was administered at a rate of 2 to 3 mcg/kg/min (begun at least 4 hours prior to dialysis) or as a bolus dose of 250 mcg/kg at the start of dialysis followed by a continuous infusion of 2 mcg/kg/min. Although these regimens did not achieve the goal of maintaining ACT values at 1.8 times the baseline value throughout most of the hemodialysis period, the hemodialysis sessions were successfully completed with both of these regimens. The mean ACTs produced in this study ranged from 1.39 to 1.82 times baseline, and the mean aPTTs ranged from 1.96 to 3.4 times the baseline. When argatroban was administered as a continuous infusion of 2 mcg/kg/min prior to and during a 4-hour hemodialysis session, approximately 20% was cleared through dialysis.

Age, Gender: There are no clinically significant effects of age or gender on the pharmacokinetics or pharmacodynamics (e.g., aPTT) of argatroban in adults.

Drug-Drug Interactions:

Digoxin: In 12 healthy volunteers, intravenous infusion of argatroban (2 mcg/kg/min) over 5 days (study days 11 to 15) did not affect the steady-state pharmacokinetics of oral digoxin (0.375 mg daily for 15 days).

Erythromycin: In 10 healthy subjects, orally administered erythromycin (a potent inhibitor of CYP3A4/5) at 500 mg four times daily for 7 days had no effect on the pharmacokinetics of argatroban at a dose of 1 mcg/kg/min for 5 hours. These data suggest oxidative metabolism by CYP3A4/5 is not an important elimination pathway *in vivo* for argatroban.

Aspirin and Acetaminophen: Drug-drug interactions have not been demonstrated between argatroban and concomitantly administered aspirin (162.5 mg orally given 26 and 2 hours prior to initiation of argatroban 1 mcg/kg/min over 4 hours) or acetaminophen (1,000 mg orally given 12, 6, and 0 hours prior to, and 6 and 12 hours subsequent to, initiation of argatroban1.5 mcg/kg/min over 18 hours).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with argatroban have not been performed.

Argatroban was not genotoxic in the Ames test, the Chinese hamster ovary cell (CHO/HGPRT) forward mutation test, the Chinese hamster lung fibroblast chromosome aberration test, the rat hepatocyte, and WI-38 human fetal lung cell unscheduled DNA synthesis (UDS) tests, or the mouse micronucleus test.

Argatroban at intravenous doses up to 27 mg/kg/day (0.3 times the recommended maximum human dose based on body surface area) had no effect on fertility and reproductive function of male and female rats.

14 CLINICAL STUDIES

14.1 Heparin-Induced Thrombocytopenia

The safety and efficacy of argatroban were evaluated in a historically controlled efficacy and safety study (Study 1) and a follow-on efficacy and safety study (Study 2). These studies were comparable with regard to study design, study objectives, dosing regimens as well as study outline, conduct, and monitoring. In these studies, 568 adult patients were treated with argatroban and 193 adult patients made up the historical control group. Patients had a clinical diagnosis of heparin-induced thrombocytopenia, either without thrombosis (HIT) or with thrombosis (HITTS [heparin-induced thrombocytopenia and thrombosis syndrome]) and were males or non-pregnant females between the age of 18 and 80 years old. HIT/HITTS was defined by a fall in platelet count to less than 100,000/μL or a 50% decrease in platelets after the initiation of heparin therapy with no apparent explanation other than HIT. Patients with HITTS also had an arterial or venous thrombosis documented by appropriate imaging techniques or supported by clinical evidence such as acute myocardial infarction, stroke, pulmonary embolism, or other clinical indications of vascular occlusion. Patients who had documented histories of positive heparin-dependent antibody tests without current thrombocytopenia or heparin challenge (e.g., patients with latent disease) were also included if they required anticoagulation.

These studies did not include patients with documented unexplained aPTT >200% of control at baseline, documented coagulation disorder or bleeding diathesis unrelated to HIT, a lumbar puncture within the past 7 days or a history of previous aneurysm, hemorrhagic stroke, or a thrombotic stroke within the past 6 months unrelated to HIT.

The initial dose of argatroban was 2 mcg/kg/min. Two hours after the start of the argatroban infusion, an aPTT level was obtained and dose adjustments were made (up to a maximum of 10 mcg/kg/min) to achieve a steady-state aPTT value that was 1.5 to 3.0 times the baseline value, not to exceed 100 seconds. Overall the mean aPTT level for HIT and HITTS patients during the Argatroban infusion increased from baseline values of 34 and 38 seconds, respectively, to 62.5 and 64.5 seconds, respectively.

The primary efficacy analysis was based on a comparison of event rates for a composite endpoint that included death (all causes), amputation (all causes) or new thrombosis during the treatment and follow-up period (study days 0 to 37). Secondary analyses included evaluation of the event rates for the components of the composite endpoint as well as time-to-event analyses.

In Study 1, a total of 304 patients were enrolled as follows: active HIT (n = 129), active HITTS (n =144), or latent disease (n = 31). Among the 193 historical controls, 139 (72%) had active HIT, 46 (24%) had active HITTS, and 8 (4%) had latent disease. Within each group, those with active HIT and those with latent disease were analyzed together. Positive laboratory confirmation of HIT/HITTS by the heparin-induced platelet aggregation test or serotonin release assay was demonstrated in 174 of 304 (57%) argatroban-treated patients (i.e., in 80 with HIT or latent disease and 94 with HITTS) and in 149 of 193 (77%) historical controls (i.e., in 119 with HIT or latent disease and 30 with HITTS). The test results for the remainder of the patients and controls were either negative or not determined.

There was a significant improvement in the composite outcome in patients with HIT and HITTS treated with argatroban versus those in the historical control group (see Table 9). The components of the composite endpoint are shown in Table 9.

Table 9. Efficacy Results of Study 1: Composite Endpoint[a] and Individual Components, Ranked by Severity[b]						
Parameter, N (%)	**HIT**		**HITTS**		**HIT/HITTS**	
	Control n = 147	**Argatroban n = 160**	**Control n = 46**	**Argatroban n = 144**	**Control n = 193**	**Argatroban n = 304**
Composite Endpoint	57 (38.8)	41 (25.6)	26 (56.5)	63 (43.8)	83 (43.0)	104 (34.2)
Individual Components[b]						
Death	32 (21.8)	27 (16.9)	13 (28.3)	26 (18.1)	45 (23.3)	53 (17.4)
Amputation	3 (2.0)	3 (1.9)	4 (8.7)	16 (11.1)	7 (3.6)	19 (6.2)
New Thrombosis	22 (15.0)	11 (6.9)	9 (19.6)	21 (14.6)	31 (16.1)	32 (10.5)

a) Death (all cause), amputation (all cause), or new thrombosis within 37-day study period.
b) Reported as the most severe outcome among the components of composite endpoint (severity ranking: death > amputation > new thrombosis); patients may have had multiple outcomes.

Time-to-event analyses showed significant improvements in the time-to-first event in patients with HIT or HITTS treated with argatroban versus those in the historical control group. The between-group differences in the proportion of patients who remained free of death, amputation, or new thrombosis were statistically significant in favor of argatroban by these analyses.

A time-to-event analysis for the composite endpoint is shown in Figure 3 for patients with HIT and Figure 4 for patients with HITTS.

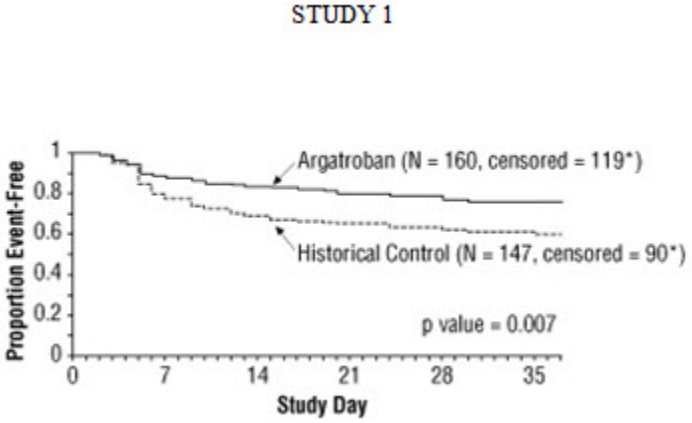


Figure 3. Time to First Event for the Composite Efficacy Endpoint: HIT Patients

*** Censored indicates no clinical endpoint (defined as death, amputation, or new thrombosis) was observed during the follow-up period (maximum period of follow-up was 37 days).**

STUDY 1

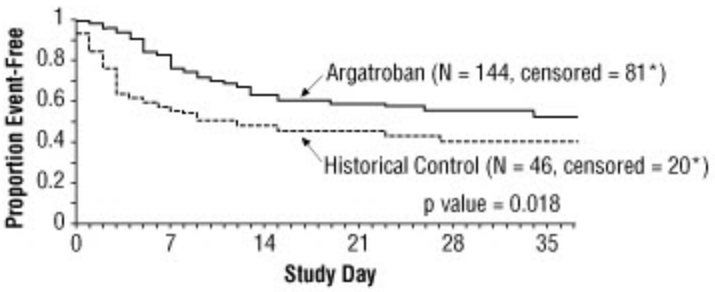


Figure 4. Time to First Event for the Composite Efficacy Endpoint: HITTS Patients

*** Censored indicates no clinical endpoint (defined as death, amputation, or new thrombosis) was observed during the follow-up period (maximum period of follow-up was 37 days).**

In Study 2, a total of 264 patients were enrolled as follows: HIT (n = 125) or HITTS (n = 139). There was a significant improvement in the composite efficacy outcome for argatroban-treated patients, versus the same historical control group from Study 1, among patients having HIT (25.6% vs. 38.8%), patients having HITTS (41.0% vs. 56.5%), and patients having either HIT or HITTS (33.7% vs. 43.0%). Time-to-event analyses showed significant improvements in the time-to-first event in patients with HIT or HITTS treated with argatroban versus those in the historical control group. The between-group differences in the proportion of patients who remained free of death, amputation, or new thrombosis were statistically significant in favor of argatroban.

Anticoagulant Effect
In Study 1, the mean (± SE) dose of argatroban administered was 2.0 ± 0.1 mcg/kg/min in the HIT arm and 1.9 ± 0.1 mcg/kg/min in the HITTS arm. Seventy-six percent of patients with HIT and 81% of patients with HITTS achieved a target aPTT at least 1.5-fold greater than the baseline aPTT at the first assessment occurring on average at 4.6 hours (HIT) and 3.9 hours (HITTS) following initiation of argatroban therapy.

No enhancement of aPTT response was observed in subjects receiving repeated administration of argatroban.

Platelet Count Recovery
In Study 1, 53% of patients with HIT and 58% of patients with HITTS, had a recovery of platelet count by Day 3. Platelet Count Recovery was defined as an increase in platelet count to >100,000/μL or to at least 1.5-fold greater than the baseline count (platelet count at study initiation) by Day 3 of the study.

14.2 Percutaneous Coronary Intervention (PCI) Patients with or at Risk for HIT

In 3 similarly designed trials, argatroban was administered to 91 patients with current or previous clinical diagnosis of HIT or heparin-dependent antibodies, who underwent a total of 112 percutaneous coronary interventions (PCIs) including percutaneous transluminal coronary angioplasty (PTCA), coronary stent placement, or atherectomy. Among the 91 patients undergoing their first PCI with argatroban, notable ongoing or recent medical history included myocardial infarction (n = 35), unstable angina (n = 23), and chronic angina (n = 34). There were 33 females and 58 males. The average age was 67.6 years (median 70.7, range 44 to 86), and the average weight was 82.5 kg (median 81.0 kg, range 49 to 141).

Twenty-one of the 91 patients had a repeat PCI using argatroban an average of 150 days after their initial PCI. Seven of 91 patients received glycoprotein IIb/IIIa inhibitors. Safety and efficacy were assessed against historical control populations who had been anticoagulated with heparin.

All patients received oral aspirin (325 mg) 2 to 24 hours prior to the interventional procedure. After venous or arterial sheaths were in place, anticoagulation was initiated with a bolus of argatroban of 350 mcg/kg via a

large-bore intravenous line or through the venous sheath over 3 to 5 minutes. Simultaneously, a maintenance infusion of 25 mcg/kg/min was initiated to achieve a therapeutic activated clotting time (ACT) of 300 to 450 seconds. If necessary to achieve this therapeutic range, the maintenance infusion dose was titrated (15 to 40 mcg/kg/min) and/or an additional bolus dose of 150 mcg/kg could be given. Each patient's ACT was checked 5 to 10 minutes following the bolus dose. The ACT was checked as clinically indicated. Arterial and venous sheaths were removed no sooner than 2 hours after discontinuation of argatroban and when the ACT was less than 160 seconds.

If a patient required anticoagulation after the procedure, argatroban could be continued, but at a lower infusion dose between 2.5 and 5 mcg/kg/min. An aPTT was drawn 2 hours after this dose reduction and the dose of argatroban then was adjusted as clinically indicated (not to exceed 10 mcg/kg/min), to reach an aPTT between 1.5 and 3 times baseline value (not to exceed 100 seconds).

In 92 of the 112 interventions (82%), the patient received the initial bolus of 350 mcg/kg and an initial infusion dose of 25 mcg/kg/min. The majority of patients did not require additional bolus dosing during the PCI procedure. The mean value for the initial ACT measurement after the start of dosing for all interventions was 379 sec (median 338 sec; 5^{th} percentile-95^{th} percentile 238 to 675 sec). The mean ACT value per intervention over all measurements taken during the procedure was 416 sec (median 390 sec; 5^{th} percentile-95^{th} percentile 261 to 698 sec). About 65% of patients had ACTs within the recommended range of 300 to 450 seconds throughout the procedure. The investigators did not achieve anticoagulation within the recommended range in about 23% of patients. However, in this small sample, patients with ACTs below 300 seconds did not have more coronary thrombotic events, and patients with ACTs over 450 seconds did not have higher bleeding rates.

Acute procedural success was defined as lack of death, emergent coronary artery bypass graft (CABG), or Q-wave myocardial infarction. Acute procedural success was reported in 98.2% of patients who underwent PCIs with argatroban anticoagulation compared with 94.3% of historical control patients anticoagulated with heparin (p = NS). Among the 112 interventions, 2 patients had emergency CABGs, 3 had repeat PTCAs, 4 had non-Q-wave myocardial infarctions, 3 had myocardial ischemia, 1 had an abrupt closure, and 1 had an impending closure (some patients may have experienced more than 1 event). No patients died.

16 HOW SUPPLIED/STORAGE AND HANDLING

Argatroban Injection is available in packages as follows:

NDC	Strength	Packaged
0143-9674-01	250 mg/2.5 mL (100mg/mL)	Single Dose Vial
0143-9559-01	50 mg/50 mL (1 mg/mL)	Single Dose Vial

Storage and Handling

Store the vials in original carton at 20° - 25° C (68° - 77° F) [See USP Controlled Room Temperature]. Do not freeze. Retain in the original carton to protect from light. If the solution is cloudy, or if an insoluble precipitate is noted, the vial should be discarded.

17 PATIENT COUNSELING INFORMATION

Inform patients of the risks associated with Argatroban Injection as well as the plan for regular monitoring during administration of the drug. Specifically, inform patients to report:

- the use of any other products known to affect bleeding.
- any medical history that may increase the risk for bleeding, including a history of severe hypertension; recent lumbar puncture or spinal anesthesia; major surgery, especially involving the brain, spinal cord, or eye; hematologic conditions associated with increased bleeding tendencies such as congenital or acquired bleeding disorders and gastrointestinal lesions such as ulcerations.

- any bleeding signs or symptoms [*see Warnings and Precautions (5.1)*].
- the occurrence of any signs or symptoms of allergic reactions (e.g., airway reactions, skin reactions and vasodilation reactions) *[see Adverse Reactions (6.1)]*.

Manufactured by:
Exela Pharma Sciences, LLC
Lenoir, NC 28645

Distributed by:
West-Ward
A HIKMA COMPANY
Eatontown, NJ 07724

Revised September 2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203049Orig1s004

MEDICAL REVIEW(S)

FILE MEMORANDUM

Memo Date:	July 27, 2015
To NDA:	203049
Sponsor:	Hikma Pharmaceuticals Co. Ltd.
Submission Date:	April 24, 2015
FDA Received Date:	April 25, 2015
EDR Location:	\\CDSESUB4\NONECTD\NDA203049\5800007
From:	Hyon-Zu Lee, Pharm.D., Clinical Reviewer; Division of Hematology Products (DHP)
Subject:	Argatroban
Via:	Virginia Kwitkowski, MS, ACNP-BC, Clinical Team Leader, DHP

ISSUE: N/A

ACTIONS RECOMMENDED: Tentative approval

Summary of Review Findings: No clinical safety or efficacy data were submitted in this sNDA. The proposed label is acceptable from clinical perspective. For recommendations regarding this supplement, please refer to reviews by other disciplines.

Background:
This NDA was granted approval in January 2012 under section 505(b)(2). The current submission was submitted as a "Changes Being Effected in 30 Days (CBE-30)" supplement providing a ready to use dilution presentation, Argatroban Injection 50mg/50mL (1mg/mL) single use injection. However, after administrative review the submission was classified as a "Prior Approval Supplement".

The current labeling of the Drug Product states that Argatroban Injection 250 mg/2.5 mL (100 mg/mL) must be diluted prior to infusion in 0.9% Sodium Chloride Injection, 5% Dextrose Injection, or Lactated Ringer's Injection to a final concentration of 1 mg/mL. Specifically, the labeling instructs the practitioner to 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 Injection, or Lactated Ringer's Injection to a final concentration of 1 mg/mL.

The proposed presentation is (b) (4) to the final drug product prepared by the dilution using one of the diluents described in the current approved labeling. (b) (4)

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

/s/

HYON-ZU LEE
07/27/2015

VIRGINIA E KWITKOWSKI
07/28/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

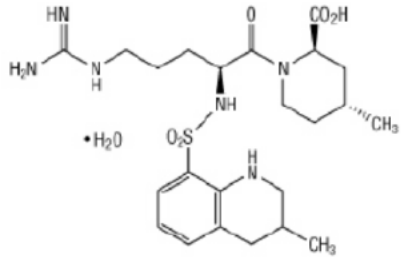
APPLICATION NUMBER:

203049Orig1s004

CHEMISTRY REVIEW(S)

CHEMISTRY REVIEW #2	1. ORGANIZATION	2. NDA NUMBER
	OPQ/OLDP/DPMA I/Branch I	N203049 (Approved 05-Jan-2012)
3. NAME AND ADDRESS OF APPLICANT		**4. SUPPLEMENT NUMBER, DATE**
Hikma Pharmaceutical Pvt. Ltd. Industrial Area Bayader Wadi El Seer Amman, Jordan	US Agent: Exela Pharma Sciences P.O. Box 818 1245 Blowing Rock Blvd. Lenoir, NC 28645	**S-004, 24-Apr-2015** **PAS/Labeling**
5. PROPRIETARY NAME	**6. NAME OF THE DRUG**	**7. AMENDMENTS, REPORT, DATE**
Argatroban Injection®	Argatroban	**S-004-RESUB-045, 31-Mar-2016** **S-004-RESUB-051, 29-Jul-2016** **S-004-RESUB, 19-Sep-2016** Other Labeling amendments: RESUB-046, RESUB-047, RESUB-048, RESUB-049, and RESUB-050
8. SUPPLEMENT PROVIDES INFORMATION FOR		
Addition of a new Ready to Use drug product- Argatroban Injection in strength of 50 mg/50 mL (1 mg/mL).		
9. PHARMACOLOGICAL CATEGORY	**10. HOW DISPENSED**	**11. RELATED IND, NDA, DMF**
Anti-coagulant	Rx	
12. DOSAGE FORM	**13. POTENCY**	
Injection	250 mg/2.5 mL (100 mg/mL) requiring dilution to 1 mg/mL Proposed: Ready to use 50 mg/50 mL (1mg/mL)	
14. CHEMICAL NAME AND STRUCTURE		

Argatroban



Chemical name: (b) (4)

Molecular formula: (b) (4)

Molecular Weight: (b) (4)

Indicated for treatment of thrombosis after heparin induced thrombocytopenia (HIT), and as an anticoagulant in patients with or at risk for HIT undergoing percutaneous coronary intervention.

15. COMMENTS

In the subject PAS labeling supplement S-004, the applicant proposed to introduce a Ready to Use drug product- Argatroban Injection 50 mg/50 mL (1 mg/mL) in 0.9% sodium chloride. The proposed drug product is a 1/100 dilution of the currently approved drug product, Argatroban Injection 250 mg/2.5 mL (100 mg/mL).

In the first cycle review, the S-004 was given a CR on 26-Oct-2015 with 6 deficiencies, three of which were CMC related deficiencies and three were Biopharm related comments. **The applicant provided adequate responses** to the CR in the amendment dated 31-Mar-2016 (RESUB-045). The CR deficiencies and the applicant's responses are reproduced below in the review notes.

In addition, it should be noted that during the first cycle review there were two deficiencies noted by the Microbiology reviewer Dr. Jonathan Swoboda in his review on 18-Nov-2015 **that were not included in the CR letter**. The Micro deficiencies were communicated subsequently via email on 26-Jul-2016 and thus the applicant

did not address them in the amendment dated 31-Mar-2016 (RESUB-045). A separate amendment with responses to Micro deficiencies was submitted in RESUB-51 on 28-Jul-2016 that **was found to be adequate by Micro reviewer Dr. Swoboda (Micro review dated 02-Aug-2016).**

The CMC related Sections in the PI, namely the Highlights of prescribing information, Dosage forms and strengths, Dosage and administration, Description, and How supplied/storage and handling were reviewed and comments relevant for the proposed 50 mg/50 mL Ready to Use strength were entered in Sharepoint on 09-Aug-2016.

