CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203049Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # NDA 203049 SUPPL # HFD #

Trade Name Argatroban

Generic Name

Applicant Name Hikma Pharmaceuticals, Co. Ltd

Approval Date, If Known January 5, 2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Lara Akinsanya, M.S.
Title: Regulatory Project Manager
Date:

Name of Office/Division Director signing form: Ann T. Farrell
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

MONSURAT O AKINSANYA
01/04/2012

ANN T FARRELL
01/05/2012

EXELA
Pharma Sciences
P.O. Box 818
1325 William White Place
Lenoir, N.C. 28645

DEBARMENT AND CONVICTION CERTIFICATION

I hereby certify that Exela Pharma Sciences, LLC did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application. Exela Pharma Sciences, LLC did not use in any capacity the services of any person convicted under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Jonathan Sterling
Director of Quality, Regulatory & Product Development
Exela Pharma Sciences, LLC

Afton Scientific
CORPORATION
cGMP Processing of Sterile Products

DEBARMENT CERTIFICATION

As required by the Generic Drug Enforcement Act of 1992, Afton Scientific Corporation certifies that we have not nor will we use in any capacity the services of any person debarred under subsections (a) or (b) [section 306 (a) or (b)] of the Act, in connection with our application for Argatroban Injection, 100 mg/mL.

There have been no convictions of crimes (as specified in section 306 (a) and (b) of the Act) within the previous five years of any Afton Scientific Corporation employees or affiliated company, or employees of the affiliated companies responsible for the development or submission of this application for Argatroban Injection, 100 mg/mL.

2 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Thomas Thorpe
President

Date

2030 Avon Court ■ Charlottesville, VA 22902 ■ (434) 979-3737 ■ Facsimile (434) 979-3738 ■ www.AftonScientific.com

Establishment Information:

Exela Pharma Sciences
1325 William White Place
Lenoir, NC 28645.
Telephone Number: (828) 758-5474
Fax Number: (828) 757-7888
Contact: Jonathan Sterling, Director of Quality
Email: jsterling@galexe.us
Establishment Registration Number: *pending*
Function: Formulation Development, Filing Agent
Exela is ready for FDA inspection.

Afton Scientific Corporation
2030 Avon Court, Charlottesville, VA 22902
Telephone Number: (434) 979-3737
Fax Number: (434) 979-3738
Contact : Thomas Thorpe, President
Function: Manufacturing Site, (b) (4) (b) (4)
Establishment Registration Number: 1123053/BLT
Afton Scientific is ready for FDA inspection.

(b) (4)

Additional details are provided in the Drug Substance Manufacturer and Drug Product Manufacturers Sections of this submission.

NDA 203-049
Argatroban Injection

Financial Disclosure Review

Financial Disclosure is not needed for this application because no clinical efficacy or safety data were submitted in this NDA.

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

/s/

MONSURAT O AKINSANYA
12/28/2011

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 203049 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: N/A Established/Proper Name: Argatroban Injection Dosage Form: Injection		Applicant: Hikma Pharmaceuticals, Co. Ltd. Agent for Applicant (if applicable): Exela Pharmaceuticals, Inc.
RPM: Lara Akinsanya		Division: Division of Hematology Products

NDAs:
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

NDA 20-883

Provide a brief explanation of how this product is different from the listed drug.

This application provides for a change in product formulation. Hikma's proposed drug product contains a different quality and quantity of excipients than the referenced product. The formulation change has been made to the solubilizing agent. In Hikma's formulation, propylene glycol replaces D-sorbitol as the solubilizing agent.

If no listed drug, explain.
- ☐ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain)

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☒ No changes ☐ Updated Date of check: January 5, 2012

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is January 28, 2012	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [2]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☒ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☒ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☒ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☒ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	January 5, 2012
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval, January 5, 2012
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	December 12, 2011
• Original applicant-proposed labeling	March 18, 2011
• Example of class labeling, if applicable	

[3] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	December 12, 2011
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	N/A N/A
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM December 23, 2011 ☒ DMEPA November 22, 2011 ☐ DRISK ☒ DDMAC December 20, 2011 ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	RPM Filing Review - May 11, 2011 ☐ Not a (b)(2) January 3, 2012 ☐ Not a (b)(2) January 4, 2012
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: This is a 505(b) 2 Application • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☐ Included

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	December 1, 2011; November 22, 2011; October 24, 2011; September 16, 2011; August 16, 2011; August 12, 2011; August 5, 2011; July 1, 2011; May 31, 2011; March 30, 2011; March 28, 2011
❖ Internal memoranda, telecons, etc.	None
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg December 2, 2008
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	None
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None January 4, 2012
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None January 4, 2012
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	December 2, 2011
• Clinical review(s) *(indicate date for each review)*	December 1, 2011
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☒ and include a review/memo explaining why not *(indicate date of review/memo)*	See memo included dated December 28, 2011
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable

[5] Filing reviews should be filed with the discipline reviews.

❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None November 3, 2011
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None October 31, 2011
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None December 1, 2011
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None December 1, 2011
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None December 5, 2011
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None December 5, 2011 - CMC; November 21, 2011 - BioPharm
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed November 29, 2011
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	CMC Review - December 1, 2011
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: September 26, 2011 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

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

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

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

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

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

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

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

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

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

/s/

MONSURAT O AKINSANYA
01/05/2012

505(b)(2) ASSESSMENT

Application Information		
NDA # 203049	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: **Argatroban Injection** Established/Proper Name: **Argatroban Injection** Dosage Form: **Injection** Strengths: **100 mg/mL**		
Applicant: **Hikma Pharmaceuticals, Co. Ltd (Exela Pharmaceuticals – US Agent)**		
Date of Receipt: March 28, 2011		
PDUFA Goal Date: January 28, 2012	Action Goal Date (if different): January 05, 2012	
Proposed Indication(s): **indicated for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT); for HIT undergoing percutaneous intervention (PCI).**		

GENERAL INFORMATION

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

YES ☐ NO ☒

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

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

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

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 20-883 (Argatroban Injection [Pfizer Inc.])	**Clinical findings of safety and efficacy; findings from animal studies for reproductive toxicity and mutagenesis**
Published literature	**Safety findings**

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

In support of a waiver of *in vivo* bioequivalence (BE), the applicant conducted an *in vitro* bridging study to assess *in vitro* equivalence of the anticoagulant pharmacodynamic (PD) activity between Hikma's and Pfizer's products. PD effects were measured by determining the activated partial thromboplastin time (aPTT), the prothrombin time (PT), and the thrombin time (TT) in pooled donor human plasma spiked with clinically relevant concentrations of Hikma's or Pfizer's argatroban product.

RELIANCE ON PUBLISHED LITERATURE

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

YES ☒ NO ☐

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

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

YES ☒ NO ☐

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

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

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

YES ☒ NO ☐

RELIANCE ON LISTED DRUG(S)

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

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

YES ☒ NO ☐

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

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

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Argatroban Injection	**20-883**	**Y**

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

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

N/A ☒ YES ☐ NO ☐

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

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

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

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

YES ☐ NO ☒

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

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

b) Approved by the DESI process?

YES ☐ NO ☒

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

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

c) Described in a monograph?

YES ☐ NO ☒

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

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

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

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

Name of drug(s) discontinued from marketing:

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

YES ☐ NO ☐

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

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

This application provides for a change in product formulation. Hikma's proposed drug product contains a different quality and quantity of excipients than the referenced product. The formulation change has been made to the (b) (4). In Hikma's formulation, propylene glycol replaces D-sorbitol (b) (4)

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

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

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

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including*

potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

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

Hikma's proposed drug product has the same active ingredient, dosage form, strength, route of administration, and conditions of use as Pfizer's Argatroban Injection.

YES ☒ NO ☐

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

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

YES ☒ NO ☐

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

YES ☒ NO ☐

*If "**YES**" to (c) <u>and</u> there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" <u>or</u> if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do <u>not</u> have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

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

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

No patents listed ☐ *proceed to question #14*

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

YES ☒ NO ☐

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

Listed drug/Patent number(s):

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

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

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

Patent number(s): Expiry date(s):

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

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

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

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

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

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

(a) Patent number(s): **5,214,052**
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☒ NO ☐

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

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

YES ☒ NO ☐

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

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

Date(s): *June 6, 2011*

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

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

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

approval

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

/s/

MONSURAT O AKINSANYA
01/04/2012

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Tuesday, November 22, 2011 4:33 PM
To: 'Jonathan Sterling'
Cc: Akinsanya, Lara
Subject: NDA 203049 : FDA Proposed PI

Attachments: FDA proposed PI_redline_111811.docx

Dear Jonathan,

Please see attached revised draft of the PI for NDA 203049. Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)

FDA proposed PI_redline_111811..