The proposed container and carton labels submitted in the amendments for the proposed Ready to Use strength were reviewed and comments were entered in the Sharepoint (on 09-Aug-2016) to be communicated to the applicant. The proposed container and carton labels are reproduced below in this review for reference. It should be noted that the applicant proposed to label the Ready to Use strength as "Single Use Vial". The CMC recommendation is to change the labeling of package type term to "**Single Dose Vial**" since the Agency is getting rid of the term "single-use" per the Draft Guidance "Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use" published in October 2015. This is to promote consistent use of correct package type terms.

In response to the Agency comments, the applicant revised the PI namely in the Highlights of prescribing information, Dosage forms and strengths, Dosage and administration, Description, and How supplied/storage and handling sections in the labeling amendments submitted on 16-Sep-2016 and 19-Sep-2016. The changes incorporated in the latest labeling amendment are adequate from the CMC review perspective.

The container and closure labels for the 50 mg RTU presentation were also revised to state "Single Dose Vial" as recommended. The revised container and carton labels from the latest amendment are reproduced below in this review for reference.

16. CONCLUSION AND RECOMMENDATION

The information submitted in the PAS as amended is adequate from the CMC, Biopharm and Microbiology perspectives. The supplement as amended is recommended for Approval.

17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
Pallaiah Thammana	See electronic signature sheet	19-Sep-2016

DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE
DHP

AP

Chemist's Review Notes

Background

The original NDA 203-049 was approved as a 505 (b) (2) application that relied on safety and effectiveness for Pfizer's Listed Drug Argatroban Injection under the approved NDA 20-883.

In the subject PAS labeling supplement S-004, the applicant proposed to introduce a Ready to Use Argatroban Injection (1 mg/mL) in 0.9% sodium chloride. The proposed drug product is a 1/100 dilution of the currently approved drug product, Argatroban Injection 250 mg/2.5 mL (100 mg/mL), in 0.9% sodium chloride. The applicant claimed that the ready to use Argatroban Injection is (b) (4) to the reference drug product, Argatroban Injection 250 mg/2.5 mL (100 mg/mL), when diluted in 0.9% Sodium Chloride Injection. [The approved drug product is supplied as a sterile, clear, and colorless to pale yellow solution in 5 mL single-use, clan amber glass vials. Each mL contains 100 mg Argatroban, (b) (4) mg dehydrated alcohol, and 520 mg propylene glycol in Water for Injection. The Argatroban Injection 250 mg/2.5 mL (100 mg/mL) must be diluted prior to infusion in 0.9% Sodium Chloride Injection, 5% Dextrose Injection, or Lactated Ringer's Injection to a final concentration of 1 mg/mL. Specifically, the labeling instructs the practitioner to 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 Injection, or Lactated Ringer's Injection to a final concentration of 1 mg/mL].

CMC deficiencies in CR letter dated 26-Oct-2015 are reproduced below in Bold and applicant's responses in the amendment RESUB-45 are reproduced in Italics:

CR Deficiency # 1: The analytical method QCTM-047-04 for the proposed lower strength product, Ready to Use Argatroban Injection (1 mg/mL), is not acceptable due to its inadequate method validation report, (b) (4)

- **Provide a complete validation report for the revised analytical methods QCTM- 047-04, for the proposed lower strength product, Ready to Use Argatroban Injection (1 mg/mL), including specificity, linearity, range, accuracy (with recovery), precision, detection limit, quantitation limit, robustness, and system suitability testing. Refer to ICH Q2A Text on *"Validation of Analytical Procedures and ICH Q2B Validation of Analytical Procedures: Methodology."***

- **The above validation report should include raw experimental data, calculation results, and acceptance criteria for each validation parameter along with acceptable chromatograms (i.e. there should be a baseline separation between peaks). For method validation report format, refer to the earlier method validation reports by (b) (4) for test method number: CO-AN-013-R1 submitted in NDA 203049/S-000 and NDA/S-002 for Determination of Impurities in Argatroban Injection (100 mg/mL) by HPLC.**

- **In addition, provide justification with comparative supporting data for the changes made to the method QCTM-047-02 (refer to #CCR/QC/2014/029) as summarized in P.9 of QCTM-047-04 for testing samples for drug product in 100 mg/mL strength and the proposed drug product in 1 mg/mL strength. Confirm when the changes were submitted to the Agency for review (refer to #CCR/QC/2014/029).**

Applicant's response:

Exela's Ready to Use Argatroban Injection, 1 mg/mL is tested for assay and related compounds (impurities) according to test methods QCTM-046-03, "Determination of Assay of Argatroban in Argatroban Injection (100 mg/mL or 1 mg/mL) by High Performance Liquid Chromatography" and QCTM-047-04, "Determination of Impurities in Argatroban Injection (100 mg/mL or 1 mg/mL) by HPLC".

The HPLC methodologies for determination of assay and determination of impurities in Argatroban Injection (100 mg/mL) drug product were developed and validated at (b) (4) *. The analytical validation reports for the determination of assay and the determination of impurities as submitted and approved in the original NDA are provided with this response for the reviewer's efficiency.*

Formal method transfers were executed between (b) (4) *and Exela Pharma Sciences for the determination of assay and determination of impurities in Argatroban Injection (100 mg/mL) drug product to support the addition of Exela Pharma Sciences as an approved testing site for the drug product. This was filed as Supplement 002 to NDA 203049 and was approved on 02/13/2013. For the reviewer's convenience, copies of the method transfer reports for the determination of assay and determination of impurities in Argatroban Injection (100 mg/mL) drug product are provided with this response. Since the approval of the Argatroban Injection (100 mg/mL), Exela has been manufacturing and releasing the Argatroban Injection (100 mg/mL) drug product using the above referenced assay and impurities test methods.*

In April 2015, Supplement 004 was filed to the Division requesting approval of a Ready to Use Formulation of Argatroban Injection (1 mg/mL), specifically, a 1/100 dilution of the current approved Argatroban Injection, 100 mg/mL, in 0.9% sodium chloride. The following table compares the current approved formulation and the proposed diluted presentation.

Comparison of the current Approved Drug Product and Proposed Ready to Use Diluted Presentation

Component	Approved NDA Drug Product	Proposed Ready to Use Diluted Presentation
Vial Size	5 mL	50 mL
Vial Type	(b) (4)	
Fill Volume	2.5 mL	50 mL
Stopper	(b) (4)	
Overseal		
Argatroban / vial	250 mg	50 mg
Argatroban / mL	100 mg/mL	1 mg/mL
Propylene Glycol / mL	520 mg/mL	5.2 mg/mL
Dehydrated Alcohol / mL	304 mg/mL	3.04 mg/mL
Sodium Chloride / mL	None	9 mg/mL
Water for Injection	q.s. to volume	q.s. to volume
Argatroban concentration post labeling dilution with 0.9% Sodium Chloride Injection	1 mg/mL	No dilution. 1 mg/mL
Composition (per mL) Comparison – as Administered (per labeling)		
Argatroban / mL	1 mg/mL	1 mg/mL
Propylene Glycol / mL	5.2 mg/mL	5.2 mg/mL
Dehydrated Alcohol / mL	3.04 mg/mL	3.04 mg/mL
Sodium Chloride / mL	9 mg/mL	9 mg/mL

As demonstrated in the above table, the proposed ready to use product, Argatroban Injection, 1 mg/mL, in 0.9% sodium chloride, is equivalent to the current approved formulation, Argatroban Injection, 100 mg/mL, post labeling dilution with 0.9% Sodium Chloride Injection. Based on the equivalency of the current approved formulation and the proposed ready to use formulation, full method validations of the HPLC methodologies for the determination of assay and the determination of impurities were not deemed necessary. Specifically:

1. No additional method validation work was determined to be required for test method QCTM-046-03, "Determination of Assay of Argatroban in Argatroban Injection (100 mg/mL or 1 mg/mL) by High Performance Liquid Chromatography" as the HPLC injection sample of Argatroban Injection (100 mg/mL) is same as that of the HPLC injection sample of Argatroban Injection (1 mg/mL).

2. Supplemental validation was determined to be required for test method QCTM-047-05, "Determination of Impurities in Argatroban Injection (100 mg/mL or 1 mg/mL) by HPLC", for the determination of impurities in Argatroban Injection 1 mg/mL. Specifically, Limit of Quantitation and Specificity and both the parameters were validated. For the reviewer's convenience, a copy of the supplemental validation report supporting the determination of impurities in Argatroban Injection (1 mg/mL) drug product is provided with this response.

In support the above, a discussion of the justification for the non-necessity of additional validation for the assay method and partial validation for the impurities method are provided below as a direct response to the information request presented by the Division.

Reviewer's evaluation: The applicant's response is adequate. Applicant's suggestion that "*No additional method validation work was determined to be required for test method QCTM-046-03*" is acceptable because the higher strength sample diluted to 1 mg/mL is equivalent to the Ready to use formulation of the proposed strength. This argument that revalidation of assay method is not necessary was noted in the first cycle CMC review following a T-con with the applicant held on 01-Oct-2015. However, the applicant addressed the validation of method for impurity analysis with adequate supporting data and documentation. The data and documents submitted can be found in the attachments to the amendment S-004-RESUB-045.

CR Deficiency # 2: The three-month stability data generated under 40°C/75% RH and 25°C/60% RH storage conditions (for batches XLNH425, XLNH1426, and XLNH1427) do not support the proposed twenty-four (24) months expiration dating period for the proposed lower strength product, Ready to Use Argatroban Injection (1 mg/mL), refer to ICH Q1A(R2), Section 2.2.7.

- **Provide a minimum of 12-month stability data under the long term storage condition (25°C/60% RH) and 6-month stability data under the accelerated storage condition (40°C/75% RH) for three primary batches of the proposed product (1 mg/mL). You may also provide supporting data from batches in 1 mg/mL strength if available.**

Applicant's response:

Six (6) month accelerated (40°C/75% RH) and twelve (12) month long term (25°C/60% RH) stability data for the three primary submission batches of Exela's Ready to Use Argatroban Injection, 1 mg/mL, in 0.9% sodium chloride are provided with this deficiency response.

Reviewer's evaluation: The stability data submitted were reviewed and found to be adequate.

CR Deficiency # 3: Provide updated batch records based on an adequately validated method as required in Comments No. 1 and No. 2.

Applicant's response:

Reference is made to Exela's response for Deficiency 1. The generated data from QCTM-047 is considered valid.

Reviewer's evaluation: Adequate. The applicant adequately responded to the issues raised with method validation for proposed Ready to use strength.

Biopharm deficiencies in CR letter dated 26-Oct-2015 are reproduced below in Bold and applicant's responses are reproduced in Italics:

CR Deficiency # 4: Submit a side-by-side tabular comparison of the physicochemical properties (such as concentration/amount, pH and osmolality) of the proposed drug product and the listed drug, before and after dilution or reconstitution.

Applicant's response:

The physicochemical properties for Exela's Ready to Use Argatroban Injection (1 mg/mL) in 0.9% sodium chloride are comparable to Argatroban Injection 250 mg/ 2.5 mL (100 mg/mL) diluted in 0.9% Sodium Chloride Injection per the current NDA approved labeling, as reported in the table below.

Physicochemical Properties of Argatroban Injection (100 mg/mL), Argtroban Injection (100 mg/mL) Diluted with 0.9% Sodium Chloride Injection (per current approved labeling) and Proposed Ready to Use Argatroban Injection (1 mg/mL) in 0.9% sodium chloride

	Argatroban Injection (100 mg/mL)	Argtroban Injection (100 mg/mL) Diluted with 0.9% Sodium Chloride Injection (per current approved labeling)	Proposed Ready to Use Argatroban Injection (1 mg/mL) in 0.9% sodium chloride
Argatroban Concentration	100 mg/mL	1 mg	1 mg
Appearance/Description	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution
pH	(b) (4)	5.5	(b) (4)
Osmolality	(b) (4)		

CR Deficiency # 5: Submit a side-by-side tabular comparison of the qualitative and quantitative composition of the proposed product and the reference product.

Applicant's response:

The table below provides a side-by-side qualitative and quantitative composition of Argatroban Injection 250 mg/ 2.5 mL (100 mg/mL), the reference drug product, Argatroban Injection 250 mg/ 2.5 mL (100 mg/mL) diluted in 0.9% saline per the current NDA approved labeling, and proposed drug product, Exela's Ready to Use Argatroban Injection (1 mg/mL) in 0.9% sodium chloride. As shown in the table, Exela's Ready to Use Argatroban Injection (1 mg/mL) in 0.9% sodium chloride is an exact qualitative and quantitative match to Argatroban Injection 250 mg/ 2.5 mL (100 mg/mL) diluted in of 0.9% Sodium Chloride Injection per the current NDA approved labeling.

Qualitative and Quantitative Composition of Argatroban Injection (100 mg/mL), Argtroban Injection (100 mg/mL) Diluted with 0.9% Sodium Chloride Injection (per current approved labeling) and Proposed Ready to Use Argatroban Injection (1 mg/mL) in 0.9% sodium chloride

Component	Argatroban Injection (100 mg/mL)	Argtroban Injection (100 mg/mL) Diluted with 0.9% Sodium Chloride Injection (per current approved labeling)	Proposed Ready to Use Argatroban Injection (1 mg/mL) in 0.9% sodium chloride
Argatroban	100 mg	1.0 mg	1.0 mg
Dehydrated Alcohol (b) (4)	304 mg	3.04 mg	3.04 mg
Propylene Glycol (b) (4)	520 mg	5.2 mg	5.2 mg
Sodium Chloride	N/A	9 mg	9 mg
Water for Injection	(b) (4)		

Reviewer's evaluation: Adequate. See Biopharm review by Dr. Om Anand for details (10-Aug-2016).

CR Deficiency # 6: Include a biowaiver request with supporting data/information in your resubmission; in particular, submit data demonstrating that the physiologic disposition of Argatroban is similar between the proposed and the reference product.

Applicant's response:

The biowaiver request for Exela's Ready to Use Argatroban Injection (1 mg/mL) in 0.9% sodium chloride is provided in Module 1 of this deficiency response.

Reviewer's evaluation: The response to Biowaiver request is Adequate. See Biopharm review by Dr. Om Anand for details (10-Aug-2016).

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

Reviewer's evaluation:

The proposed container and carton labels for Ready to Use strength 50 mg/50 mL are reproduced above in this review for reference.

The proposed container and carton labels submitted in the amendments for the Ready to Use strength were reviewed and comments were entered in the Sharepoint to be communicated to the applicant.

It should be noted that the applicant proposed to label the Ready to Use 50 mg/50 mL strength as "Single Use Vial" (see the highlighted text in the labels reproduced above). The CMC recommendation is to change the labeling of package type term to Single Dose Vial since the Agency is getting rid of the term "single-use" per the Draft Guidance "Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use", published in October 2015. This is to promote consistent use of correct package type terms.

See below for the revised Container and Carton labels reproduced from S-004-RESUB-052 (19-Sep-2016)

Revised Container and Carton labels reproduced from S-004-RESUB-052 (19-Sep-2016)

Revised Container Label

Revised Carton Label

Evaluation: Adequate. The requested change to "Single Dose Vial" was made to the revised labels (for clarity of the reviewer the revision is highlighted in the labeling text).

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Ramesh Raghavachari -S

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Office of Life Cycle Drug Product
Division of Post Marketing Activities I (DPMA I)
Review of Chemistry, Manufacturing, and Controls

1. NDA Supplement Number: NDA 203049 / S-004

2. Submissions Being Reviewed

Submission /Type	DARRTS SD Number	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
S-004 Labeling supplement changed from CBE-30 to PAS	40	24-Apr-2015	27-Apr-2015	14-May-2015	27-Oct-2015	22-Oct-2015

3. Proposed Changes: This labeling supplement requests the following:

- Addition of a Ready to Use Argatroban Injection in strength of 1 mg/mL (50 mg/50 mL)

4. Review #: 1

5. Clinical Review Division: DHP

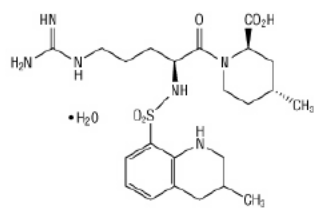
6. Name and Address of Applicant:

Hikma Pharmaceuticals Co. Ltd
Industrial Area
Bayader Wadi El Seer
Amman, Jordan
US Agent: Exela Pharma Sciences
P.O. Box 818; 1325 William White Pl NE
Lenoir, NC 28645

7. Drug Product:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC
Argatroban Injection	injection solution	250 mg/2.5 mL (100 mg/mL)	intravenous	Rx
Ready to Use Argatroban Injection	injection solution	1 mg/mL	intravenous	Rx

8. Chemical name and structure of drug substance:

	**USAN:** Argatroban **Chemical name:** (b) (4) **Molecular formula:** (b) (4) **MW:** (b) (4)

9. Pharmacological Category/Indication: Treatment of thrombosis after heparininduced thrombocytopenia

10. Supporting/Relating Documents: N/A

11. Consults: Facility, Product Quality Microbiology, Biopharmaceutics, and DMEPA

12. Executive Summary

This PAS labeling Supplement was initially submitted as CBE-30 and then was converted to PAS by OND/DHP. The supplement proposes the following: Addition of 1 mg/mL (50 mg/50 mL) presentation to the existing drug product strength (100 mg/mL). The new proposed strength is (b) (4) to the final drug product prepared by the dilution using one of the diluents described in the current approved labeling. Specifically, the proposed presentation is a 1/100 dilution of 100 mg/ml drug product strength in 0.9% sodium chloride Injection.

In support of this PAS Supplement, the following eCTD sections are being submitted:

3.2.P.1	Description and Composition of the Drug Product
3.2.P.2	Pharmaceutical Development
3.2.P.3	Manufacture For All Products
3.2.P.4	Control of Excipients
3.2.P.5	Control of Drug Product
3.2.P.6	Reference Standards and Materials
3.2.P.7	Container Closure System
3.2.P.8	Stability

The Biopharmaceutics review by Dr. Om Anand found deficiencies related to Section P.1 and P.2.Refer to the biopharm review and comments for deficiencies.

The manufacturing process of the ready to use dilution presentation (1 mg/mL) is similar to the currently approved manufacturing process of the Argatroban Injection 250 mg/Vial, 100 mg/mL, with the exception of the addition of sodium chloride. (b) (4) . Also refer to the pending product quality microbiology review for sterility assurance for the proposed manufacturing process.

Though the applicant claims that are no changes to the drug product analytical methods, in addition to the current approved Drug Product Release Specifications, Drug Product Stability Specifications, Drug Substance Release Specifications, Drug Substance Analytical Methods, Drug Product Container Closure System (excepting the vial size), Excipient Specifications (excepting the addition of Sodium Chloride (b) (4)), or sources of the Drug Product excipients (excepting the addition of Sodium Chloride (b) (4)). However, the CMC reviewer found that the HPLC method for determination of impurities in the proposed Ready to Use Argotroban Injection (1 mg/mL) is not acceptable, due to the inadequate validation study for this method.

The CMC reviewer also found it is not adequate for the provided stability data (3-months under both long term and accelerated conditions) to support the proposed 24months shelf life for the proposed drug product.

The product quality microbiology review is pending. Any potential possible information request related to the sterility assurance of the drug product will be conveyed to the applicant separately.

DMEPA has reviewed the proposed labeling and found it acceptable.

13. Conclusions & Recommendations: This supplement is NOT recommended for approval due to the deficiencies in CMC and Biopharmaceutics.

The detailed identified deficiencies are the following:

CMC:

1. *The analytical method QCTM-047-04 for the proposed lower strength product, Ready to Use Argatroban Injection (1 mg/mL), is not acceptable due to its inadequate method validation report,* (b) (4)

    - *Provide a complete method validation report for the revised analytical methods QCTM-047-04, for the proposed lower strength product, Ready to Use Argatroban Injection (1 mg/mL), including specificity, linearity, range, accuracy (with recovery), precision, detection limit, quantitation limit, robustness, and system suitability testing. Refer to ICH Q2A Text on Validation of Analytical Procedures and ICH Q2B Validation of Analytical Procedures: Methodology".*

    - *The above validation report should include raw experimental data, calculation results, and acceptance criteria for each validation along with acceptable chromatograms (i.e. there should be a baseline separation between peaks). For method validation report format, refer to the earlier method validation reports by* (b) (4) *for test method number: CO-AN-013-R1 submitted in NDA 203049/S-000 and NDA/S-002 for Determination of Impurities in Argoatroban Injection (100 mg/mL) by HPLC.*

- *In addition, provide justification with comparative supporting data for the changes made to the method QCTM-047-02 (refer to #CCR/QC/2014/029) as summarized in P.9 of QCTM-047-04 for testing samples for drug product in 100 mg/mL strength and the proposed drug product in 1 mg/mL strength. Confirm when the changes were submitted to the Agency for review (refer to #CCR/QC/2014/029).*

2. *The data provided for 3-months stability under 40°C, 75% RH and 25°C, 60% RH conditions for batches XLNH425, XLNH1426, and XLNH1427, do not support the proposed twenty-four (24) months expiration dating period for the proposed lower strength product, Ready to Use Argatroban Injection (1 mg/mL), refer to ICH Q1A(R2), Section 2.2.7.*

    - *Provide minimum 12-months stability data under 25°C, 60% RH condition and 6-months stability data under accelerated condition from three primary batches of the proposed product (1 mg/mL). You may also provide supporting data from batches in 1 mg/mL strength if available.*

3. *Provide updated batch records based on an adequately validated method as required in Comments No. 1 and No. 2.*

From Biopharmaceutics review:

4. Submit a side-by-side tabular comparison of the physicochemical properties (such as concentration/amount, pH and osmolality) of the proposed drug product and the listed drug, before and after dilution or reconstitution.

5. A separate side-by-side tabular comparison of the qualitative and quantitative composition of the proposed and the reference product.

6. Include a biowaiver request with supporting data/information in your resubmission; in particular, submit data demonstrating that the physiologic disposition of argatroban is similar between the proposed and the reference product.