After you have made the changes, feel free to send me the revised tracked change before you make your official submission electronically.

Please provide a revised PI to me by next week Thursday, **December 1, 2011**.

Thanks
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

25 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

MONSURAT O AKINSANYA
12/01/2011

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Tuesday, November 22, 2011 4:44 PM
To: 'Jonathan Sterling'
Cc: Akinsanya, Lara
Subject: Information Request - OSE: NDA 203049 -DUE December 1

Hi Jonathan,

Please respond to the following information request from the office of Surveillance and Epidemiology:

Container Label and Carton Labeling

1. Revise the presentation of the established name from all UPPERCASE letters to Title Case to improve readability and revise the presentation of the strength to read as follows:
   Argatroban Injection
   250 mg/2.5 mL
   (100 mg/mL)
2. Revise the font size and weight of the word *Injection* to match *Argatroban*.
3. Delete the statement, [redacted] (b) (4), from the principal display panel
4. Delete the blue bar that covers a large area and overpowers important information. Consider using the blue color more strategically to highlighting important information on the label, such as the strength expression.
5. Revise the statement, [redacted] (b) (4), to read as follows:
   Dilute Prior to Administration
6. Increase the prominence of the statement, *Dilute Prior to Administration*, by increasing the font size and improving the color contrast between the font color of this statement and the background.
7. Revise the dangerous abbreviation, *IV*, to read, *intravenous*. IV is a dangerous abbreviation, which appears on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations2 because the abbreviation 'IV' has been confused with the abbreviations 'IM' (intramuscular), 'IU' (international units), and 'IN' (intranasal).
8. Increase the prominence of the statement, *For Intravenous Infusion Only*.
9. Add the statement, *Single-Use Vial – Discard Unused Portion*.

Carton Labeling

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

Please respond to the above information request by **Thursday, December 1**, 2011.

Please let me know if you have any questions.

Thank You

Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products

Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

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

/s/

MONSURAT O AKINSANYA
11/22/2011

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Thursday, December 01, 2011 11:39 AM
To: 'Jonathan Sterling'
Cc: Akinsanya, Lara
Subject: Information Request - Microbiology: NDA 203049 -DUE December 9

Hi Jonathan,

Please respond to the following information request:

1) Regarding the endotoxin testing:

(b) (4)

2) Regarding the product (b) (4) sterilization:

(b) (4)

3) Regarding the depyrogenation of the vials: (b) (4)

Please respond to the above information request by **Friday, December 9**, 2011.

Please let me know if you have any questions.

Thank You

Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

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

/s/

MONSURAT O AKINSANYA
12/01/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

PIND (b) (4)

(b) (4)

Dear (b) (4)

Please refer to your Pre-Investigational New Drug Application (PIND) file for Argatroban.

We also refer to the teleconference between representatives of your firm and the FDA on December 2, 2008. The purpose of the meeting was to obtain guidance from the FDA on the appropriateness of the 505(b)(2) regulatory pathway for a new formulation of injectable Argatroban.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3691.

Sincerely,

{See appended electronic signature page}

Ebla Ali Ibrahim, M.S.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	December 2, 2008
TIME:	1 PM – 2 PM
LOCATION:	White Oak Building
APPLICATION:	IND (b) (4)
DRUG NAME:	Argatroban
TYPE OF MEETING:	Pre-IND Type B

MEETING CHAIR: Kathy Robie Suh, M.D., Ph.D.

MEETING RECORDER: Ebla Ali Ibrahim, M.S.

FDA ATTENDEES:

Division of Medical Imaging and Hematology Products (DMIHP)

Kathy Robie Suh, M.D., Ph.D., Medical Team Leader, Hematology
Kassa Ayalew, M.D., Medical Team Leader
Ronald Honchel, Ph.D., Toxicologist
Florence Moore, M.S., Regulatory Project Manager Acting Team Leader
Ebla Ali Ibrahim, M.S., Regulatory Project Manager

Office of Pharmaceutical Science, Office of New Drug Quality Assurance, Division of Pre-Marketing Assessment and Manufacturing Science, Branch V

Eldon Leutzinger, Ph.D., Pre-Marketing Assessment Leader
Mark Sassaman, Ph.D., Chemist
Milagros Salazar Driver, Ph.D., Chemist

Office of Pharmaceutical Science, New Drug Microbiology Team (NDMS)

Stephen Langille, Ph.D., Microbiologist

Office of Clinical Pharmacology (OCP)

Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader
Joseph Grillo, Pharm.D., Clinical Pharmacologist

EXTERNAL CONSTITUENT ATTENDEES:

Exela PharmSci, Inc.