14. Comments/Deficiencies to be Conveyed to Applicant: None

15. Primary Reviewer: Joyce Crich, Ph.D, CMC reviewer, DPMA I, OLDP, OPQ

16. Secondary Reviewer: Ramesh Raghavachari, Ph.D., Branch Chief for Branch I, DPMA I, OLDP, OPQ

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(b) (4)

Joyce Crich -S

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Ramesh Raghavachari -S

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Initial Quality Assessment - OLDP Division of Post-Marketing Activities I

NDA: 203049	**NME:** Yes☐ No☒	**Original NDA Approval Date:** 01/05/2012
Supplement: 4	**Applicant:** HIKMA PHARM CO LTD	**Product:** Argatroban Injection, 100mg/ml
Clinical Division: DHP		
Managed by: OND ☒ *Efficacy* ☐ *Labeling* ☒		**OPQ** ☐
Receipt Date: April 27, 2015		**PDUFA Goal Date:** October 27, 2015
Proposed changes: addition of a ready to use Argatroban Injection, 1mg/mL, 50mg/50mL.		
Submitted as: Paper ☐ Electronic ☒	Resubmission: Yes☐ No☒ Previous Reviewer:	
Submitted Category: CBE-0☐ CBE-30☒ PA☐		**Final Category:** CBE-0☐ CBE-30☐ PA☒
Expedited Review Requested: Yes☐ No☒	**Drug Shortage:** Yes☐ No☒	**Bundled Supplements:** Yes☐ No☒

Facility Entry/Consults Needed:

Facility Entry: ☒ Micro: ☒ Biopharm: ☒ Pharm/tox: ☐

Statistics: ☐ CDRH: ☐ OPF: ☐ DMEPA: ☒

Other:

DMF Review: ☒ The DMF for the (b) (4) glass vial may need to be reviewed depending on whether sufficient information is provided in the submission.

Comments:

The supplement provides for a ready-to-use dilution presentation of the current approved argatroban drug product. Essentially the full set of CMC information is provided in the submission, even though applicant claims that no changes are proposed to the currently approved drug product release and stability specifications, drug product container closure system (except for the vial size), and excipients (except for the addition of sodium chloride (b) (4)). Changes are proposed in the formulation components and composition, manufacturing process, container closure (vial size). The batch analysis and stability data (three months under both long term and accelerated storage conditions) for three lots of product are provided. Due to the change in formulation composition, reviewer will need to decide whether additional stability data are needed to support the currently approved 24 months shelf life. Also, reviewer will need to determine whether there are any changes made to the analytical procedures and if any additional validation is needed.

Facility (FEI: 3008563008) needs to be entered into Panorama. Also, a waiver request for bioequivalence studies for the new presentation should be submitted. Therefore, biopharmaceutics consult is needed. Product Quality Microbiology and DMEPA consults are also needed.

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Assigned Reviewer: Joyce Crich	**RBPM:** Teicher Agosto

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203049Orig1s004

PHARMACOLOGY REVIEW(S)

Memorandum

Date: September 19, 2016

From: Shwu-Luan Lee, PhD

NDA: 203049 (Argatroban Injection: 50 mg/mL) (Supplement 4, SDN #45)

Applicant: Hikma USA, LLC (c/o Exela Pharmaceuticals as Agent)

Subject: Response to Complete Response letter of October 26, 2015

Regulatory background:
On 04/27/15 Hikma submitted a CMC supplement 004 to NDA 203049 which proposed a lower strength ready-to-use formulation. On 10/26/15, DHP issued a Complete Response based on CMC deficiencies. On 4/01/2016, the Sponsor submitted the response to CR.

There is no new pharmacology/toxicology data in this submission. The current labeling remains in the PLR format. The NDA is recommended for approval from a pharmacology/toxicology perspective.

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/s/

SHWU LUAN LEE
09/19/2016

CHRISTOPHER M SHETH
09/20/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203049Orig1s004

MICROBIOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 02 August 2016

TO: File: NDA 203049

FROM: Jonathan G. Swoboda, PhD, RAC
Microbiology Reviewer
CDER/OPQ/OPF/Division of Microbiology Assessment

THROUGH: Jessica Cole, PhD
Quality Assessment Lead (Acting)
CDER/OPQ/OPF/Division of Microbiology Assessment

SUBJECT: Microbiology Review of NDA 203049-Suppl-004 (CBE-30) amendment containing responses to microbiology deficiencies
Received Date: 29 July 2016
Drug Product: Argatroban Injection, 100 mg/ml and 1 mg/mL
Applicant: Hikma Pharmaceuticals Co. Ltd.
U.S. Agent: Exela Pharma Sciences, LLC

Reviewer's conclusion: The subject CBE-30 Supplement **is recommended** for approval based on product quality microbiology.

Background: The applicant submitted a CBE-30 Supplement proposing the production of a ready-to-use formulation of the subject drug product in single-use vials for intravenous infusion in the submission dated 24 April 2015. Prior to completion of the microbiology review, the Agency sent a Complete Response letter to the applicant dated 26 October 2015. The microbiology review was completed on 18 November 2015, and deficiencies were provided to the project manager with instructions indicating the applicant should reply to the microbiology deficiencies when responding to the Complete Response letter. The response to the Complete Response letter was received on 1 April 2016; however, the microbiology deficiencies were not found in this submission. The applicant subsequently received the microbiology deficiencies in an email dated 26 July 2016. The review below evaluates the applicant's responses to the microbiology deficiencies received in the 29 July 2016 submission. The original questions are italicized, and the applicant's responses are summarized.

Microbiology Deficiencies:

1. *Page 4 of 175 in the document entitled, "product-process-validation.pdf" indicates that the* (b) (4) *validation studies are for Palonosetron Hydrochloride. However, the subject drug*

product is Argatroban Injection 1 mg/mL. Explain this discrepancy.

Summary of applicant's response: The applicant indicates this was a typographical error, and provides an updated version of this document with the appropriate correction.

Acceptable

(b) (4)

[redacted]

END

Jonathan Swoboda -S

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Jessica Cole -S

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 18 November 2015

TO: File: NDA 203049

FROM: Jonathan G. Swoboda, PhD, RAC
Microbiology Reviewer
CDER/OPQ/OPF/Division of Microbiology Assessment

THROUGH: John W. Metcalfe, PhD
Quality Assessment Lead (Acting)
CDER/OPQ/OPF/Division of Microbiology Assessment

SUBJECT: Microbiology Review of NDA 203049-Suppl-004 (CBE-30)
Submission Date: 24 April 2015
Drug Product: Argatroban Injection, 100 mg/ml and 1 mg/mL
Applicant: Hikma Pharmaceuticals Co. Ltd.
U.S. Agent: Exela Pharma Sciences, LLC

Reviewer's conclusion: The subject CBE-30 Supplement **is not recommended** for approval on the basis of sterility assurance.

Background: The applicant proposes the production of a ready-to-use formulation of the subject drug product in a single-use vial for intravenous infusion. The drug product is approved as a 100 mg/mL unpreserved, sterile solution that needs to be diluted in labeled-specified diluents prior to use. (b) (4) . The approved configuration of the subject drug product is manufactured using (b) (4) sterilization with (b) (4) . The proposed configuration uses an equivalent manufacturing process; however, the formulation is different from that which is currently approved. The applicant has provided a comparison of the two configurations, which is reproduced below from page 3 of 6 in the document entitled, "cover-letter.pdf." On the same page, the applicant confirms that "There are **no changes** to the approved specifications of the Drug Product, or test methods."

Comparison of the current Approved Drug Product and Proposed Ready to Use Diluted Presentation

Component	Approved NDA Drug Product	Proposed Ready to Use Diluted Presentation
Vial Size	5 mL	50 mL
Vial Type	(b) (4)	
Fill Volume	2.5 mL	50 mL
Stopper	(b) (4)	
Overseal		
Argatroban / vial	250 mg	50 mg
Argatroban / mL	100 mg/mL	1 mg/mL
Propylene Glycol / mL	520 mg/mL	5.2 mg/mL
Dehydrated Alcohol / mL	304 mg/mL	3.04 mg/mL
Sodium Chloride / mL	None	9 mg / mL
Water for Injection	q.s. to volume	q.s. to volume
Argatroban concentration post labeling dilution	1 mg/mL	No dilution. 1 mg/mL

The applicant has provided an extensive description of the comparison of the manufacturing processes of both configurations on page 4 of 6 in the document entitled, "cover-letter.pdf." Based on this comparison validation studies are required for the (b) (4) sterilization of the larger vial size (i.e., 5 mL to 50 mL vials).

The tracked changes revision to the package insert did not contain any modification that would alter sterility assurance. (b) (4) . Specific pediatric dosing information is not provided in the package insert, other than indicating it is "lower for seriously ill pediatric patients compared to adults with normal hepatic function" (b) (4) On page (b) (4), the applicant indicates that safety and efficacy has not been established in pediatric patients. Since pediatric use has not been previously reviewed by the Agency, microbiology post-dilution hold studies will not be requested.

Reviewer's comment: The applicant has two facilities approved for making the concentrated form of the drug product [i.e., (b) (4) and Exela Pharma Sciences (Lenoir, NC)]. The application clearly indicates that the manufacturing of the ready-to-use formulation will take place at the Lenoir, NC facility.

Microbiology Review:

(b) (4)

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3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

NDA: 203049 APPLICANT: Hikma Pharmaceuticals Co. Ltd.

DRUG PRODUCT: Argatroban Injection, 100 mg/ml and 1 mg/mL

Microbiology Deficiencies:

1. Page 4 of 175 in the document entitled, "product-process-validation.pdf" indicates that the (b) (4) validation studies are for Palonosetron Hydrochloride. However, the subject drug product is Argatroban Injection 1 mg/mL. Explain this discrepancy.

(b) (4)

END

Jonathan Swoboda -A

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John W. Metcalfe -A

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203049Orig1s004

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW **Division of Biopharmaceutics/Office of New Drug Products**			
Application No.:	NDA 203049/S-004	**Reviewer:** Om Anand, Ph.D.	
Submission Date:	April 24, 2015 (Original) March 31, 2016 (resubmission)		
Division:	Division of Hematology Products (DHP)	**Acting Biopharmaceutics Lead:** Okpo Eradiri, Ph.D.	
Applicant:	Exela Pharma Sciences.	**Acting Branch Chief:** Angelica Dorantes, Ph.D.	
Trade Name:	Argatroban Injection	**Date Assigned:**	June 21, 2016
Established Name:	Argatroban Injection	**Date of Review:**	August 08, 2016
Indication:	Prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia; for heparin induced thrombocytopenia undergoing percutaneous coronary intervention (PCI)	**Type of Submission:** Prior Approval Supplement (PAS), labeling	
Formulation/ strengths	Injection, 1 mg/mL (ready to use)		
Route of Administration	Intravenous, Infusion		
Type of Review:	Biowaiver Request for a new ready to use formulation of Argatroban Injection (1 mg/mL)		

BIOPHARMACEUTICS REVIEW SUMMARY:

Background: Exela Pharma Sciences previously submitted NDA 203-049 for Argatroban Injection 100 mg/mL. This 505 (b)(2) application relied for approval on FDA's findings of safety and effectiveness for the Listed Drug, Argatroban Injection marketed by Pfizer under the approved NDA 20-883. According to the provided information, the Office of New Drug Quality Assessment (ONDQA)-Biopharmaceutics granted biowaiver for the proposed Argatroban Injection[1].

Submission: In the current "Prior Approval" labeling supplement (PAS) [S-004], the Applicant introduced a Ready to Use Argatroban Injection (1 mg/mL) in 0.9% sodium chloride. The original submission [S-004: April 24, 2015] was found inadequate due to CMC issues[2]. The Applicant was also recommended to submit a biowaiver request with supporting data/information in the resubmission. The resubmission [March 31, 2016] contains a biowaiver request for the proposed Ready to Use Argatroban Injection (1 mg/mL) in 0.9% sodium chloride. The supplement also includes comparison of the qualitative and quantitative composition and the physicochemical properties of the proposed drug product and the approved product.

Review: The Biopharmaceutics review is focused on the evaluation and acceptability of the biowaiver request for Exela's Ready to Use Argatroban Injection (1 mg/mL) in 0.9% sodium chloride.

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 203049/S-04 for Exela's Ready to Use Argatroban Injection (1 mg/mL) in 0.9% sodium chloride is recommended for **APPROVAL**.

Note that the CMC aspects of the proposed changes will be reviewed by the CMC Reviewer.

Om Anand -S
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Signature

Om Anand, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products/OPQ

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Signature

Okpo Eradiri, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products/OPQ

[1] DARRTS: NDA-203049: REV-QUALITY-03(General Review): Original-1: 11/21/2011: LAKHANI, DEEPIKA
[2] DARRTS: NDA-203049: COR-SNDAACTION-10(Complete Response): Supplement-4 (Labeling): 10/26/2015: BAIRD, AMY C

BIOPHARMACEUTICS ASSESSMENT

In the current "Prior Approval" labeling supplement (PAS) [S-004], the Applicant introduced a Ready to Use Argatroban Injection (1 mg/mL) in 0.9% sodium chloride. The approved drug product is supplied as a sterile, clear, and colorless to pale yellow solution in 5 mL single-use, clan amber glass vials. Each mL contains 100 mg Argatroban, (b) (4) mg dehydrated alcohol, and 520 mg propylene glycol in Water for Injection.

The label of the drug product states that Argatroban Injection 250 mg/2.5 mL (100 mg/mL) must be diluted prior to infusion in 0.9% Sodium Chloride Injection, 5% Dextrose Injection, or Lactated Ringer's Injection to a final concentration of 1 mg/mL. Specifically, the labeling instructs the practitioner to 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 Injection, or Lactated Ringer's Injection to a final concentration of 1 mg/mL.

The proposed drug product, ready to use Argatroban Injection (1 mg/mL) in 0.9% sodium chloride, is a 1/100 dilution of the currently approved drug product, Argatroban Injection 250 mg/2.5 mL (100 mg/mL), in 0.9% sodium chloride. The Applicant claimed that the ready to use Argatroban Injection (1 mg/mL) in 0.9% sodium chloride, is (b) (4) to the reference drug product, Argatroban Injection 250 mg/2.5 mL (100 mg/mL), when diluted in 0.9% Sodium Chloride Injection as required by and according to the current NDA approved labeling.

Comparison of the approved drug product (reference) and the proposed Ready to Use Argatroban Injection (1 mg/mL) in 0.9% sodium chloride is presented in table 1 below:

Table 1: Comparison of the current approved drug product (reference) and proposed Ready to Use Argatroban Injection (1 mg/mL) in 0.9% sodium chloride

Component	Approved Drug Product (Reference)	Proposed Ready to Use Argatroban Injection (1 mg/mL) in 0.9% sodium chloride
Vial Size	5 mL	50 mL
Vial Type	(b) (4)	
Fill Volume	2.5 mL	50 mL
Stopper	(b) (4)	
Overseal		
Argatroban / vial	250 mg	50 mg
Argatroban / mL	100 mg/mL	1 mg/mL
Propylene Glycol / mL	520 mg/mL	5.2 mg/mL
Dehydrated Alcohol / mL	304 mg/mL	3.04 mg/mL
Sodium Chloride / mL	None	9 mg / mL
Water for Injection	q.s. to volume	q.s. to volume
Argatroban concentration post labeling dilution	1 mg/mL	No dilution. 1 mg/mL

Table 2 below provides a side-by-side qualitative and quantitative composition of Argatroban Injection 250 mg/ 2.5 mL (100 mg/mL), the reference drug product, Argatroban Injection 250 mg/ 2.5 mL (100 mg/mL) diluted in 0.9% Sodium Chloride Injection per the current NDA approved labeling, and the proposed drug product, Exela's ready to use Argatroban Injection (1 mg/mL) in 0.9% sodium chloride.

Table 2: Qualitative and quantitative composition of Argatroban Injection (100 mg/mL), Argatroban Injection (100 mg/mL) diluted with 0.9% Sodium Chloride Injection (per current approved labeling) and proposed Ready to Use Argatroban Injection (1 mg/mL) in 0.9% sodium chloride

Component	Argatroban Injection (100 mg/mL)	Argtroban Injection (100 mg/mL) Diluted with 0.9% Sodium Chloride Injection (per current approved labeling)	Proposed Ready to Use Argatroban Injection (1 mg/mL) in 0.9% sodium chloride
Argatroban	100 mg	1.0 mg	1.0 mg
Dehydrated Alcohol, (b) (4)	304 mg	3.04 mg	3.04 mg
Propylene Glycol, (b) (4)	520 mg	5.2 mg	5.2 mg
Sodium Chloride,	N/A	9 mg	9 mg
Water for Injection	(b) (4)		

The physicochemical properties for Exela's Ready to Use Argatroban Injection (1 mg/mL) in 0.9% sodium chloride and Argatroban Injection 250 mg/ 2.5 mL (100 mg/mL) diluted in 0.9% Sodium Chloride Injection are presented below in table 3.

Table 3: Physicochemical properties of Argatroban Injection (100 mg/mL), Argatroban Injection (100 mg/mL) diluted with 0.9% Sodium Chloride Injection (per current approved labeling) and proposed Ready to Use Argatroban Injection (1 mg/mL) in 0.9% sodium chloride

	Argatroban Injection (100 mg/mL)	Argtroban Injection (100 mg/mL) Diluted with 0.9% Sodium Chloride Injection (per current approved labeling)	Proposed Ready to Use Argatroban Injection (1 mg/mL) in 0.9% sodium chloride
Argatroban Concentration	100 mg/mL	1 mg	1 mg
Appearance/Description	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution
pH	(b) (4)	5.5	(b) (4)
Osmolality	(b) (4)		

(b) (4)

Overall Reviewer's Assessment: **SATISFACTORY**

- According to CFR 320.22(b), for certain drug products the in vivo bioavailability (BA) or bioequivalence (BE) of the drug product may be self-evident and the Agency can waive the requirement for the submission of in vivo BA/BE data of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident if the drug product meets the following criteria:

  "It is a parenteral solution intended solely for administration by injection, and contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application."

- The proposed drug product is a parenteral solution for administration by injection, and the proposed drug product has the same active ingredient (Argatroban), same inactive ingredients, and has the same dosage form, route of administration and indication as the currently approved drug product, Argatroban Injection 250 mg/Vial, 100 mg/mL.

- The physicochemical properties of the proposed Ready to Use Argatroban Injection (1 mg/mL) in 0.9% sodium chloride are comparable to Argatroban Injection 250 mg/ 2.5 mL (100 mg/mL) diluted in 0.9% Sodium Chloride Injection.

- Therefore, the Applicant's request for a waiver of the in vivo study for their proposed product**,** Ready to Use Argatroban Injection (1 mg/mL) in 0.9% sodium chloride is granted.

Recommendation:

From the Biopharmaceutics perspective, NDA 203049/S-04 for Exela's Ready to Use Argatroban Injection (1 mg/mL) in 0.9% sodium chloride is recommended for APPROVAL.

Note that the CMC aspects of the proposed changes will be reviewed by the CMC Drug Product Reviewer.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203049Orig1s004

OTHER REVIEW(S)

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

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

Memorandum

Date: 09/21/16

To: Amy Tilley, Regulatory Project Manager
Division of Hematology Products (DHP)

From: Rachael Conklin, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Susannah O'Donnell, Team Leader (Acting), OPDP

Subject: Comments on draft labeling (Package Insert, Carton/Container Labeling) for ARGATROBAN Injection for intravenous use
NDA 203049 S-4

In response to your labeling consult request dated June 21, 2016, we have reviewed the draft Package Insert for ARGATROBAN Injection for intravenous use (Argatroban) that includes updates based on S-4. This review is based upon the version of the draft PI emailed to OPDP on September 19, 2016 and the Carton and Container Labeling emailed to OPDP on September 16, 2016.

We acknowledge that this is a supplement for an approved product; however, some of our comments included within this review apply to existing sections of the labeling that are already approved.

If you have any questions, please contact Rachael Conklin at (240) 402-8189 or Rachael.Conklin@fda.hhs.gov.

PI

Section	**Statement from Draft (if applicable)**	**OPDP Comment**
HIGHLIGHTS OF PRESCRIBING INFORMATION: ADVERSE REACTIONS	• "HIT patients: The most common (>5%) adverse reactions were dyspnea, hypotension, fever, diarrhea, sepsis, and cardiac arrest (6.1)"	We note that "Overall Bleeding" is listed in Table 4 at a rate of 5.3%. Should "Overall Bleeding" be included in the list of the most common Adverse Reactions >5% in HIT patients? If not, should a caveat be added to specify that these are the most common *non-hemorrhagic* reactions? I.e.:

		"HIT patients: The most common (>5%) non-hemorrhagic adverse reactions were . . ."
	• "Heparin: Allow sufficient time for heparin's effect on **aPTT** to decrease before initiating Argatroban Injection therapy. (7.1)" (emphasis added) • "Warfarin: Concomitant use results in increased prolongation of **PT** and **INR**. (7.2)" (emphasis added)	OPDP notes that the acronyms aPTT, PT, and INR are not defined at the time of first use. OPDP recommends defining acronyms at the time of first use in order to ensure clarity of the concepts being presented.
14.1 Heparin-Induced Thrombocytopenia	"There was a **significant** improvement in the composite outcome in patients with HIT and HITTS treated with argatroban versus those in the historical control group (see Table 9)." (emphasis added) "Time-to-event analyses showed **significant** improvements in the time-to-first event in patients with HIT or HITTS treated with argatroban versus those in the historical control group." (emphasis added)	As it is currently written the phrasing "significant improvement(s)" is vague and promotional in tone. Were these "significant" improvements statistically significant? If so, OPDP recommends revising to clarify (i.e., to state "statistically significant" and to include the p value). If these improvements were not statistically significant, OPDP recommends deleting the word "significant" in order to be consistent with the recommendations made in the Labeling Review Tool and to remove promotional implications.
17 Patient Counseling Information		OPDP recommends revising this section of the PI to ensure consistency with the Guidance for Industry *Patient Counseling Information Section of Labeling for Human Prescription Drugs and Biological Products—Content and Format* dated December, 2014. Specifically, this section should be revised to include subheadings in order to allow the reader to quickly identify the major concepts. For example: Risk of Hemorrhage

		Advise patients to report the use of any other products know to affect bleeding. . . . Allergic Reactions Advise patients to report the occurrence of any signs or symptoms of allergic reactions . . .

Carton/Container Labeling

OPDP acknowledges and concurs with the August 22, 2016, review of the carton and container labeling by the Division of Medication Error Prevention and Analysis (DMEPA) and has no additional comments on the carton and container labeling.

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/s/

RACHAEL E CONKLIN
09/21/2016

Division of Hematology Products (DHP) Labeling Review

NDA Number	**203049, S-004**
Supporting Document Number	**45**
Nonproprietary name	**Argatroban Injection** **505(b)2**
Receipt Date	**04/01/16**
PDUFA Goal Date	**10/01/16**
Review Classification	**Response to CR (issued 10/25/16)**
Proposed Indication (or current indication if unchanged)	**Current:** Argatroban is a direct thrombin inhibitor indicated: • For prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT) • As an anticoagulant in adults patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI)
Dosing Regimen	<u>Heparin-Induced Thrombocytopenia</u> The dose for heparin-induced thrombocytopenia without hepatic impairment is 2 mcg/kg/min administered as a continuous infusion. <u>Percutaneous Coronary Intervention</u> The dose for patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention is started at 25 mcg/kg/min and a bolus of 350 mcg/kg administered via a large bore intravenous line over 3 to 5 minutes.
From	**Virginia Kwitkowski, MS, ACNP-BC** **Associate Director for Labeling, DHP**

Background of Application:

This Argatroban Injection is a 505(b)2 from Hikma (c/o Exela Pharmaceuticals as Agent) originally approved on 01/05/12 and referenced the originator Pfizer product.

History of S-004: On 04/27/15 Hikma submitted a CMC supplement 004 to NDA 203049 which proposed a lower strength ready-to-use formulation. On 10/26/15, DHP issued a Complete Response based on CMC deficiencies (see CR letter for S-004).

On 04/01/16, Hikma submitted their response to CR to the Agency. This review is regarding that submission. This supplement is managed by DHP.

In this review, I propose labeling recommendations and edits in the Argatroban Injection (Hikma) labeling to ensure that the prescribing information is a useful communication tool for healthcare providers and uses clear, concise language; is based on regulations and guidances; and conveys the essential scientific information needed for the safe and effective use of Argatroban Injection.

Upon receipt, Amy Tilley (DOP1 RPM) sent a consult to OSE requesting that DMEPA review the labeling changes. During the review, the DMEPA reviewer TingTing Gao, identified discrepancies in the labeling with regard to whether this drug had a pediatric indication. I was notified of this discrepancy and evaluated the labeling for compliance with existing labeling regulations and guidances.

Dr. Ann Marie Trentacosti and Dr. Eric Brodsky (Labeling Development Team) collaborated on the review and revision of the Pediatric Use labeling for this product.

Labeling Recommendations

Per 21CFR201.57(c)(2)(F)(iv), "indications or uses must not be implied or suggested in other sections of the labeling if not included in this section." As currently approved, there is a recommended dose for pediatric dosing, which could be misinterpreted as an implied pediatric indication. The labeling was revised to remove language that may imply a pediatric indication that this product does not have.

Other revisions were made to the labeling to the label to ensure compliance with regulations and guidances. The changes made to the labeling are summarized below:

1. Per the Guidance for Industry: Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling, "when it is determined that evidence is insufficient to support a pediatric indication, all relevant pediatric information related to the unapproved use should be placed only in USE IN SPECIFIC POPULATIONS, Pediatric Use, except where required by law, so as not to imply an approved pediatric indication. If a specific risk has been identified for pediatric patients, the risk information must be placed in the Pediatric Use subsection or, if appropriate, in the Contraindications section or the WARNINGS AND PRECAUTIONS section, as required by regulation (21CFR 201.57(C)(9)(iv)(E))."

   Accordingly, pediatric information was removed from Section 2, to avoid the implication of a pediatric indication. Section 8.4 has been reworded to avoid the appearance of a pediatric indication or recommended dose.

2. The product title was revised to reflect best labeling practice. The chemical portion of the non-proprietary name should appear in upper case for a consistent presentation for all product titles for products without a proprietary name.

3. Per the Adverse Reactions Guidance, adverse Reactions identified from clinical trials must be a separate listing from AR identified from domestic and foreign spontaneous reports. Each listing must be captured under a separate subsection heading depending on the **nature of the report** (either Clinical Trials Experience or Postmarketing Experience). Section 6 had adverse reactions from clinical trials spread out between 6.1, 6.2, 6.3, and 6.4. There were no post-marketing adverse reactions listed. Section 6 was revised to include all clinical trial adverse reactions in subsection 6.1.

4. Per the FDA Draft Guidance: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple -Dose, Single-Dose, and Single-Patient-Use Containers for Human Use, the Agency recommends consistent use of the appropriate package terms and discard statements. Appropriate package terms for describing containers for injectable drugs for parenteral administration (e.g., intravenous use, subcutaneous use, intramuscular use) are:

   *single-dose: intended for single use for one patient

   **single-patient use: intended to be used multiple times for a single patient

   ***multiple-dose: for multiple patient uses (e.g., single patient or multiple patients)

   The appropriate package term for this product is “Single-Dose”. Single-use was revised to single-dose throughout labeling.

5. For all sections of the Full Prescribing Information, when a subsection heading is used, capture all information under a subsection heading. For example, labeling should not include information between Section 2 and subsection 2.1 or Section 5 and subsection 5.1. However, this does not apply when listing serious adverse reactions described elsewhere in labeling (i.e., between section 6 ADVERSE REACTIONS and subsection 6.1 Clinical Trials Experience. Text included between sections and subsections may not be captured by electronic labeling information providers.
   There were several sections in the Argatroban Injection labeling where text was present between the section heading and the first subsection; this text was relocated to within subsections.

6. Per 21CFR201.57: This section must describe the overall adverse reaction profile of the drug based on the entire safety database. For purposes of prescription drug labeling, an adverse reaction is an undesirable effect, reasonably associated with use of a drug that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.

Within section 6 (Adverse Reactions) the term adverse event was used multiple times. The term "adverse events" were updated to "adverse reactions" where appropriate.

7. The format of several cross-references was corrected.

8. Per the 'Patient Counseling Section of Labeling Guidance', a cross-reference should be inserted to direct the health care provider to the more detailed discussion elsewhere in labeling. The Patient Counseling section (17) had no cross-references to sections of labeling that contain details of the issue. I revised this section to add cross-references to the locations where more detailed information were located.

The following pages contain the working version of the Argatroban Injection labeling with recommended edits and comments from me identified as the comments 'VK1' through 'VK17'). This labeling version also includes comments from other members of the review team and Dr. Brodsky and Dr. Trentacosti.

Given that the scientific review of the labeling is ongoing, my labeling recommendations in this review should be considered preliminary and may not represent DHP's final recommendations for the Argatroban Injection labeling.

Recommended Action for other argatroban labels: *I recommend that once action is taken on this labeling supplement, supplement request letters should be sent to the Pfizer innovator and the approved argatroban 505(b)(2) products, requesting similar changes to labeling.*

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/s/

VIRGINIA E KWITKOWSKI
09/10/2016

LABEL AND LABELING REVIEW

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)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	August 22, 2016
Requesting Office or Division:	Division of Oncology Products 1 (DOP1) Division of Hematology Products (DHP)
Application Type and Number:	NDA 203049/S-004
Product Name and Strength:	Argatroban Injection, 50 mg/50 mL (1 mg/mL)
Product Type:	Single ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	**NDA holder:** Hikma Pharmaceutical Pvt. Ltd **Acting agent:** Exela Pharma Sciences, LLC
Submission Date:	April 13, 2016 and July 25, 2016
OSE RCM #:	2016-1416
DMEPA Primary Reviewer:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

Argatroban Injection is marketed as a 250 mg/2.5 mL (100 mg/mL) single use vial. Exela Pharma Sciences is proposing a new formulation of 50 mg/50 mL (1 mg/mL) single use vial in addition to the currently marketed 250 mg/2.5 mL (100 mg/mL) single use vial.

The Division of Oncology Products 1 (DOP1) requested that we review the proposed Argatroban container label, carton labeling, and prescribing information (PI) for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Exela Pharma is proposing a new additional strength 50 mg/50 mL and concentration 1 mg/mL for Argatroban Injection. Our review found that an Argatroban Injection, 50 mg/50 mL (1 mg/mL), is already marketed by another Applicant (NDA 022434) since 2011 (See Appendix B). We are not aware of medication errors through our routine postmarket safety surveillance, thus we do not anticipate the introduction of Argatroban Injection 50 mg/50 mL (1mg/mL) from Exela Pharm will increase the risk of medication errors.

We evaluated the proposed Argatroban Injection container label and carton labeling and recommend revising the order of the statements on the principal display panel of the container label so that the “Discard Unused Portion” statement is placed after the “Single Use Vial” statement to ensure safe use of the drug product. We noted the use of “single use vial” on the container label and carton labeling and the use of “single use injection vial” on the PI. We defer

to Office of Pharmaceutical Quality (OPQ) for the determination of the appropriate package type term on labels and labeling.

We evaluated the proposed Argatroban Injection PI that was submitted on July 25, 2016, and noticed that the Dosage and Administration section in the Highlights of the PI suggests that Argatroban Injection may be used for pediatric patients.

(b) (4)

However, we note the first sentence in section 8.4 states "The safety and effectiveness of argatroban, including the appropriate anticoagulation goals and duration of therapy, have not been established among pediatric patients." Additionally, dosage instructions for Argatroban Injection in pediatric patients aren't clear, (b) (4) We alerted the Associate Director of Labeling (ADL) in Division of Hematology Products (DHP) who will work with the Argatroban Injection review team to remove the pediatric indication from the Highlights of the PI, and will relocate all pediatric information to Section 8.4 in the PI labeling. Therefore, we defer to the Argatroban Injection review team to reconcile the pediatric information in the PI labeling.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed container label and carton labeling for Argatroban Injection may be improved to promote the safe use of the product as described in Section 4.1. However, the proposed PI is acceptable from a medication error perspective, and we have no further recommendations for the proposed PI at this time.

4.1 RECOMMENDATIONS FOR EXELA PHARMA SCIENCES, LLC

We recommend the following be implemented prior to approval of this NDA supplement:

A. Container label
    1. Revise the order of the statements on the principal display panel of the container label so that the "Discard Unused Portion" statement is placed after the "Single Use Vial" statement to ensure safe use of the drug product.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Argatroban that Exela Pharma Sciences, LLC submitted on June 16, 2016.

Table 2. Relevant Product Information for Argatroban	
Initial Approval Date	January 5, 2012
Active Ingredient	Argatroban
Indication	• For prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT) • As an anticoagulant in adults patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI)
Route of Administration	Intravenous infusion
Dosage Form	Injection
Strength	**Currently marketed:** 250 mg/2.5 mL (100 mg/mL) **Proposed:** 50 mg/50 mL (1 mg/mL)
Dose and Frequency	**Heparin-Induced Thrombocytopenia** The dose for heparin-induced thrombocytopenia without hepatic impairment is 2 mcg/kg/min administered as a continuous infusion **Percutaneous Coronary Intervention** The dose for patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention is started at 25 mcg/kg/min and a bolus of 350 mcg/kg administered via a large bore intravenous line over 3 to 5 minutes
How Supplied	**Currently marketed:** 250 mg/2.5 mL (100 mg/mL) single-use injection vial. **Proposed:** 50 mg/50 mL (1 mg/mL) single-use injection vial.
Storage	Store the vials in original carton at 20° - 25° C (68° - 77° F) [See USP Controlled Room Temperature]. Do not freeze. Retain in the original carton to protect from light.
Container Closure	**Currently marketed:** 5 mL (b) (4) vial **Proposed:** 50 mL (b) (4) vial

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On June 30, 2016, we searched the L:drive and AIMS using the terms, Argatroban, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous review[1], and we confirmed that our previous recommendations were implemented for Hikma Pharma's Argatroban Injection 250 mg/2.5 mL (100 mg/mL) product. We also reviewed our previous recommendations for the 505(b)(2) Argatroban Injection products to ensure our recommendations for Hikma Pharma's Argatroban Injection product are consistent with our previous recommendations for other argatroban products.

Argatroban Injection products				
Application	Applicant	Strength	Status	OSE Review
NDA 020883 RLD	Pfizer	250 mg/2.5 mL (100 mg/mL)	Approved 6/30/2000	Unknown
NDA 203049	Hikma Pharma	**Currently marketed:** 250 mg/2.5 mL (100 mg/mL) **Proposed:** 50 mg/50 mL (1 mg/mL)	Approved 6/17/2010	2011-2008[1] Subject of this review
NDA 201811	Fresenius Kabi USA, LLC	**Single dose vial:** 250 mg/2.5 mL (100 mg/mL)	Approved 3/23/2015	2015-2342[2] 2012-2764[3] 2010-1531[4]
NDA 206769	Teva Pharmaceuticals	**Single use polyolefin bag:** 250 mg/250 mL (1 mg/1 mL) in Sodium Chloride	Approved 12/15/2014	2014-842[5]
NDA 022434	Eagles Pharmaceuticals	**Single use vial:** 50 mg/50 mL (1 mg/mL)	Approved 6/29/2011	2014-1224[6] 2011-323[7]
NDA 022359	Baxter Healthcare Corp.	250 mg/250 mL (1 mg/mL)	**Drugs@FDA:** Tentative approval (b) (4)	2011-1411[8]
NDA 022485	Sandoz	**Single use vial:** 125 mg/125 mL (1 mg/ml) in Sodium Chloride	Approved 5/9/2011	2010-1010 and 2010-1341[9]
NDA 201743	Sandoz	**Single use vial:** 125 mg/125 mL (1mg/mL) in Dextrose	Approved 5/9/2011 **Discontinued**	
ANDA 079238	Pliva Hrvatska Doo	250 mg/2.5 mL (100 mg/mL)	Tentative approval as of 12/29/2010	N/A
ANDA 091665	Par Sterile Products	250 mg/2.5 mL (100 mg/mL)	Approved 6/30/2014	N/A
ANDA 202626	Mylan Institutional	250 mg/2.5 mL (100 mg/mL)	Approved 6/30/2014	N/A

[1] Abdus-Samad, J. Label and Labeling Review for Argatroban Injection (NDA 203049). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2011 NOV 22. RCM No.: 2011-2008.
[2] Garrison, N. Label and Labeling Review for Argatroban Injection (NDA 201811/S-001). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 OCT 22. RCM No.: 2015-2342.
[3] Mistry, M. Label and Labeling Review for Argatroban Injection (NDA 201811). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 MAR 4. RCM No.: 2012-2764.
[4] Maslov, Y. Label and Labeling Review for Argatroban Injection (NDA 201811). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2010 DEC 13. RCM No.: 2010-1531.
[5] Rutledge, M. Label and Labeling Review for Argatroban Injection (NDA 206769). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 OCT 2. RCM No.: 2014-842.
[6] Rutledge, M. Label and Labeling Review for Argatroban Injection (NDA 022434/S-006). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 JULY 17. RCM No.: 2014-1224.
[7] Tobenkin, A. Label and Labeling Review for Argatroban Injection (NDA 022434). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2011 MAY 3. RCM No.: 2011-323.
[8] Wilkins Parker, J. Label and Labeling Review for Argatroban Injection (NDA 022359). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 JULY 17. RCM No.: 2011-1411.
[9] Maslov, Y. Label and Labeling Review for Argatroban Injection (NDA 201743 and NDA 022485). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2010 DEC 13. RCM No.: 2010-1010 and 2010-1341.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On July 1, 2016, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newletter(s)	Acute Care and Community
Search Strategy and Terms	Match Exact Word or Phrase: Argatroban

D.2 Results

Our search identified 12 articles that contain the word "argatroban", with 4 potential relevant articles that we evaluated further for medication errors possibly associated with label and labeling.

Newsletter	Date	Issue	Relevance
Acute Care	May 19, 2016	Aggrastat-argatroban mix-ups due to look-alike drug names	Not related to label or labeling
Acute Care	March 24, 2016	Argatroban package insert lists the infusion rate in mg/min instead of mcg/minute.	This was addressed in postmarket review.[10] The proposed PI correctly listed the confusion infusion dose in mcg/min.
Acute Care	February 20, 2002	Argatroban confused as Orgaran via a verbal order.	Not related to label or labeling
Acute Care	July 25, 2001	Confusion between Aggrastat and argatroban due to unfamiliarity with argatroban.	Not related to label or labeling

[10] Wyeth, J. Postmarket Medication Error Review for Argatroban Injection (NDA 020883, 022434, 022485, 201743, 201811, 203049, 206769). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 MAR 11. RCM No.: 2016-563.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[11] along with postmarket medication error data, we reviewed the following Argatroban labels and labeling submitted by Exela Pharma Sciences, LLC.

- Proposed container label submitted on April 13, 2016
- Proposed carton labeling submitted on April 13, 2016
- Proposed Prescribing Information submitted on June 16, 2016
- Currently marketed container label (submitted to FDA on October 9, 2012)
- Currently marketed carton labeling (submitted to FDA on October 9, 2012)

G.2 Label and Labeling Images

(b) (4)

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

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

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/s/

TINGTING N GAO
08/22/2016

CHI-MING TU
08/22/2016

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

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

Memorandum

Date: 11/25/2015

To: Jacquin Jones, Regulatory Project Manager
Division of Hematology Products

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

Through: Katie Davis, Team Leader
Office of Prescription Drug Promotion

Subject: Comments on draft labeling (Package Insert) for Argatroban/NDA 203049, S-004

This memo is in response to your labeling consult request on August 12, 2015. DHP issued a Complete Response (CR) letter on October 26, 2015. Therefore, OPDP defers comment on the Applicant's labeling at this time. A comprehensive review of the proposed labeling will be performed after the Applicant submits a complete response to the CR letter. Please send us a new consult request at such time.

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/s/

JAMES S DVORSKY
11/25/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203049Orig1s004

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Kacuba, Alice

From: Kacuba, Alice
Sent: Thursday, September 22, 2016 6:06 PM
To: 'jsterling@excela.us'
Subject: 9-22-16 "FDA revised" Argatroban PI.docx

Importance: High

Hi Mr. Sterling,

My name is Alice Kacuba, Chief, Project Management Staff for DOP1.

Amy Tilley, who has been your RPM, will be on extended leave. Therefore, I will reassign coverage of your application in order to meet the goal date. However, for the near future, I will be your contact to assure that nothing falls through the cracks with this supplement. My contact information is below.

Please see attached, the "FDA revised" labeling.

Please respond by 4 pm Friday, Sept 23, 2016 with 1) An email to me, to facilitate review and 2) An official submission to your supplement.

Please respond with 1) accepting changes that we are proposing and you agree with and 2) comment on changes that you do not agree with.

In addition, please confirm by return email that you have secure email with FDA.

Thank you.

Alice

Alice Kacuba, RN, MSN, GWCPM, RAC
Chief, Project Management Staff
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
301-796-1381
Alice.kacuba@fda.hhs.gov

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/s/

ALICE KACUBA
09/22/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Monday, September 19, 2016 7:22 AM
To: 'Jonathan Sterling'
Cc: Tilley, Amy
Subject: RE: TIME SENSITIVE re sNDA 203049-S-4 Argatroban - FDA Revised PI - Carton Container Labels

Importance: High

Hi Jonathan,

I'm sending this request on behalf of my colleague Amy Tilley, in reference to the revised PI that you submitted to the Agency on September 16, 2016 to sNDA 203049/S-4, please note that in the revised PI the highlights section are not in the two column format. Please re-submit the PI with Highlights in the two column format as soon as possible. Please let me know if you have any questions and kindly confirm receipt of this email communication.

Thank you,
Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP1
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993
sakar.wahby@fda.hhs.gov
(P): 240-402-5364
(F): 301-796-9845

From: Jonathan Sterling [mailto:jsterling@exela.us]
Sent: Friday, September 16, 2016 12:48 AM
To: Tilley, Amy
Cc: Wahby, Sakar
Subject: RE: TIME SENSITIVE re sNDA 203049-S-4 Argatroban - FDA Revised PI - Carton Container Labels

Please see the attached revised carton and container labels as well as the revised labeling.

All changes requested by the Division were accepted.

JES

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
Sent: Thursday, September 15, 2016 12:53 PM
To: Jonathan Sterling
Cc: Wahby, Sakar

Subject: RE: TIME SENSITIVE re sNDA 203049-S-4 Argatroban - FDA Revised PI - Carton Container Labels
Importance: High

John, are you still on track for emailing us the revised PI and labels by 10 am tomorrow? As always, follow up with an official submission to the NDA. Make sure all documents are in tracked changes, accepting FDA edits and showing your edits. If you have edits to the labels please insert them in a comment in the pdf label.

Be sure to include Sakar Wahby in your emailed response as I will be out of the office and she is covering for me.

Please let me know today whether or not you will be sending your emailed revisions of the PI and labels by 10 am tomorrow.
Thanks.

Amy

From: Tilley, Amy
Sent: Tuesday, September 13, 2016 2:50 PM
To: 'jsterling@exela.us'
Cc: Wahby, Sakar
Subject: TIME SENSITIVE re sNDA 203049-S-4 Argatroban - FDA Revised PI - Carton Container Labels
Importance: High

Jonathan, attached are the FDA revised PI and Carton & Container Labels. We request your emailed response **in tracked changes no later than 10 am on Friday Sept 16, 2016**, then follow up with an official submission to the NDA.

When responding via email please reply to all as my colleague Sakar Wahby will be covering for me as I will be out of the office on Friday, Sept 16th.

Kindly confirm receipt of this email.

Regards.
Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1
CDER | FDA 10903 New Hampshire Avenue | Room 2108 | Silver Spring,
MD 20993 | O 301.796.3994 | F 301.796.9845 | amy.tilley@fda.hhs.gov

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/s/

SAKAR M WAHBY
09/19/2016

From:	Tilley, Amy
To:	"jsterling@exela.us"
Cc:	Wahby, Sakar
Bcc:	Kwitkowski, Virginia; Gormley, Nicole
Subject:	TIME SENSITIVE re sNDA 203049-S-4 Argatroban - FDA Revised PI - Carton Container Labels
Date:	Tuesday, September 13, 2016 2:50:00 PM
Attachments:	NDA 203049 S004 Argatroban HIKMA FDA revd 9-13-16.docx Argatroban carton label 50 mL 03-2015 FDA revd 9-13-16.pdf Argatroban container label 50 mL 03-2015 FDA revd 9-13-16.pdf
Importance:	High

Jonathan, attached are the FDA revised PI and Carton & Container Labels. We request your emailed response **in tracked changes no later than 10 am on Friday Sept 16, 2016**, then follow up with an official submission to the NDA.

When responding via email please reply to all as my colleague Sakar Wahby will be covering for me as I will be out of the office on Friday, Sept 16th.

Kindly confirm receipt of this email.

Regards.
Amy Tilley

Amy Tilley|Regulatory Project Manager|Division of Oncology Products 1 CDER | FDA 10903 New Hampshire Avenue | Room 2108|Silver Spring, MD 20993 | 301.796.3994 | F 301.796.9845|amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
09/13/2016

From:	Tilley, Amy
To:	"Jonathan Sterling"
Bcc:	Swoboda, Jonathan; Cole, Jessica; Langille, Stephen
Subject:	RE: URGENT sNDA 203049 Argatroban - Micro Deficiencies
Date:	Tuesday, July 26, 2016 3:00:19 PM
Importance:	High

Jonathan, thanks we look forward to receiving your response to both deficiencies via email tomorrow and as an official submission to the NDA.
Regards.

Amy

From: Jonathan Sterling [mailto:jsterling@exela.us]
Sent: Tuesday, July 26, 2016 2:24 PM
To: Tilley, Amy
Subject: RE: URGENT sNDA 203049 Argatroban - Micro Deficiencies

#1 is a typo. I will correct

I will respond tomorrow to both

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
Sent: Tuesday, July 26, 2016 2:18 PM
To: Jonathan Sterling
Subject: URGENT sNDA 203049 Argatroban - Micro Deficiencies
Importance: High

Jonathan,

Please respond to the Microbiology Deficiencies as soon as possible both via email and as an official submission to the NDA.

Microbiology Deficiencies:

1. Page 4 of 175 in the document entitled, "product-process-validation.pdf" indicates that the (b) (4) validation studies are for Palonosetron Hydrochloride. However, the subject drug product is Argatroban Injection 1 mg/mL. Explain this discrepancy.

(b) (4)

Please confirm receipt of this email.

Regards.
Amy Tilley

Amy Tilley|Regulatory Project Manager|Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2108|Silver Spring, MD 20993
☎301.796.3994 (phone)● 301.796.9845 (fax)|✉amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
07/26/2016

From: Tilley, Amy
To: "Jonathan Sterling"
Subject: RE: PI Incorrect Format URGENT NDA 203049 Argatroban S-004 SN 0024 - PI Information Request
Date: Sunday, July 24, 2016 11:34:10 AM
Attachments: sNDA 203049 Argatroban S-005 Approval Letter.pdf

---

Jonathan, the sentence "In other words the supplement 005 labeling that was recently approved is not in proper format either." is not a completely true statement as S-5's approved label does have the Highlights in a 2 column format, single spacing and what appears to be an 8 point font. See attached Supplement 5 Approval letter with PI attached. However, you are correct in that S-5 does not have the PI in PLLR Format. Since S-4 was not originally submitted in PLLR Format you do not need to convert S-4 PI to PLLR format at this point in time.

We expect to receive the corrected PI for Supplement 4 with the following revisions:

1) Proposed revisions to **Supplement 4 in Tracked Changes.**
2) PI should also contain all the revisions from Supplement 5 **NOT** in tracked changes
3) Correct Format, i.e., Highlights in 2 Column Format.
4) Use 8 point font and single spacing throughout the PI.

We request your submission as soon as possible. Please send me an email notifying me that the submission has been sent.

Regards.
Amy

From: Jonathan Sterling [mailto:jsterling@exela.us]
Sent: Saturday, July 23, 2016 3:32 PM
To: Tilley, Amy
Subject: Re: PI Incorrect Format URGENT NDA 203049 Argatroban S-004 SN 0024 - PI Information Request

I will convert the file to he new pllr format.

In other words the supplement 005 labeling that was recently approved is not in proper format either.

I will revise it into the latest format and send to you.

I thought I was supposed to maintain the current formatting that the approved label is in.

Thanks

Jes

On Jul 23, 2016, at 3:06 PM, Tilley, Amy <Amy.Tilley@fda.hhs.gov> wrote:

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203049/S-005

SUPPLEMENT APPROVAL

Hikma Pharmaceuticals Co. Ltd.
c/o Exela Pharma Sciences, LLC
Authorized US Agent
Attention: Jonathan Sterling
Vice President of Quality and Regulatory Affairs
P.O. Box 818
1245 Blowing Rock Blvd.
Lenoir, NC 28645

Dear Mr. Sterling:

Please refer to your Supplemental New Drug Application (sNDA) dated March 21, 2016, received March 21, 2016, and your amendment, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Argatroban, Injection 100 mg/mL.

We also refer to our letter dated March 11, 2016, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for Argatroban products. This information pertains to the risk of medication errors.

This supplemental new drug application provides for revisions to the labeling for Argatroban. The agreed upon changes to the language included in our March 11, 2016, Safety labeling Change Notification Letter, and agreed upon revisions included in our electronic correspondence dated April 19, 2016, are as follows (additions are noted by underline and deletion are noted by ~~strikethrough~~).

In the **HIGHLIGHTS** section, addition of RECENT MAJOR CHANGES section that reads:

"----------**RECENT MAJOR CHANGES**----------
Dosing and Administration, Dosing in Patients Undergoing Percutaneous Coronary Intervention (2.3) 5/2016"

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We note that your May 24, 2016, submission includes final printed labeling (FPL) for your package insert. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROPRIETARY NAME

If you intend to have a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit a request for a proposed proprietary name review. (See the guidance for industry titled, "Contents of a Complete Submission for the Evaluation of Proprietary Names", at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Ms. Diane Leaman, Safety Regulatory Project Manager, at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Barry W. Miller
Acting Deputy Division Director for Safety
Division of Hematology Products
Office of Hematology Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Argatroban Injection safely and effectively. See full prescribing information for Argatroban.

ARGATROBAN INJECTION for Intravenous administration
Initial U.S. Approval: 2000

----------RECENT MAJOR CHANGES----------
Dosing and Administration, Dosing in Patients Undergoing Percutaneous Coronary Intervention (2.3) 5/2016

----------INDICATIONS AND USAGE----------
Argatroban is a direct thrombin inhibitor indicated:

- For prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT) (1.1)
- As an anticoagulant in adult patients with or at risk of HIT undergoing percutaneous coronary intervention (PCI) (1.2)

----------DOSAGE AND ADMINISTRATION ----------
- Argatroban Injection must be diluted 100-fold by mixing with 0.9% Sodium Chloride Injection, 5% Dextrose Injection, or Lactated Ringer's Injection to a final concentration of 1 mg/mL (2.1). Argatroban dosage may be adjusted for pediatric use (8.4).

Heparin-Induced Thrombocytopenia (2.2)
The dose for heparin-induced thrombocytopenia without hepatic impairment is 2 mcg/kg/min administered as a continuous infusion (2.2)
Percutaneous Coronary Intervention (2.3)
The dose for patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention is started at 25 mcg/kg/min and a bolus of 350 mcg/kg administered via a large bore intravenous line over 3 to 5 minutes (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
- 250 mg/2.5 mL (100 mg/mL) single-use injection vial. (3)

----------CONTRAINDICATIONS----------
- Major bleeding (4)
- History of hypersensitivity to this product (4)

----------WARNINGS AND PRECAUTIONS----------
- Hemorrhage can occur. Unexplained fall in hematocrit or blood pressure may indicate hemorrhage (5.1)
- Hepatic impairment: Adjust starting dose and titrate carefully in patients with HIT who have moderate or severe hepatic impairment. Avoid use in PCI in patients with clinically significant hepatic impairmtnty (5.2)
- **----------ADVERSE REACTIONS----------**
- HIT patients: The most common (> 5%) adverse reactions were dyspnea, hypotension, fever, diarrhea, sepsis, and cardiac arrest (6.1)
- PCI patients: The most common (> 5%) adverse reactions were chest pain, hypotension, back pain, nausea, vomiting and headache (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact West-Ward Pharmaceuticals Corp. at 1-877-233-2001 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Heparin: Allow sufficient time for heparin's effect on aPTT to decrease before initiating Argatroban Injection therapy (7.1)
- Warfarin: Concomitant use results in increased prolongation of PT and INR (7.2)
- Thrombolytic agents or glycoprotein IIb/IIIa antagonists: Safety and effectiveness of concomitant use with argatroban have not been established (7.4, 7.5)

----------USE IN SPECIFIC POPULATIONS----------
- Nursing Mothers: Discontinue nursing or drug, taking into account the importance of the drug to the mother (8.3)
- Pediatric use: Safety and effectiveness have not been established; if used, initial infusion doses are lower than in adult patients (2.4, 8.4, 12.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised 05/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Heparin-Induced Thrombocytopenia

Argatroban Injection is indicated for prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT).

1.2 Percutaneous Coronary Intervention

Argatroban Injection is indicated as an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI).

2 DOSAGE AND ADMINISTRATION

Argatroban Injection must be diluted 100-fold prior to infusion. Argatroban should not be mixed with other drugs prior to dilution.

2.1 Preparation for Intraveneous Administration:

Argatroban 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. The contents of each 2.5-mL vial should be diluted 100-fold by mixing with 250 mL of diluent. Use 250 mg (2.5 mL) per 250 mL of diluent or 500 mg (5 mL) per 500 mL of diluent.

The constituted solution must be mixed by repeated inversion of the diluent bag for 1 minute. Upon preparation, the solution may show slight but brief haziness due to the formation of microprecipitates that rapidly dissolve upon mixing. Use of diluent at room temperature is recommended. The final solution must be clear before use. The pH of the intravenous solution prepared as recommended is 3.2 to 7.5. Solutions prepared as recommended are stable at controlled room temperature, 20° to 25°C (68° to 77°F) (see USP) in ambient indoor light for 24 hours; therefore, light-resistant measure such as foil protection for intravenous lines are unnecessary. Solutions are physically and chemically stable for up to 96 hours when protected from light and stored at controlled room temperature, 20° to 25°C (68° to 77°F) (see USP) or at refrigerated conditions, 5°±3°C (41°±5°F). Prepared solutions should not be exposed to direct sunlight. No significant potency losses have been noted following simulated delivery of the solution through intravenous tubing.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

2.2 Dosing in Patients with Heparin- Induced Thrombocytopenia

Initial Dosage:

Before administering argatroban, discontinue heparin therapy and obtain a baseline aPTT. The recommended initial dose of argatroban for adult patients without hepatic impairment is 2 mcg/kg/min, administered as a continuous infusion (see Table 1).

Table 1. Recommended Doses and Infusion Rates for 2 mcg/kg/min Dose of Argatroban for Patients With HIT* and Without Hepatic Impairment (1 mg/mL Final Concentration)		
Body Weight (kg)	**Dose (mcg/min)**	**Infusion Rate (mL/hr)**
50	100	6
60	120	7
70	140	8
80	160	10
90	180	11
100	200	12
110	220	13
120	240	14
130	260	16
140	280	17

*with or without thrombosis

Monitoring Therapy:
For use in HIT, therapy with Argatroban Injection is monitored using the aPTT with a target range of 1.5 to 3 times the initial baseline value (not to exceed 100 seconds). Tests of anticoagulant effects (including the aPTT) typically attain steady-state levels within 1 to 3 hours following initiation of Argatroban Injection.

Check the aPTT 2 hours after initiation of therapy and after any dose change to confirm that the patient has attained the desired therapeutic range.

Dosage Adjustment:
After the initiation of Argatroban Injection, adjust the dose (not to exceed 10 mcg/kg/min) as necessary to obtain a steady-state aPTT in the target range [see *Clinical Studies (14.1)*].

2.3 Dosing in Patients Undergoing Percutaneous Coronary Intervention

Initial Dosage:
Initiate an infusion of Argatroban Injection at 25 mcg/kg/min and administer a bolus of 350 mcg/kg via a large bore intravenous line over 3 to 5 minutes (see Table 2). Check an activated clotting time (ACT) 5 to 10 minutes after the bolus dose is completed. The PCI procedure may proceed if the ACT is greater than 300 seconds.

Dosage Adjustment:
If the ACT is less than 300 seconds, an additional intravenous bolus dose of 150 mcg/kg should be administered, the infusion dose increased to 30 mcg/kg/min, and the ACT checked 5 to 10 minutes later (see Table 2).

If the ACT is greater than 450 seconds, decrease the infusion rate to 15 mcg/kg/min, and check the ACT 5 to 10 minutes later (Table 3).

Continue titrating the dose until a therapeutic ACT (between 300 and 450 seconds) has been achieved; continue the same infusion rate for the duration of the PCI procedure.

In case of dissection, impending abrupt closure, thrombus formation during the procedure, or inability to achieve or maintain an ACT over 300 seconds, additional bolus doses of 150 mcg/kg may be administered and the infusion dose increased to 40 mcg/kg/min. Check the ACT after each additional bolus or change in the rate of infusion.

Table 2.
Recommended Starting and Maintenance Doses (Within the Target ACT Range) of Argatroban Injection in Patients Undergoing PCI Without Hepatic Impairment (1 mg/mL Final Concentration)

Body Weight (kg)	**Starting Bolus Dose (350 mcg/kg)**		**Starting and Maintenance Continuous Infusion Dosing For ACT 300-450 seconds 25 mcg/kg/min**	
	Bolus Dose (mcg)	**Bolus Volume (mL)**	**Continuous Infusion Dose (mcg/min)**	**Continuous Infusion Rate (mL/hr)**
50	17500	18	1250	75
60	21000	21	1500	90
70	24500	25	1750	105
80	28000	28	2000	120
90	31500	32	2250	135
100	35000	35	2500	150
110	38500	39	2750	165
120	42000	42	3000	180
130	45500	46	3250	195
140	49000	49	3500	210

NOTE: 1 mg = 1000mcg; 1 kg = 2.2 lbs

Table 3
Recommended Dose Adjustments of Argatroban Injection for Patients Outside of ACT Target Range Undergoing PCI Without Hepatic Impairment (1 mg/mL Final Concentration)

Body Weight	If ACT Less than 300 seconds Dosage Adjustment†	If ACT Greater than 450 seconds Dosage

(kg)	30 mcg/kg/min				Adjustment* 15 mcg/kg/min	
	Additional Bolus Dose (mcg)	Bolus Volume (mL)	Continuous Infusion Dose (mcg/min)	Continuous Infusion Rate (mL/hr)	Continuous Infusion Dose (mcg/min)	Continuous Infusion Rate (mL/hr)
50	7500	8	1500	90	750	45
60	9000	9	1800	108	900	54
70	10500	11	2100	126	1050	63
80	12000	12	2400	144	1200	72
90	13500	14	2700	162	1350	81
100	15000	15	3000	180	1500	90
110	16500	17	3300	198	1650	99
120	18000	18	3600	216	1800	108
130	19500	20	3900	234	1950	117
140	21000	21	4200	252	2100	126

NOTE: 1 mg = 1000 mcg; 1 kg = 2.2 lbs
†Additional intravenous bolus dose of 150 mcg/kg should be administered if ACT less than 300 seconds.
* No bolus dose is given if ACT greater than 450 seconds

Monitoring Therapy:
For use in PCI, therapy with Argatroban Injection is monitored using ACT. Obtain ACTs before dosing, 5 to 10 minutes after bolus dosing, following adjustments in the infusion rate, and at the end of the PCI procedure. Obtain additional ACTs every 20 to 30 minutes during prolonged procedure.

Continued Anticoagulation after PCI:
If a patient requires anticoagulation after the procedure, Argatroban Injection may be continued, but at a rate of 2 mcg/kg/min and adjusted as needed to maintain the aPTT in the desired range [*see Dosage and Administration (2.1)*].

2.4 Dosing in Patients With Hepatic Impairment

Initial Dosage:

For adult patients with HIT and moderate or severe hepatic impairment (based on Child-Pugh classification), an initial dose of 0.5 mcg/kg/min is recommended, based on the approximately 4-fold decrease in argatroban clearance relative to those with normal hepatic function. Monitor the aPTT closely, and adjust the dosage as clinically indicated.

Monitoring Therapy:
Achievement of steady state aPTT levels may take longer and require more dose adjustments in patients with hepatic impairment compared to patients with normal hepatic function.

For patients with hepatic impairment undergoing PCI and who have HIT or are at risk for HIT, carefully titrate argatroban until the desired level of anticoagulation is achieved. Use of Argatroban in PCI patients with clinically significant hepatic disease or AST/ALT levels ≥3 times the upper limit of normal should be avoided [*see Warnings and Precautions (5.2)*].

2.5 Dosing in Pediatric Patients With Heparin-Induced Thrombocytopenia/Heparin-Induced Thrombocytopenia and Thrombosis Syndrome

Initial Dosage:
Initial argatroban infusion doses are lower for seriously ill pediatric patients compared to adults with normal hepatic function [*see Use in Specific Populations (8.4)*].

Monitoring Therapy:
In general, therapy with argatroban is monitored using the aPTT. Tests of anticoagulant effects (including the aPTT) typically attain steady-state levels within one to three hours following initiation of argatroban in patients without hepatic impairment [*see Warnings and Precautions (5.2)*]. Dose adjustment may be required to attain the target aPTT. Check the aPTT two hours after initiation of therapy and after any dose change to confirm that the patient has attained the desired therapeutic range.

Dosage Adjustment: [*see Use in Specific Populations (8.4)*]

2.6 Conversion to Oral Anticoagulant Therapy

Initiating Oral Anticoagulant Therapy:
When converting patients from Argatroban to oral anticoagulant therapy, consider the potential for combined effects on INR with co-administration of Argatroban and warfarin. A loading dose of warfarin should not be used. Initiate therapy using the expected daily dose of warfarin. To avoid prothrombotic effects and to ensure continuous anticoagulation when initiating warfarin, it is suggested that Argatroban and warfarin therapy be overlapped. There are insufficient data available to recommend the duration of the overlap.

Co-Administration of Warfarin and Argatroban Injection at Doses Up to 2 mcg/kg/min:
Measure INR daily while Argatroban Injection and warfarin are co-administered. In general, with doses of Argatroban Injection up to 2 mcg/kg/min, Argatroban Injection can be discontinued when the INR is >4 on combined therapy. After Argatroban Inection is discontinued, repeat the INR measurement in 4 to 6 hours. If the repeat INR is below the desired therapeutic range, resume the infusion of Argatroban Injection and repeat the procedure daily until the desired therapeutic range on warfarin alone is reached.

Co-Administration of Warfarin and Argatroban Injection at Doses Greater than 2 mcg/kg/min: For doses greater than 2 mcg/kg/min, the relationship of INR between warfarin alone to the INR on warfarin plus argatroban is less predictable. In this case, in order to predict the INR on warfarin alone, temporarily reduce the dose of Argatroban Injection to a dose of 2 mcg/kg/min. Repeat the INR on Argatroban Injection and warfarin 4 to 6 hours after reduction of the Argatroban Injection dose and follow the process outlined above for administering Argatroban Injection at doses up to 2 mcg/kg/min.

3 DOSAGE FORMS AND STRENGTHS

250 mg/2.5 mL (100 mg/mL) single-use injection vial.

4 CONTRAINDICATIONS

Argatroban is contraindicated in:

- Patients with major bleeding, *[see Warnings and Precautions (5.1)]*

- Patients with a history of hypersensitivity to argatroban. Airway, skin, and generalized hypersensitivity reactions have been reported *[see Adverse Reactions (6.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Hemorrhage

Hemorrhage can occur at any site in the body in patients receiving argatroban. Unexplained fall in hematocrit or blood pressure may indicate hemorrhage. Intracranial and retroprtiotoneal hemorrahage [*see Adverse Reactions (6.2 and 6.3)]* have been reported. The risk of hemorrahage with argatroban may be increased in severe hypertension; immediately following lumbar puncture, spinal anesthesia, major surgery (especially involving the brain, spinal cord, or eye), hematologic conditions associated with increased bleeding tendencies such as congenital or acquired bleeding disorders, and gastrointestinal lesions such as ulcerations.

Concomitant use of argatroban with antiplatelet agents, thrombolytics, and other anticoagulants may increase the risk of bleeding.

5.2 Use in Hepatic Impairment

When administering argatroban to patients with hepatic impairment, start with a lower dose and carefully titrate until the desired level of anticoagulation is achieved. Achievement of steady state aPTT levels may take longer and require more argatroban dose adjustments in patients with hepatic impairment compared to patients with normal hepatic function [*see Use in Specific Populations (8.6)*]. Also, upon cessation of argatroban infusion in the hepatically impaired patient, full reversal of anticoagulant effects may require longer than 4 hours due to decreased clearance and increased elimination half-life of argatroban [*see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)*]. Avoid the use of high doses of argatroban in patients undergoing PCI who have clinically significant hepatic disease or AST/ALT levels ≥3 times the upper limit of normal.

5.3 Laboratory Tests

Anticoagulation effects associated with Argatroban infusion at doses up to 40 mcg/kg/min correlate with increases of the activated partial thromboplastin time (aPTT). Although other global clot-based tests including prothrombin time (PT), the International Normalized Ratio (INR), and thrombin time (TT) are affected by Argatroban, the therapeutic ranges for these tests have not been identified for argatroban therapy. In clinical trials in PCI, the activated clotting time (ACT) was used for monitoring argatroban anticoagulant activity during the procedure. The concomitant use of argatroban and warfarin results in prolongation of the PT and INR beyond that produced by warfarin alone [*see Dosage and Administration (2.5) and Clinical Pharmacology (12.2)*].

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse event 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.

The following adverse reaction is also discussed in other sections of the labeling: Risk of Hemorrhage [*see Warnings and Precautions (5.1)*].

6.1 Adverse Events in Patients with HIT (With or Without Thrombosis)

The following safety information is based on all 568 patients treated with argatroban in Study 1 and Study 2. The safety profile of the patients from these studies is compared with that of 193 historical controls in which the adverse events were collected retrospectively. Adverse events are separated into hemorrhagic and non-hemorrhagic events Major bleeding was defined as bleeding that was overt and associated with a hemoglobin decrease $\geq$ 2 g/dL, that led to a transfusion of $\geq$ 2 units, or that was intracranial, retroperitoneal, or into a major prosthetic joint. Minor bleeding was overt bleeding that did not meet the criteria for major bleeding.

Table 4 gives an overview of the most frequently observed hemorrhagic events, presented separately by major and minor bleeding, sorted by decreasing occurrence among argatroban-treated patients with HIT (with or without thrombosis).

Table 4.
Major and Minor Hemorrhagic Adverse Events in Patients With HIT*

Major Hemorrhagic Events[a]		
	Argatroban-treated Patients (Study 1 and Study 2) (n = 568) %	**Historical Control**[c] **(n = 193) %**
Overall bleeding	5.3	6.7
Gastrointestinal	2.3	1.6
Genitourinary and hematuria	0.9	0.5
Decrease in hemoglobin and hematocrit	0.7	0
Multisystem hemorrhage and DIC	0.5	1
Limb and BKA stump	0.5	0
Intracranial hemorrhage	0[b]	0.5
Minor Hemorrhagic Events[a]		
	Argatroban-treated Patients (Study 1 and Study 2) (n = 568) %	**Historical Control**[c] **(n = 193) %**
Gastrointestinal	14.4	18.1
Genitourinary and hematuria	11.6	0.8
Decrease in hemoglobin and hematocrit	10.4	0
Groin	5.4	3.1
Hemoptysis	2.9	0.8
Brachial	2.4	0.8

* with or without thrombosis
a) Patients may have experienced more than 1 adverse event.
b) One patient experienced intracranial hemorrhage 4 days after discontinuation of argatroban and following therapy with urokinase and
oral anticoagulation.
c) The historical control group consisted of patients with a clinical diagnosis of HIT (with or without thrombosis) that were considered eligible by an independent medical panel.
DIC = disseminated intravascular coagulation.
BKA = below the knee amputation.

Table 5 gives an overview of the most frequently observed non-hemorrhagic events sorted by decreasing frequency of occurrence (≥2%) among argatroban-treated HIT/HITTS patients.

Table 5.
Non-hemorrhagic Adverse Events in Patients[a] With HIT[b]

	Argatroban-treated Patients (Study 1 and Study 2) (n = 568) %	**Historical Control[c] (n = 193) %**
Dyspnea	8.1	8.8
Hypotension	7.2	2.6
Fever	6.9	2.1
Diarrhea	6.2	1.6
Sepsis	6.0	12.4
Cardiac arrest	5.8	3.1
Nausea	4.8	0.5
Ventricular tachycardia	4.8	3.1
Pain	4.6	3.1
Urinary tract infection	4.6	5.2
Vomiting	4.2	0
Infection	3.7	3.6
Pneumonia	3.3	9.3
Atrial fibrillation	3.0	11.4
Coughing	2.8	1.6
Abnormal renal function	2.8	4.7

Abdominal pain	2.6	1.6
Cerebrovascular disorder	2.3	4.1

a) Patients may have experienced more than 1 adverse event.
b) with or without thrombosis
c) The historical control group consisted of patients with a clinical diagnosis of HIT (with or without thrombosis) that were considered eligible by an independent medical panel.

6.2 Adverse Events in Patients with or at Risk for HIT Patients Undergoing PCI

The following safety information is based on 91 patients initially treated with argatroban and 21 patients subsequently re-exposed to argatroban for a total of 112 PCIs with argatroban anticoagulation. Adverse events are separated into hemorrhagic (Table 6) and non-hemorrhagic (Table 7) events.

Major bleeding was defined as bleeding that was overt and associated with a hemoglobin decrease ≥5 g/dL, that led to a transfusion of ≥2 units, or that was intracranial, retroperitoneal, or into a major prosthetic joint. The rate of major bleeding events in patients treated with argatroban in the PCI trials was 1.8%.

Table 6.
Major and Minor Hemorrhagic Adverse Events in Patients With HIT Undergoing PCI

Major Hemorrhagic Events[a]	
	Argatroban-treated Patients (n = 112)[b] %
Retroperitoneal	0.9
Gastrointestinal	0.9
Intracranial	0
Minor Hemorrhagic Events[a]	
	Argatroban-treated Patients (n = 112)[b] %
Groin (bleeding or hematoma)	3.6
Gastrointestinal (includes hematemesis)	2.6
Genitourinary (includes hematuria)	1.8
Decrease in hemoglobin and/or hematocrit	1.8
CABG (coronary arteries)	1.8

Access site	0.9
Hemoptysis	0.9
Other	0.9

a) Patients may have experienced more than 1 adverse event.
b) 91 patients who underwent 112 interventions.
CABG = coronary artery bypass graft.

Table 7 gives an overview of the most frequently observed non-hemorrhagic events (>2%), sorted by decreasing frequency of occurrence among argatroban-treated PCI patients.

Table 7.
Non-hemorrhagic Adverse Events[a] in Patients With HIT Undergoing PCI

	Argatroban Procedures[a] (n = 112)[b] %
Chest pain	15.2
Hypotension	10.7
Back pain	8.0
Nausea	7.1
Vomiting	6.3
Headache	5.4
Bradycardia	4.5
Abdominal pain	3.6
Fever	3.6
Myocardial infarction	3.6

a) Patients may have experienced more than 1 adverse event.
b) 91 patients who underwent 112 interventions.

There were 22 serious adverse events in 17 PCI patients (19.6% in 112 interventions). Table 8 lists the serious adverse events occurring in argatroban-treated patients with or at risk for HIT undergoing PCI.

Table 8.
Serious Adverse Events in Patients With HIT Undergoing PCI[a]

Coded Term	Argatroban Procedures[b] (n = 112)
Myocardial infarction	4 (3.5%)
Angina pectoris	2 (1.8%)
Coronary thrombosis	2 (1.8%)
Myocardial ischemia	2 (1.8%)
Occlusion coronary	2 (1.8%)
Chest pain	1 (0.9%)
Fever	1 (0.9%)
Retroperitoneal hemorrhage	1 (0.9%)
Aortic stenosis	1 (0.9%)
Arterial thrombosis	1 (0.9%)
Gastrointestinal hemorrhage	1 (0.9%)
Gastrointestinal disorder (GERD)	1 (0.9%)
Cerebrovascular disorder	1 (0.9%)
Lung edema	1 (0.9%)
Vascular disorder	1 (0.9%)

a) Individual events may also have been reported elsewhere (see Table 6 and 7).
b) 91 patients underwent 112 procedures. Some patients may have experienced more than 1 event.

6.3 Intracranial Bleeding in Other Populations

Increased risks for intracranial bleeding have been observed in investigational studies of argatroban for other uses. In a study of patients with acute myocardial infarction receiving both argatroban and thrombolytic therapy (streptokinase or tissue plaminogen activator), the overall frequency of intracranial bleeding was 1% (8 out of 810 patients). Intracranial bleeding was not observed in 317 subjects or patients who did not receive concomitant thrombolysis [*see Drug Interactions (7.4)*].

The safety and effectiveness of argatroban for cardiac indications other than PCI in patients with HIT have not been established. Intracranial bleeding was also observed in a prospective, placebo-controlled study of argatroban in patients who had onset of acute stroke within 12 hours of study entry. Symptomatic intracranial hemorrhage was reported in 5 of 117 patients (4.3%) who received argatroban at 1 to 3 mcg/kg/min and in none of the 54 patients who received placebo. Asymptomatic intracranial hemorrhage occurred in 5 (4.3%) and 2 (3.7%) of the patients, respectively.

6.4 Allergic Reactions

One hundred fifty-six allergic reactions or suspected allergic reactions were observed in 1,127 individuals who were treated with argatroban in clinical pharmacology studies or for various clinical indications. About 95% (148/156) of these reactions occurred in patients who concomitantly received thrombolytic therapy (e.g., streptokinase) or contrast media.

Allergic reactions or suspected allergic reactions in populations other than patients with HIT (with or without thrombosis) include (in descending order of frequency):

- Airway reactions (coughing, dyspnea): 10% or more
- Skin reactions (rash, bullous eruption): 1 to <10%
- General reactions (vasodilation): 1 to 10%

Limited data are available on the potential formation of drug-related antibodies. Plasma from 12 healthy volunteers treated with argatroban over 6 days showed no evidence of neutralizing antibodies. No loss of anticoagulant activity was noted with repeated administration of argatroban to more than 40 patients.

7 DRUG INTERACTIONS

7.1 Heparin

If argatroban is to be initiated after cessation of heparin therapy, allow sufficient time for heparin's effect on the aPTT to decrease prior to initiation of argatroban therapy.

7.2 Oral Anticoagulant Agents

Pharmacokinetic drug-drug interactions between argatroban and warfarin (7.5 mg single oral dose) have not been demonstrated. However, the concomitant use of argatroban and warfarin (5 to 7.5 mg initial oral dose, followed by 2.5 to 6 mg/day orally for 6 to 10 days) results in prolongation of the prothrombin time (PT) and International Normalized Ratio (INR) [*see Dosage and Administration (2.5) and Clinical Pharmacology (12.2)*].

7.3 Aspirin/Acetaminophen

No drug-drug interactions have been demonstrated between argatroban and concomitantly administered aspirin or acetaminophen *[see Clinical Pharmacology (12.3)]*.

7.4 Thrombolytic Agents

The safety and effectiveness of argatroban with thrombolytic agents have not been established *[see Adverse Reactions (6.3)]*

7.5 Glycoprotein IIb/IIIa Antagonists

The safety and effectiveness of argatroban with glycoprotein IIb/IIIa antagonists have not been established.

8 USE IN SPECIFIC POPULATIONS

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 impaired fertility or harm to the fetus. 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

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.

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. Argatroban was studied among 18 seriously ill pediatric patients who required an alternative to heparin anticoagulation. Most patients were diagnosed with HIT or suspected HIT. Age ranges of patients were <6 months, n = 8; six months to <8 years, n = 6; 8 to 16 years, n = 4. All patients had serious underlying conditions and were receiving multiple concomitant medications. Thirteen patients received argatroban solely as a continuous infusion (no bolus dose). Dosing was initiated in the majority of these 13 patients at 1 mcg/kg/min. Dosing was titrated as needed to achieve and maintain an aPTT of 1.5 to 3 times the baseline value. Most patients required multiple dose adjustments to maintain anticoagulation parameters within the desired range. During the 30-day study period, thrombotic events occurred during argatroban administration to two patients and following argatroban discontinuation in three other patients. Major bleeding occurred among two patients; one patient experienced an intracranial hemorrhage after 4 days of argatroban therapy in the setting of sepsis and thrombocytopenia. Another patient completed 14 days of argatroban treatment in the study, but experienced an intracranial hemorrhage while receiving argatroban following completion of the study treatment period.

When argatroban is used among seriously ill pediatric patients with HIT/HITTS who require an alternative to heparin and who have normal hepatic function, initiate a continuous infusion of argatroban at a dose of 0.75 mcg/kg/min. Initiate the infusion at a dose of 0.2 mcg/kg/min among seriously ill pediatric patients with impaired hepatic function [*see Clinical Pharmacology (12.3)*]. Check the aPTT two hours after the initiation of the argatroban infusion and adjust the dose to achieve the target aPTT. Increments of 0.1 to 0.25 mcg/kg/min for pediatric patients with normal hepatic function and increments of 0.05 mcg/kg/min or lower for pediatric patients with impaired hepatic function may be considered but dose selection must take into account multiple factors including the current Argatroban dose, the current aPTT, target aPTT, and the clinical status of the patient. These dose recommendations are based upon a goal of aPTT prolongation of 1.5 to 3 times the baseline value and avoidance of an aPTT >100 seconds.

8.5 Geriatric Use

Of the total number of subjects (1340) in clinical studies of argatroban, 35% were 65 and over. In the clinical studies of adult patients with HIT (with or without thrombosis), the effectiveness of argatroban was not affected by age. No trends were observed across age groups for both aPTT and the ACT. The safety analysis did suggest that older patients had increased underlying conditions, which may predispose them to events. The studies were not sized appropriately to detect differences in safety between age groups.

8.6 Hepatic Impairment

Dose reduction and careful titration are required when administering argatroban to patients with hepatic impairment. Reversal of anticoagulation effect may be prolonged in this population *[see Dosage and Administration (2.3), Warning and Precautions (5.2), Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

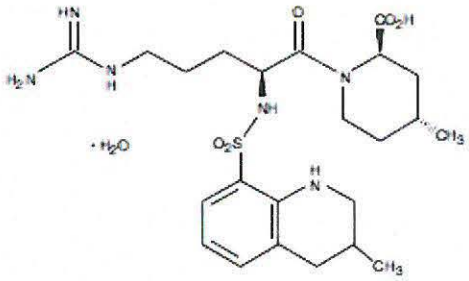
Excessive anticoagulation, with or without bleeding, may be controlled by discontinuing argatroban or by decreasing the argatroban dose. In clinical studies, anticoagulation parameters generally returned from therapeutic levels to baseline within 2 to 4 hours after discontinuation of the drug. Reversal of anticoagulant effect may take longer in patients with hepatic impairment. No specific antidote to argatroban is available; if life-threatening bleeding occurs and excessive plasma levels of argatroban are suspected, discontinue argatroban immediately and measure aPTT and other coagulation parameters. When argatroban was administered as a continuous infusion (2 mcg/kg/min) prior to and during a 4-hour hemodialysis session, approximately 20% of argatroban was cleared through dialysis.

Single intravenous doses of argatroban at 200, 124, 150, and 200 mg/kg were lethal to mice, rats, rabbits, and dogs, respectively. The symptoms of acute toxicity were loss of righting reflex, tremors, clonic convulsions, paralysis of hind limbs, and coma.

11 DESCRIPTION

Argatroban is a synthetic direct thrombin inhibitor and the chemical name is 1-[5-[(aminoiminomethyl)amino]-1-oxo-2-[[(1,2,3,4-tetrahydro-3-methyl-8- quinolinyl)sulfonyl]amino]pentyl]-4-methyl-2-piperidinecarboxylic acid, monohydrate. Argatroban has 4 asymmetric carbons. One of the asymmetric carbons has an R configuration (stereoisomer Type I) and an S configuration (stereoisomer Type II). Argatroban consists of a mixture of R and S stereoisomers at a ratio of approximately 65:35.

The molecular formula of Argatroban is C23H36N6O5S•H2O. Its molecular weight is 526.66 g/mol. The structural formula is shown below:



Argatroban is a white, odorless crystalline powder that is freely soluble in glacial acetic acid, slightly soluble in ethanol, and insoluble in acetone, ethyl acetate, and ether. Argatroban Injection is a sterile clear, colorless to pale yellow, slightly viscous solution. Argatroban is available in 250-mg (in 2.5-mL) single-use amber vials, with white flip-top caps. Each mL of sterile, nonpyrogenic solution contains 100 mg Argatroban. Inert ingredients: 1300 mg Propylene glycol, 760 mg Dehydrated alcohol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Argatroban is a direct thrombin inhibitor that reversibly binds to the thrombin active site. Argatroban does not require the co-factor antithrombin III for antithrombotic activity. Argatroban exerts its anticoagulant effects by inhibiting thrombin-catalyzed or -induced reactions, including fibrin formation; activation of coagulation factors V, VIII, and XIII; activation of protein C; and platelet aggregation.

Argatroban inhibits thrombin with an inhibition constant (Ki) of 0.04 μM. At therapeutic concentrations, argatroban has little or no effect on related serine proteases (trypsin, factor Xa, plasmin, and kallikrein).

Argatroban is capable of inhibiting the action of both free and clot-associated thrombin.

12.2 Pharmacodynamics

When argatroban is administered by continuous infusion, anticoagulant effects and plasma concentrations of argatroban follow similar, predictable temporal response profiles, with low intersubject variability. Immediately upon initiation of argatroban infusion, anticoagulant effects are produced as plasma argatroban concentrations begin to rise. Steady-state levels of both drug and anticoagulant effect are typically attained within 1 to 3 hours and are maintained until the infusion is discontinued or the dosage adjusted. Steady-state plasma argatroban concentrations increase proportionally with dose (for infusion doses up to 40 mcg/kg/min in healthy subjects) and are well correlated with steady-state anticoagulant effects. For infusion doses up to 40 mcg/kg/min, argatroban increases in a dose-dependent fashion, the activated partial thromboplastin time (aPTT), the activated clotting time (ACT), the prothrombin time (PT), the International Normalized Ratio (INR), and the thrombin time (TT) in healthy volunteers and cardiac patients. Representative steady-state plasma argatroban concentrations and anticoagulant effects are shown below for argatroban infusion doses up to 10 mcg/kg/min (see Figure 1).

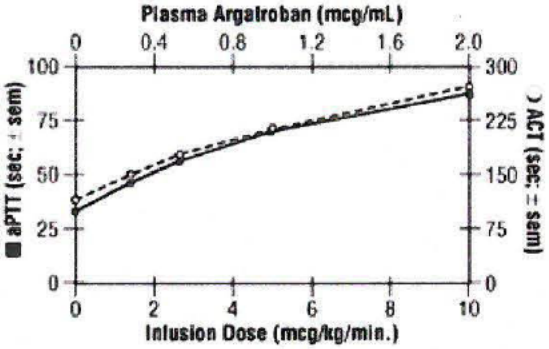


Figure 1. Relationship at Steady State Between Argatroban Dose, Plasma Argatroban Concentration and Anticoagulant Effect

Effect on International Normalized Ratio (INR): Because argatroban is a direct thrombin inhibitor, co-administration of argatroban and warfarin produces a combined effect on the laboratory measurement of the INR. However, concurrent therapy, compared to warfarin monotherapy, exerts no additional effect on vitamin K–dependent factor Xa activity.

The relationship between INR on co-therapy and warfarin alone is dependent on both the dose of argatroban and the thromboplastin reagent used. This relationship is influenced by the International Sensitivity Index (ISI) of the thromboplastin. Data for 2 commonly utilized thromboplastins with ISI values of 0.88 (Innovin, Dade) and 1.78 (Thromboplastin C Plus, Dade) are presented in Figure 2 for an argatroban dose of 2 mcg/kg/min. Thromboplastins with higher ISI values than shown result in higher INRs on combined therapy of warfarin and argatroban. These data are based on results obtained in normal individuals *[see Dosage and Administration (2.6), Warnings and Precautions (5.3)]*.

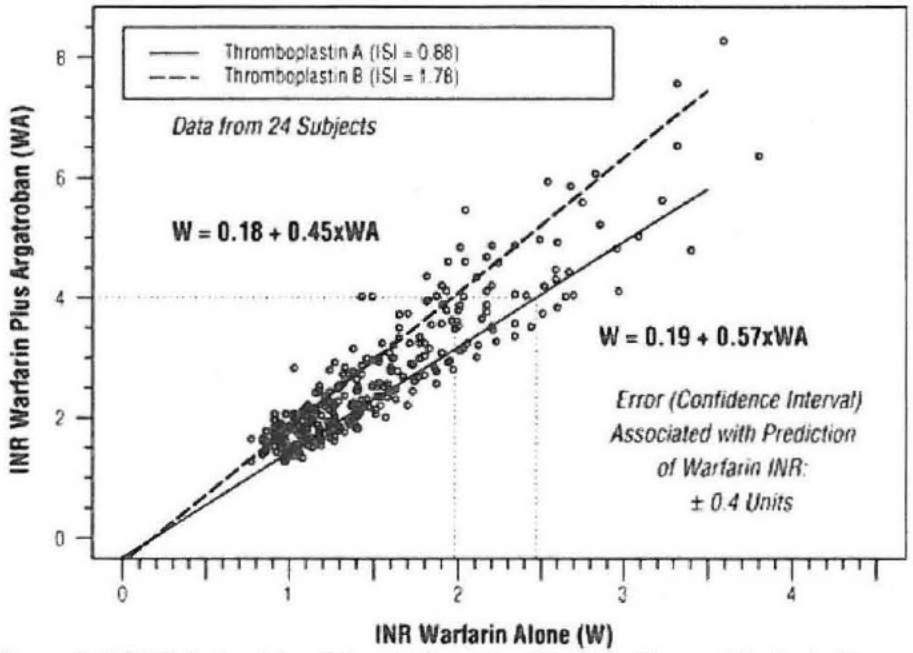


Figure 2. INR Relationship of Argatroban Plus Warfarin Versus Warfarin Alone

Figure 2 demonstrates the relationship between INR for warfarin alone and INR for warfarin co-administered with argatroban at a dose of 2 mcg/kg/min. To calculate INR for warfarin alone (INR_W), based on INR for co-therapy of warfarin and argatroban (INR_{WA}), when the argatroban dose is 2 mcg/kg/min, use the equation next to the appropriate curve. Example: At a dose of 2 mcg/kg/min and an INR performed with Thromboplastin A, the equation 0.19 + 0.57 (INR_{WA}) = INR_W would allow a prediction of the INR on warfarin alone (INR_W). Thus, using an INR_{WA} value of 4.0 obtained on combined therapy: INR_W = 0.19 + 0.57 (4) = 2.47 as the value for INR on warfarin alone. The error (confidence interval) associated with a prediction is ± 0.4 units. Similar linear relationships and prediction errors exist for argatroban at a dose of 1 mcg/kg/min. Thus, for argatroban doses of 1 or 2 mcg/kg/min, INR_W can be predicted from INR_{WA}. For argatroban doses greater than 2 mcg/kg/min, the error associated with predicting INR_W from INR_{WA} is ± 1. Thus, INR_W cannot be reliably predicted from INR_{WA} at doses greater than 2 mcg/kg/min.

12.3 Pharmacokinetics

Distribution:
Argatroban distributes mainly in the extracellular fluid as evidenced by an apparent steady-state volume of distribution of 174 mL/kg (12.18 L in a 70-kg adult). Argatroban is 54% bound to human serum proteins, with binding to albumin and α_1-acid glycoprotein being 20% and 34%, respectively.

Metabolism:
The main route of argatroban metabolism is hydroxylation and aromatization of the 3-methyltetrahydroquinoline ring in the liver. The formation of each of the 4 known metabolites is catalyzed *in vitro* by the human liver microsomal cytochrome P450 enzymes CYP3A4/5. The primary metabolite (M1) exerts 3- to 5-fold weaker anticoagulant effects than argatroban. Unchanged argatroban is the major component in plasma. The plasma concentrations of M1 range between 0% and 20% of that of the parent drug. The other metabolites (M2 to M4) are found only in very low quantities in the urine and have not been detected in plasma or feces. These data, together with the lack of effect of erythromycin (a potent CYP3A4/5 inhibitor) on argatroban pharmacokinetics, suggest that CYP3A4/5-mediated metabolism is not an important elimination pathway *in vivo*.

Total body clearance is approximately 5.1 mL/kg/min (0.31 L/kg/hr) for infusion doses up to 40 mcg/kg/min. The terminal elimination half-life of argatroban ranges between 39 and 51 minutes.

There is no interconversion of the 21–(R):21–(S) diastereoisomers. The plasma ratio of these diastereoisomers is unchanged by metabolism or hepatic impairment, remaining constant at 65:35 (± 2%).

Excretion:
Argatroban is excreted primarily in the feces, presumably through biliary secretion. In a study in which 14C-argatroban (5 mcg/kg/min) was infused for 4 hours into healthy subjects, approximately 65% of the radioactivity was recovered in the feces within 6 days of the start of infusion with little or no radioactivity subsequently detected. Approximately 22% of the radioactivity appeared in the urine within 12 hours of the start of infusion. Little or no additional urinary radioactivity was subsequently detected. Average percent recovery of unchanged drug, relative to total dose, was 16% in urine and at least 14% in feces.

Special Populations:
Hepatic Impairment: The dosage of argatroban should be decreased in patients with hepatic impairment *[see Dosage and Administration (2.3) and Warnings and Precautions (5.2)]*. Patients with hepatic impairment were not studied in percutaneous coronary intervention (PCI) trials. At a dose of 2.5 mcg/kg/min, hepatic impairment is associated with decreased clearance and increased elimination half-life of argatroban (to 1.9 mL/kg/min and 181 minutes, respectively, for patients with a Child-Pugh score greater than 6).

Renal Impairment: No dosage adjustment is necessary in patients with renal dysfunction. The effect of renal disease on the pharmacokinetics of argatroban was studied in 6 subjects with normal renal function (mean Clcr = 95 ± 16 mL/min) and in 18 subjects with mild (mean Clcr = 64 ± 10 mL/min), moderate (mean Clcr = 41 ± 5.8 mL/min), and severe (mean Clcr = 5 ± 7 mL/min) renal impairment. The pharmacokinetics and pharmacodynamics of argatroban at dosages up to 5 mcg/kg/min were not significantly affected by renal dysfunction.

Use of argatroban was evaluated in a study of 12 patients with stable end-stage renal disease undergoing chronic intermittent hemodialysis. Argatroban was administered at a rate of 2 to 3 mcg/kg/min (begun at least 4 hours prior to dialysis) or as a bolus dose of 250 mcg/kg at the start of dialysis followed by a continuous infusion of 2 mcg/kg/min. Although these regimens did not achieve the goal of maintaining ACT values at 1.8 times the baseline value throughout most of the hemodialysis period, the hemodialysis sessions were successfully completed with both of these regimens. The mean ACTs produced in this study ranged from 1.39 to 1.82 times baseline, and the mean aPTTs ranged from 1.96 to 3.4 times the baseline. When argatroban was administered as a continuous infusion of 2 mcg/kg/min prior to and during a 4-hour hemodialysis session, approximately 20% was cleared through dialysis.

Age, Gender: There are no clinically significant effects of age or gender on the pharmacokinetics or pharmacodynamics (e.g., aPTT) of argatroban in adults.

Pediatric: Argatroban clearance is decreased in seriously ill pediatric patients. Pharmacokinetic parameters of argatroban were characterized in a population pharmacokinetic/pharmacodynamic analysis with sparse data from 15 seriously ill pediatric patients. Clearance in pediatric patients (0.16 L/hr/kg) was 50% lower compared to healthy adults (0.31 L/hr/kg). Four pediatric patients with elevated bilirubin (secondary to cardiac complications or hepatic impairment) had, on average, 80% lower clearance (0.03 L/hr/kg) when compared to pediatric patients with normal bilirubin levels. *[see Use in Specific Populations (8.4).]*

Drug-Drug Interactions:

Digoxin: In 12 healthy volunteers, intravenous infusion of argatroban (2 mcg/kg/min) over 5 days (study days 11 to 15) did not affect the steady-state pharmacokinetics of oral digoxin (0.375 mg daily for 15 days).

Erythromycin: In 10 healthy subjects, orally administered erythromycin (a potent inhibitor of CYP3A4/5) at 500 mg four times daily for 7 days had no effect on the pharmacokinetics of argatroban at a dose of 1 mcg/kg/min for 5 hours. These data suggest oxidative metabolism by CYP3A4/5 is not an important elimination pathway *in vivo* for argatroban.

Aspirin and Acetaminophen: Drug-drug interactions have not been demonstrated between argatroban and concomitantly administered aspirin (162.5 mg orally given 26 and 2 hours prior to initiation of argatroban 1 mcg/kg/min over 4 hours) or

acetaminophen (1,000 mg orally given 12, 6, and 0 hours prior to, and 6 and 12 hours subsequent to, initiation of argatroban1.5 mcg/kg/min over 18 hours).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with argatroban have not been performed.

Argatroban was not genotoxic in the Ames test, the Chinese hamster ovary cell (CHO/HGPRT) forward mutation test, the Chinese hamster lung fibroblast chromosome aberration test, the rat hepatocyte, and WI-38 human fetal lung cell unscheduled DNA synthesis (UDS) tests, or the mouse micronucleus test.

Argatroban at intravenous doses up to 27 mg/kg/day (0.3 times the recommended maximum human dose based on body surface area) had no effect on fertility and reproductive function of male and female rats.

14 CLINICAL STUDIES

14.1 Heparin-Induced Thrombocytopenia

The safety and efficacy of argatroban were evaluated in a historically controlled efficacy and safety study (Study 1) and a follow-on efficacy and safety study (Study 2). These studies were comparable with regard to study design, study objectives, dosing regimens as well as study outline, conduct, and monitoring. In these studies, 568 adult patients were treated with argatroban and 193 adult patients made up the historical control group. Patients had a clinical diagnosis of heparin-induced thrombocytopenia, either without thrombosis (HIT) or with thrombosis (HITTS [heparin-induced thrombocytopenia and thrombosis syndrome]) and were males or non-pregnant females between the age of 18 and 80 years old. HIT/HITTS was defined by a fall in platelet count to less than 100,000/μL or a 50% decrease in platelets after the initiation of heparin therapy with no apparent explanation other than HIT. Patients with HITTS also had an arterial or venous thrombosis documented by appropriate imaging techniques or supported by clinical evidence such as acute myocardial infarction, stroke, pulmonary embolism, or other clinical indications of vascular occlusion. Patients who had documented histories of positive heparin-dependent antibody tests without current thrombocytopenia or heparin challenge (e.g., patients with latent disease) were also included if they required anticoagulation.

These studies did not include patients with documented unexplained aPTT >200% of control at baseline, documented coagulation disorder or bleeding diathesis unrelated to HIT, a lumbar puncture within the past 7 days or a history of previous aneurysm, hemorrhagic stroke, or a thrombotic stroke within the past 6 months unrelated to HIT.

The initial dose of argatroban was 2 mcg/kg/min. Two hours after the start of the argatroban infusion, an aPTT level was obtained and dose adjustments were made (up to a maximum of 10 mcg/kg/min) to achieve a steady-state aPTT value that was 1.5 to 3.0 times the baseline value, not to exceed 100 seconds. Overall the mean aPTT level for HIT and HITTS patients during the Argatroban infusion increased from baseline values of 34 and 38 seconds, respectively, to 62.5 and 64.5 seconds, respectively.

The primary efficacy analysis was based on a comparison of event rates for a composite endpoint that included death (all causes), amputation (all causes) or new thrombosis during the treatment and follow-up period (study days 0 to 37). Secondary analyses included evaluation of the event rates for the components of the composite endpoint as well as time-to-event analyses.

In Study 1, a total of 304 patients were enrolled as follows: active HIT (n = 129), active HITTS (n =144), or latent disease (n = 31). Among the 193 historical controls, 139 (72%) had active HIT, 46 (24%) had active HITTS, and 8 (4%) had latent disease. Within each group, those with active HIT and those with latent disease were analyzed together. Positive

laboratory confirmation of HIT/HITTS by the heparin-induced platelet aggregation test or serotonin release assay was demonstrated in 174 of 304 (57%) argatroban-treated patients (i.e., in 80 with HIT or latent disease and 94 with HITTS) and in 149 of 193 (77%) historical controls (i.e., in 119 with HIT or latent disease and 30 with HITTS). The test results for the remainder of the patients and controls were either negative or not determined.

There was a significant improvement in the composite outcome in patients with HIT and HITTS treated with argatroban versus those in the historical control group (see Table 9). The components of the composite endpoint are shown in Table 9.

Table 9.
Efficacy Results of Study 1: Composite Endpoint[a] and Individual Components, Ranked by Severity[b]

Parameter, N (%)	HIT		HITTS		HIT/HITTS	
	Control n = 147	Argatroban n = 160	Control n = 46	Argatroban n = 144	Control n = 193	Argatroban n = 304
Composite Endpoint	57 (38.8)	41 (25.6)	26 (56.5)	63 (43.8)	83 (43.0)	104 (34.2)
Individual Components[b]						
Death	32 (21.8)	27 (16.9)	13 (28.3)	26 (18.1)	45 (23.3)	53 (17.4)
Amputation	3 (2.0)	3 (1.9)	4 (8.7)	16 (11.1)	7 (3.6)	19 (6.2)
New Thrombosis	22 (15.0)	11 (6.9)	9 (19.6)	21 (14.6)	31 (16.1)	32 (10.5)

a) Death (all cause), amputation (all cause), or new thrombosis within 37-day study period.
b) Reported as the most severe outcome among the components of composite endpoint (severity ranking: death > amputation > new thrombosis); patients may have had multiple outcomes.

Time-to-event analyses showed significant improvements in the time-to-first event in patients with HIT or HITTS treated with argatroban versus those in the historical control group. The between-group differences in the proportion of patients who remained free of death, amputation, or new thrombosis were statistically significant in favor of argatroban by these analyses.

A time-to-event analysis for the composite endpoint is shown in Figure 3 for patients with HIT and Figure 4 for patients with HITTS.

STUDY 1

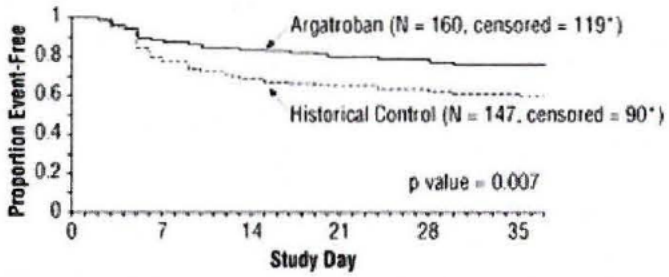


Figure 3. Time to First Event for the Composite Efficacy Endpoint: HIT Patients

*** Censored indicates no clinical endpoint (defined as death, amputation, or new thrombosis) was observed during the follow-up period (maximum period of follow-up was 37 days).**

STUDY 1

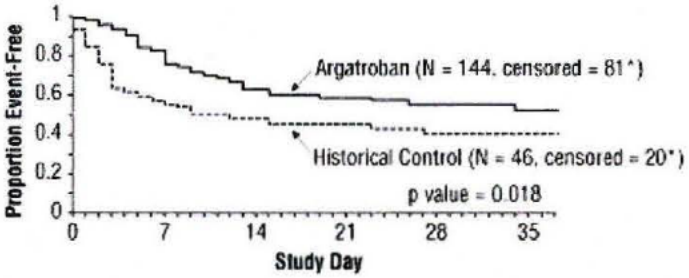


Figure 4. Time to First Event for the Composite Efficacy Endpoint: HITTS Patients

*** Censored indicates no clinical endpoint (defined as death, amputation, or new thrombosis) was observed during the follow-up period (maximum period of follow-up was 37 days).**

In Study 2, a total of 264 patients were enrolled as follows: HIT (n = 125) or HITTS (n = 139). There was a significant improvement in the composite efficacy outcome for argatroban-treated patients, versus the same historical control group from Study 1, among patients having HIT (25.6% vs. 38.8%), patients having HITTS (41.0% vs. 56.5%), and patients having either HIT or HITTS (33.7% vs. 43.0%). Time-to-event analyses showed significant improvements in the time-to-first event in patients with HIT or HITTS treated with argatroban versus those in the historical control group. The between-group differences in the proportion of patients who remained free of death, amputation, or new thrombosis were statistically significant in favor of argatroban.

Anticoagulant Effect:
In Study 1, the mean (± SE) dose of argatroban administered was 2.0 ± 0.1 mcg/kg/min in the HIT arm and 1.9 ± 0.1 mcg/kg/min in the HITTS arm. Seventy-six percent of patients with HIT and 81% of patients with HITTS achieved a target aPTT at least 1.5-fold greater than the baseline aPTT at the first assessment occurring on average at 4.6 hours (HIT) and 3.9 hours (HITTS) following initiation of argatroban therapy.

No enhancement of aPTT response was observed in subjects receiving repeated administration of argatroban.

Platelet Count Recovery:
In Study 1, 53% of patients with HIT and 58% of patients with HITTS, had a recovery of platelet count by Day 3. Platelet Count Recovery was defined as an increase in platelet count to >100,000/μL or to at least 1.5-fold greater than the baseline count (platelet count at study initiation) by Day 3 of the study.

14.2 Percutaneous Coronary Intervention (PCI) Patients with or at Risk for HIT

In 3 similarly designed trials, argatroban was administered to 91 patients with current or previous clinical diagnosis of HIT or heparin-dependent antibodies, who underwent a total of 112 percutaneous coronary interventions (PCIs) including percutaneous transluminal coronary angioplasty (PTCA), coronary stent placement, or atherectomy. Among the 91 patients undergoing their first PCI with argatroban, notable ongoing or recent medical history included myocardial infarction (n = 35), unstable angina (n = 23), and chronic angina (n = 34). There were 33 females and 58 males. The average age was 67.6 years (median 70.7, range 44 to 86), and the average weight was 82.5 kg (median 81.0 kg, range 49 to 141).

Twenty-one of the 91 patients had a repeat PCI using argatroban an average of 150 days after their initial PCI. Seven of 91 patients received glycoprotein IIb/IIIa inhibitors. Safety and efficacy were assessed against historical control populations who had been anticoagulated with heparin.

All patients received oral aspirin (325 mg) 2 to 24 hours prior to the interventional procedure. After venous or arterial sheaths were in place, anticoagulation was initiated with a bolus of argatroban of 350 mcg/kg via a large-bore intravenous line or through the venous sheath over 3 to 5 minutes. Simultaneously, a maintenance infusion of 25 mcg/kg/min was initiated to achieve a therapeutic activated clotting time (ACT) of 300 to 450 seconds. If necessary to achieve this therapeutic range, the maintenance infusion dose was titrated (15 to 40 mcg/kg/min) and/or an additional bolus dose of 150 mcg/kg could be given. Each patient's ACT was checked 5 to 10 minutes following the bolus dose. The ACT was checked as clinically indicated. Arterial and venous sheaths were removed no sooner than 2 hours after discontinuation of argatroban and when the ACT was less than 160 seconds.

If a patient required anticoagulation after the procedure, argatroban could be continued, but at a lower infusion dose between 2.5 and 5 mcg/kg/min. An aPTT was drawn 2 hours after this dose reduction and the dose of argatroban then was adjusted as clinically indicated (not to exceed 10 mcg/kg/min), to reach an aPTT between 1.5 and 3 times baseline value (not to exceed 100 seconds).

In 92 of the 112 interventions (82%), the patient received the initial bolus of 350 mcg/kg and an initial infusion dose of 25 mcg/kg/min. The majority of patients did not require additional bolus dosing during the PCI procedure. The mean value for the initial ACT measurement after the start of dosing for all interventions was 379 sec (median 338 sec; 5^{th} percentile-95^{th} percentile 238 to 675 sec). The mean ACT value per intervention over all measurements taken during the procedure was 416 sec (median 390 sec; 5^{th} percentile-95^{th} percentile 261 to 698 sec). About 65% of patients had ACTs within the recommended range of 300 to 450 seconds throughout the procedure. The investigators did not achieve anticoagulation within the recommended range in about 23% of patients. However, in this small sample, patients with ACTs below 300 seconds did not have more coronary thrombotic events, and patients with ACTs over 450 seconds did not have higher bleeding rates.

Acute procedural success was defined as lack of death, emergent coronary artery bypass graft (CABG), or Q-wave myocardial infarction. Acute procedural success was reported in 98.2% of patients who underwent PCIs with argatroban anticoagulation compared with 94.3% of historical control patients anticoagulated with heparin (p = NS). Among the 112 interventions, 2 patients had emergency CABGs, 3 had repeat PTCAs, 4 had non-Q-wave myocardial infarctions, 3 had myocardial ischemia, 1 had an abrupt closure, and 1 had an impending closure (some patients may have experienced more than 1 event). No patients died.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

NDC 0143-9674-01 (Package of 1)

Storage and Handling

Store the vials in original carton at 20° - 25° C (68° - 77° F) [See USP Controlled Room Temperature]. Do not freeze. Retain in the original carton to protect from light. If the solution is cloudy, or if an insoluble precipitate is noted, the vial should be discarded.

17 PATIENT COUNSELING INFORMATION

Inform patients of the risks associated with Argatroban Injection as well as the plan for regular monitoring during administration of the drug. Specifically, inform patients to report:

- the use of any other products known to affect bleeding.
- any medical history that may increase the risk for bleeding, including a history of severe hypertension; recent lumbar puncture or spinal anesthesia; major surgery, especially involving the brain, spinal cord, or eye; hematologic conditions associated with increased bleeding tendencies such as congenital or acquired bleeding disorders and gastrointestinal lesions such as ulcerations.
- any bleeding signs or symptoms.
- the occurrence of any signs or symptoms of allergic reactions (e.g., airway reactions, skin reactions and vasodilation reactions).

Manufactured by:
Exela Pharma Sciences, LLC
Lenoir, NC 28645

Distributed by:
West-Ward Pharmaceuticals Corp.
Eatontown, NJ 07724

Revised May 2016

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

/s/

BARRY W MILLER
05/26/2016

Jonathan, the attached PI is **not in the proper format**. The Highlights is not in the 2 column format, the line spacing and fonts are not correct. Line spacing must be single space and it must be in 8 font.

Please resubmit the PI in the correct format. I suggest you send the PI to me via email first and I will do a quick format review and let you know whether or not the format is correct. Then you can follow up with a correct PI in the proper format.

Please confirm receipt of this email.

Regards.

Amy

From: Jonathan Sterling [mailto:jsterling@exela.us]
Sent: Friday, July 22, 2016 5:53 PM
To: Tilley, Amy
Subject: RE: URGENT NDA 203049 Argatroban S-004 SN 0024 - PI Information Request

Filed today

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
Sent: Friday, July 22, 2016 10:05 AM
To: Jonathan Sterling
Subject: RE: URGENT NDA 203049 Argatroban S-004 SN 0024 - PI Information Request

Excellent just keep me posted!

Amy

From: Jonathan Sterling [mailto:jsterling@exela.us]
Sent: Friday, July 22, 2016 10:02 AM
To: Tilley, Amy
Subject: RE: URGENT NDA 203049 Argatroban S-004 SN 0024 - PI Information Request

We are trying to file today

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
Sent: Friday, July 22, 2016 9:46 AM
To: Jonathan Sterling
Subject: RE: URGENT NDA 203049 Argatroban S-004 SN 0024 - PI Information Request

Jonathan, how soon can I expect the corrected PI to be emailed or submitted to the NDA?

We have an upcoming internal meeting to discuss the PI, hence my question regarding how soon can I expect the corrected PI.

Amy

From: Tilley, Amy
Sent: Thursday, July 21, 2016 4:23 PM
To: 'jsterling@exela.us'
Subject: URGENT NDA 203049 Argatroban S-004 SN 0024 - PI Information Request
Importance: High

Jonathan, unfortunately the revised PI that you submitted on June 16th does not contain ***Supplement 4 proposed revisions in Tracked Changes***. See attached.

We request you resubmit a corrected PI that contains 1) all the revisions from Supplement 5 ***not*** in tracked changes and 2) all the proposed revisions to ***Supplement 4 in tracked changes.***

We request your submission as soon as possible. Please send me an email notifying me that the submission has been sent.

Kindly confirm receipt of this email.

Regards.
Amy Tilley

Amy Tilley|Regulatory Project Manager|Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108|Silver Spring, MD 20993
☎301.796.3994 (phone)● 301.796.9845 (fax)| ✉ amy.tilley@fda.hhs.gov

---

From: Tilley, Amy
Sent: Tuesday, June 14, 2016 5:48 PM
To: 'jsterling@exela.us'
Subject: RE: URGENT NDA 203049 Argatroban S-004 SN 0024 - Information Request
Importance: High

Jonathan, since S-5 was approved on May 26, 2016, you must submit the revised PI and labels to any unapproved supplements.

Please submit the most current PI and labels from the approval of S-5 to S-4 asap in tracked changes.

Kindly let me know once you have submitted the revised PI and labels.

Regards.

Amy

From: Tilley, Amy
Sent: Wednesday, April 13, 2016 10:20 AM
To: 'jsterling@exela.us'
Subject: RE: URGENT NDA 203049 Argatroban S-004 SN 0024 - Information Request
Importance: High

Jonathan, this email is a follow up to my vm from earlier today.

Yesterday we discussed that you were going to submit the PI and labels that you are currently working on for Supplement 5. However, if the PI and labels for Supplement 5 *do not* contain the changes your are requesting in Supplement 4 then those labels will not work.

Please officially submit the PI in Word format with the proposed revisions in tracked changes along with the carton and container labels that were initially submitted to Supplement 4.

Please confirm receipt of this email.

Regards.
Amy

From: Tilley, Amy
Sent: Tuesday, April 12, 2016 4:56 PM
To: 'jsterling@exela.us'
Subject: URGENT NDA 203049 Argatroban S-004 SN 0024 - Information Request
Importance: High

Jonathan,

I am the Project Manager who will be managing your March 31, 2016, Complete Response (CR) submission regarding Supplement 004. In your CR submission you did not include the tracked PI in Word format or the carton and container labels.

Please submit the labeling as soon as possible and reference in your cover letter that the labeling refers to the Supplement 4 Complete Response submission dated March 31, 2016.

Kindly confirm receipt of this emailed Information Request.

Regards.
Amy Tilley

Amy Tilley|Regulatory Project Manager|Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108|Silver Spring, MD 20993
☎301.796.3994 (phone)● 301.796.9845 (fax)|✉ amy.tilley@fda.hhs.gov

<Argatroban_PI Rev07-16 clean copy.pdf>
<Argatroban_PI Rev07-16 track changes.docx>
<Argatroban_PI Rev07-16 track changes.pdf>
<Argatroban_PI Rev07-16 clean copy.docx>

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/s/

AMY R TILLEY
07/24/2016

From:	Tilley, Amy
To:	"jsterling@exela.us"
Bcc:	Kwitkowski, Virginia
Subject:	URGENT NDA 203049 Argatroban S-004 SN 0024 - PI Information Request
Date:	Thursday, July 21, 2016 4:22:52 PM
Attachments:	Argatroban PI Spon Rev June 16 after apprvl S-5.docx
Importance:	High

Jonathan, unfortunately the revised PI that you submitted on June 16th does not contain ***Supplement 4 proposed revisions in Tracked Changes***. See attached.

We request you resubmit a corrected PI that contains 1) all the revisions from Supplement 5 ***not*** in tracked changes and 2) all the proposed revisions to ***Supplement 4 in tracked changes.***

We request your submission as soon as possible. Please send me an email notifying me that the submission has been sent.

Kindly confirm receipt of this email.

Regards.
Amy Tilley

Amy Tilley|Regulatory Project Manager|Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2108|Silver Spring, MD 20993
☎301.796.3994 (phone)● 301.796.9845 (fax)|✉ amy.tilley@fda.hhs.gov

---

From: Tilley, Amy
Sent: Tuesday, June 14, 2016 5:48 PM
To: 'jsterling@exela.us'
Subject: RE: URGENT NDA 203049 Argatroban S-004 SN 0024 - Information Request
Importance: High

Jonathan, since S-5 was approved on May 26, 2016, you must submit the revised PI and labels to any unapproved supplements.

Please submit the most current PI and labels from the approval of S-5 to S-4 asap in tracked changes.

Kindly let me know once you have submitted the revised PI and labels.

Regards.

Amy

From: Tilley, Amy
Sent: Wednesday, April 13, 2016 10:20 AM
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Subject: RE: URGENT NDA 203049 Argatroban S-004 SN 0024 - Information Request
Importance: High

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Regards.
Amy

From: Tilley, Amy
Sent: Tuesday, April 12, 2016 4:56 PM
To: 'jsterling@exela.us'
Subject: URGENT NDA 203049 Argatroban S-004 SN 0024 - Information Request
Importance: High

Jonathan,

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Please submit the labeling as soon as possible and reference in your cover letter that the labeling refers to the Supplement 4 Complete Response submission dated March 31, 2016.

Kindly confirm receipt of this emailed Information Request.

Regards.
Amy Tilley

Amy Tilley|Regulatory Project Manager|Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2108|Silver Spring, MD 20993
☎301.796.3994 (phone)● 301.796.9845 (fax)|✉ amy.tilley@fda.hhs.gov

26 Page(s) of Draft Labeling has 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.

/s/

AMY R TILLEY
07/21/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Mail: OSE**			FROM: Amy Tilley/DOP1 RPM for DHP sNDA 203049-S-4/301-796-3994	
DATE June 21, 2016	IND NO.	NDA NO. 203049/S-4 SDN 45	TYPE OF DOCUMENT PAS (sub after CR)	DATE OF DOCUMENT April 1, 2016
NAME OF DRUG Argatroban Injection	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE September 1, 2016

NAME OF FIRM: Hikma Pharmaceutical Co. Ltd.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☒ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Hikma originally submitted Supplement 4 received on April 27, 2015, which proposed the addition of a ready to use dilution presentation of the current drug product. Upon review DHP issued a Complete Response on October 26, 2015. This submission, SDN 45, is a Supplement/Resubmission/After Action Complete Response. Please let me know who the DMEPA Label Reviewer and Team Leader will be.
EDR link to submission: \\CDSESUB4\NONECTD\NDA203049\6044004 (SDN 45 Supplement-Resubmission-After Action-Complete Response)

Labeling Meetings: Being reviewed under the DHP Labeling Pilot Program

SIGNATURE OF REQUESTER Amy Tilley/DOP1 RPM managing S-4 for DHP	METHOD OF DELIVERY (Check all that apply) ☒ eMAIL ☒ DARRTS ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

06/18/2013

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

/s/

AMY R TILLEY
06/21/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO: **CDER-OPDP-RPM**	FROM: (Name/Title, Office/Division/Phone number of requestor) Amy Tilley/RPM/OHOP/DHP/301-796-3994

REQUEST DATE:	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
June 21, 2016		NDA 203049/S-4	

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Argatroban Injection			September 1, 2016

NAME OF FIRM: Hikma Pharmaceuticals Co. Ltd.	PDUFA Date: September 30, 2016

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☒ PACKAGE INSERT (PI)
☐ PATIENT PACKAGE INSERT (PPI)
☒ CARTON/CONTAINER LABELING
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☐ IND
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☐ LABELING REVISION

For OSE USE ONLY
☐ REMS

EDR link to submission: \\CDSESUB4\NONECTD\NDA203049\6044004 (SDN 45 Supplement-Resubmission-After Action-Complete Response)

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS:
Hikma originally submitted Supplement 4 received on April 27, 2015, which proposed the addition of a ready to use dilution presentation of the current drug product. Upon review DHP issued a Complete Response on October 26, 2015. This submission, SDN 45, is a Supplement/Resubmission/After Action Complete Response. Therefore, we are requesting the same OPDP Reviewer who was previously assigned to Supplement 4, i.e., James Dvorsky and his Team Leader.

Labeling Meetings: Being reviewed under the DHP Labeling Pilot Program

SIGNATURE OF REQUESTER
Amy Tilley, DOP1 RPM, Managing Supplement 4 per DHP request.

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☒ eMAIL ☐ HAND

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/s/

AMY R TILLEY
06/21/2016

From: Tilley, Amy
To: "jsterling@exela.us"
Subject: RE: URGENT NDA 203049 Argatroban S-004 SN 0024 - Information Request
Date: Tuesday, June 14, 2016 5:48:17 PM
Importance: High

Jonathan, since S-5 was approved on May 26, 2016, you must submit the revised PI and labels to any unapproved supplements.

Please submit the most current PI and labels from the approval of S-5 to S-4 asap in tracked changes.

Kindly let me know once you have submitted the revised PI and labels.

Regards.

Amy

From: Tilley, Amy
Sent: Wednesday, April 13, 2016 10:20 AM
To: 'jsterling@exela.us'
Subject: RE: URGENT NDA 203049 Argatroban S-004 SN 0024 - Information Request
Importance: High

Jonathan, this email is a follow up to my vm from earlier today.

Yesterday we discussed that you were going to submit the PI and labels that you are currently working on for Supplement 5. However, if the PI and labels for Supplement 5 *do not* contain the changes your are requesting in Supplement 4 then those labels will not work.

Please officially submit the PI in Word format with the proposed revisions in tracked changes along with the carton and container labels that were initially submitted to Supplement 4.

Please confirm receipt of this email.

Regards.

Amy

From: Tilley, Amy
Sent: Tuesday, April 12, 2016 4:56 PM
To: 'jsterling@exela.us'
Subject: URGENT NDA 203049 Argatroban S-004 SN 0024 - Information Request
Importance: High

Jonathan,

I am the Project Manager who will be managing your March 31, 2016, Complete Response (CR) submission regarding Supplement 004. In your CR submission you did not include the tracked PI in Word format or the carton and container labels.

Please submit the labeling as soon as possible and reference in your cover letter that the labeling refers to the Supplement 4 Complete Response submission dated March 31, 2016.

Kindly confirm receipt of this emailed Information Request.

Regards.

Amy Tilley

Amy Tilley|Regulatory Project Manager|Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2108|Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax)|✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
06/14/2016

From: Tilley, Amy
To: "jsterling@exela.us"
Bcc: Kwitkowski, Virginia; Lee, Hyon-Zu
Subject: RE: URGENT NDA 203049 Argatroban S-004 SN 0024 - Information Request
Date: Wednesday, April 13, 2016 10:20:27 AM
Importance: High

Jonathan, this email is a follow up to my vm from earlier today.

Yesterday we discussed that you were going to submit the PI and labels that you are currently working on for Supplement 5. However, if the PI and labels for Supplement 5 *do not* contain the changes your are requesting in Supplement 4 then those labels will not work.

Please officially submit the PI in Word format with the proposed revisions in tracked changes along with the carton and container labels that were initially submitted to Supplement 4.

Please confirm receipt of this email.

Regards.

Amy

From: Tilley, Amy
Sent: Tuesday, April 12, 2016 4:56 PM
To: 'jsterling@exela.us'
Subject: URGENT NDA 203049 Argatroban S-004 SN 0024 - Information Request
Importance: High

Jonathan,

I am the Project Manager who will be managing your March 31, 2016, Complete Response (CR) submission regarding Supplement 004. In your CR submission you did not include the tracked PI in Word format or the carton and container labels.

Please submit the labeling as soon as possible and reference in your cover letter that the labeling refers to the Supplement 4 Complete Response submission dated March 31, 2016.

Kindly confirm receipt of this emailed Information Request.

Regards.

Amy Tilley

Amy Tilley|Regulatory Project Manager|Division of Oncology Products 1,

CDER, FDA 10903 New Hampshire Avenue, Room 2108|Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax)|✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
04/13/2016

From: Tilley, Amy
To: "jsterling@exela.us"
Subject: URGENT NDA 203049 Argatroban S-004 SN 0024 - Information Request
Date: Tuesday, April 12, 2016 4:56:03 PM
Importance: High

Jonathan,

I am the Project Manager who will be managing your March 31, 2016, Complete Response (CR) submission regarding Supplement 004. In your CR submission you did not include the tracked PI in Word format or the carton and container labels.

Please submit the labeling as soon as possible and reference in your cover letter that the labeling refers to the Supplement 4 Complete Response submission dated March 31, 2016.

Kindly confirm receipt of this emailed Information Request.

Regards.

Amy Tilley

Amy Tilley|Regulatory Project Manager|Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2108|Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax)|✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
04/12/2016

Jones, Jacquin

From: Jones, Jacquin
Sent: Monday, September 21, 2015 5:47 PM
To: 'Jonathan Sterling'
Subject: FDA Response: NDA 203049 FDA CMC Stability Data Comments

Good evening Mr. Sterling,

In response to your email below requesting [redacted] (b) (4) based on current submission, your request is not acceptable.

Our following response on September 21, 2015, still stands.

> CMC Stability Data Response:
> *Your proposed stability data submission is not acceptable. You will need to submit a minimum of 12-months stability data under 25°C, 60% RH condition and 6-months stability data under accelerated condition from three primary batches of the proposed product (1 mg/mL).*

If you're unable to provide the minimum of 12-months stability data, we will be unable to complete the review of your application.

Regards,

Jackie

Jacquin L. Jones, MS, BSN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Food and Drug Administration
WO Bldg 22, Rm 2222
10903 New Hampshire Ave.
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

From: Jonathan Sterling [mailto:jsterling@exela.us]
Sent: Monday, September 21, 2015 4:46 PM
To: Jones, Jacquin
Subject: RE: FDA Response: NDA 203049 FDA CMC Stability Data Comments

The 12 month data does not come off stability until November.

I cannot provide a response within that time frame.

Please advise what are my options. Can I request [redacted] (b) (4)

JES

From: Jones, Jacquin [mailto:Jacquin.Jones@fda.hhs.gov]
Sent: Monday, September 21, 2015 4:42 PM
To: Jonathan Sterling
Subject: FDA Response: NDA 203049 FDA CMC Stability Data Comments

Good afternoon Mr. Sterling,

The CMC team has provided the following response to Hikma's proposed Stability Data submission for NDA 203049 Argatroban.

> CMC Stability Data Response:
> *Your proposed stability data submission is not acceptable. You will need to submit a minimum of 12-months stability data under 25°C, 60% RH condition and 6-months stability data under accelerated condition from three primary batches of the proposed product (1 mg/mL).*

Please provide a response no later than 3pm on September 24, 2015.

Have a good evening,

Jackie

Jacquin L. Jones, MS, BSN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Food and Drug Administration
WO Bldg 22, Rm 2222
10903 New Hampshire Ave.
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

From: Jonathan Sterling [mailto:jsterling@exela.us]
Sent: Thursday, September 17, 2015 10:32 PM
To: Jones, Jacquin
Subject: RE: Status Update Rqsted: NDA 203049 FDA CMC Comments

I have looked at the stability data and at this point have 6 M ACC and 9 M RT.

I would like to request that I submit this data [redacted] (b) (4). The stability data shows no change during storage at either condition.

Also, we would request 24 months dating once all RT data has been generated.

Please advise.

JES

From: Jones, Jacquin [mailto:Jacquin.Jones@fda.hhs.gov]
Sent: Tuesday, September 15, 2015 4:44 PM
To: Jonathan Sterling
Subject: Status Update Rqsted: NDA 203049 FDA CMC Comments

Good afternoon Mr. Sterling,

I wanted to follow up to see if you received the below CMC comments and to inquire if your team has an estimated time as to when they will provide the requested data.

Your reply will help me coordinate with the review team as far as trying to complete the labeling supplement review by October 27, 2015.

Please send all responses directly to me as Laura Wall, who was covering for me last week, is out of the office this week.

Thank you for response and updates,

Jackie

Jacquin L. Jones, MS, BSN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Food and Drug Administration
WO Bldg 22, Rm 2222
10903 New Hampshire Ave.
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

From: Jones, Jacquin
Sent: Monday, September 14, 2015 7:02 AM
To: jsterling@exela.us
Cc: Wall, Laura
Subject: RE: NDA 203049 - FDA CMC Comments

Good morning Mr. Sterling,

I am back in the office and wanted to confirm that you received the below CMC comment.

Thank you for your reply,

Jackie

Jacquin L. Jones, MS, BSN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Food and Drug Administration
WO Bldg 22, Rm 2222
10903 New Hampshire Ave.
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

From: Wall, Laura
Sent: Friday, September 11, 2015 12:50 PM
To: jsterling@exela.us
Cc: Jones, Jacquin; Wall, Laura
Subject: NDA 203049 - FDA CMC Comments

Dear Jonathan,

The CMC review team has the following comments for NDA 203049:

CMC Comments:

The data provided for 3-months stability under 40°C, 75% RH and 25°C, 60% RH conditions for batches XLNH425, XLNH1426, and XLNH1427, do not support the proposed twenty-four (24) months expiration dating period for the proposed lower strength product, Ready to Use Argatroban Injection (1 mg/mL), refer to ICH Q1A(R2), Section 2.2.7.

Provide minimum 12-months stability data under 25°C, 60% RH condition and 6-months stability data under accelerated condition from three primary batches of the proposed product (1 mg/mL). You may also provide supporting data from batches in 1 mg/mL strength if available.

Kindly confirm receipt to myself and Jackie Jones (out of the office this week).

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Rm 2361
Silver Spring, MD 20993
Phone: 301-796-2237 | laura.wall@fda.hhs.gov

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/s/

JACQUIN L JONES
09/21/2015

Jones, Jacquin

From: Jones, Jacquin
Sent: Friday, September 18, 2015 5:08 PM
To: 'Jonathan Sterling'
Subject: NDA 203049 Argatroban: FDA Information Request-Please Respond by Sept 23 3pm

Good afternoon Mr. Sterling,

Please refer to Hikma Pharmaceuticals Co. Ltd. NDA 203049 Argatroban Supplement 004 dated April 24, 2015. The review team has the following CMC information request that will need a timely response.

> CMC Information Request
> Provide complete method validation reports for the revised analytical methods QCTM-046-03 and QCTM-047-04, for the proposed lower strength product, Ready to Use Argatroban Injection (1 mg/mL), including specificity, linearity, range, accuracy, and precision, etc. Refer to ICH Q2A Text on Validation of Analytical Procedures and ICH Q2B Validation of Analytical Procedures: Methodology.

Please send the ***response*** that addresses the above information request, along with any supporting documents via email no later than **3:00 PM ET on Wednesday, September 23, 2015.** Also, **officially submit** any responses and/or relevant documents to your NDA file at the same time you send the e-mail response or provide a planned date for when the submission will be submitted, followed by a notification when the official submission has been sent.

Please ***confirm*** receipt of this message.

Thank you,

Jackie

Jacquin L. Jones, MS, BSN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Food and Drug Administration
WO Bldg 22, Rm 2222
10903 New Hampshire Ave.
Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

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/s/

JACQUIN L JONES
09/18/2015

From:	Wall, Laura
To:	jsterling@exela.us
Cc:	Jones, Jacquin; Wall, Laura
Subject:	NDA 203049 - FDA CMC Comments
Date:	Friday, September 11, 2015 12:50:24 PM

Dear Jonathan,

The CMC review team has the following comments for NDA 203049:

CMC Comments:

The data provided for 3-months stability under 40°C, 75% RH and 25°C, 60% RH conditions for batches XLNH425, XLNH1426, and XLNH1427, do not support the proposed twenty-four (24) months expiration dating period for the proposed lower strength product, Ready to Use Argatroban Injection (1 mg/mL), refer to ICH Q1A(R2), Section 2.2.7.

Provide minimum 12-months stability data under 25°C, 60% RH condition and 6-months stability data under accelerated condition from three primary batches of the proposed product (1 mg/mL). You may also provide supporting data from batches in 1 mg/mL strength if available.

Kindly confirm receipt to myself and Jackie Jones (out of the office this week).

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Rm 2361
Silver Spring, MD 20993
Phone: 301-796-2237 | laura.wall@fda.hhs.gov

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/s/

LAURA C WALL
09/11/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO: **CDER-OPDP-RPM**			FROM: (Name/Title, Office/Division/Phone number of requestor) **Jacquin Jones, Regulatory Project Manager** **Division of Hematology Products**
REQUEST DATE: August 12, 2015	IND NO.	**NDA/BLA NO.** NDA 203049/S-004	**TYPE OF DOCUMENTS** Labeling- PAS (PLEASE CHECK OFF BELOW)
NAME OF DRUG: Argatroban Injection	**PRIORITY CONSIDERATION:** N/A	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) October 5, 2015
NAME OF FIRM: Hikma Pharmaceutical Pvt. Ltd.		**PDUFA Date:** October 27, 2015	

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☒ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☒ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

For OSE USE ONLY
- ☐ REMS

EDR link to submission:
Submission Link:\\CDSESUB4\NONECTD\NDA203049\5800007 (SDN: 40 /Submission Classification: MANUF (CMC))

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS:
Hikma Supplement for NDA 203049 Argatroban originally submitted as a CBE-30, but upon review it was decided that the submission would be a Labeling PAS managed by DHP. Hikma has added a new dilution presentation to the NDA for the Ready to Use Argatroban Injection has provided a draft container, carton and package insert with this submission.

6 month Goal Date: **October 27, 2015**

Labeling Meetings: Being reviewed under the DHP Labeling Pilot Program

SIGNATURE OF REQUESTER: Jacquin Jones, DHP, RPM

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☒ DARRTS ☐ eMAIL ☐ HAND

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/s/

JACQUIN L JONES
08/12/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 203049/S-004

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

Hikma Pharmaceuticals Co. Ltd.
Attention: Jonathan E. Sterling
Vice President of Quality and Regulatory
P.O. Box 818
1245 Blowing Rock Blvd.
Lenoir, NC 28645

Dear Mr. Sterling:

We have received your Supplemental New Drug Application (sNDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 203049

SUPPLEMENT NUMBER: 004

PRODUCT NAME: Argatroban injection 250mg/2.5mL and 50mg/50mL

DATE OF SUBMISSION: April 24, 2015

DATE OF RECEIPT: April 27, 2015

This supplemental application, submitted as a "Changes Being Effected in 30 days" supplement, proposes the following changes: to the US Prescribing Information including Dosage and Administration, Dosage Forms and Strengths, as well as additional changes to the concentration of the current approved drug product. Changes of this kind cannot be put into effect prior to approval of a supplement; we consider this to be a **Prior Approval Supplement**. An approved supplement is required for this proposed change prior to distributing drug product made with this change.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 26, 2015, in accordance with 21 CFR 314.101(a). If the application is filed, the goal date will be October 27, 2015.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, please call me at (240) 402-4590.

Sincerely,

{See appended electronic signature page}

Jacquin L. Jones, BSN, MS
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

JACQUIN L JONES
05/27/2015