Phanesh Koneru, Ph.D., President and CEO

Codexis, Inc.

Robert K. Sato, Ph.D., MBA, Director, Analytic Development and Quality Control

[redacted] (b) (4)

BACKGROUND:

The proposed indications for Argatroban are:

- As an anticoagulant for prophylaxis of treatment of thrombosis in patients with heparin-induced thrombocytopenia, and
- As an anticoagulant in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI).

Exela PharmaSci, Inc. requested a Type B (Pre-IND) meeting to discuss their development plans for an Argatroban product and also to discuss the plan to file a marketing application under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act.

MEETING OBJECTIVES:

The objective was to obtain guidance from the FDA on the appropriateness of the 505(b)(2) regulatory pathway for a new formulation of injectable Argatroban.

DISCUSSION POINTS:

Question 1:
FDA indicated that a clinical pharmacology bridging study is needed to address the safety and/or effectiveness of the Exela's product compared to the listed drug since excipients in Exela's drug product differ from the reference drug. Exela should establish and provide data showing that the differences in excipients are scientifically appropriate using in vitro and, if necessary, in vivo methods. FDA further explained that the bridging study is needed to provide information regarding how Exela's Argatroban drug works in humans in comparison with the reference drug. FDA recommended that Exela should consider a range of concentrations similar to that achieved in the RLD clinical trials when performing the in vitro bridging study to determine the effect of its drug formulation on the specific coagulation factors. Exela indicated that they would submit a draft protocol for FDA's review and comment. FDA emphasized the importance of the study showing equivalence between Exela's drug and the reference drug.

Question 3:
FDA reminded Exela to provide a Pediatric plan in their submission because a pediatric plan is needed to approve a new drug application. FDA explained that since the formulation of Exela's drug is different from the reference drug, Exela can not reference the reference drug labeling regarding pediatrics.

Question 6:
FDA explained to Exela that the "AP" rating determination is made after the New Drug Application (NDA) is submitted.

Exela acknowledged the clinical pharmacology and chemistry, manufacturing and control's (CMC) comments.

FDA stated that if post-constitutional holding/administration time is more than four hours, Exela would have to demonstrate that the diluted drug product does not support microbial growth.

Exela asked if they could get exclusivity if they showed that the drug is not similar. FDA explained that a sponsor can get exclusivity if the sponsor does a well controlled and adequate study to support a stand alone application. In Exela's case, Exela is submitting a 505(b)(2) application and does not plan to conduct clinical efficacy and safety study(ies) of their argatroban product.

DECISIONS (AGREEMENTS) REACHED:

- Exela will submit a Clinical Pharmacology bridging study protocol for FDA to review and comment.
- Exela will submit maximum daily dose duration data.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

- FDA would review the Exela's Clinical Pharmacology bridging study protocol and send comments.

ATTACHMENTS/HANDOUTS:

FDA's final Comments/Responses to the specific questions asked by Exela PharmSci, Inc.

Meeting Date: **December 2, 2008** **Time: 1 – 2 PM**

Sponsor: **Exela PharmSci (Camargo Pharmaceutical Services, LLC)**

Product: **Argatroban**

Type: **Pre-IND Type B (PIND (b) (4)**

Proposed Use: **As an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia and patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI).**

Purpose: **To discuss Exela's development plans for an Argatroban product for the prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia and patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI). Also to discuss the plan to file a marketing application under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act.**

Introductory Comment: This material consists of the reviewers' preliminary notes in preparation for the discussion at the meeting between Exela PharmSci (b) (4) (b) (4) and the FDA's Review Team. This material may not have been fully vetted internally and should not be considered as an official position of the FDA. This material is shared with the Sponsor solely to promote a collaborative and successful discussion at the meeting. The minutes for the meeting will reflect agreements and discussion at the meeting and may not be consistent with these reviewers' preliminary notes. These are draft comments by FDA to Exela PharmSci (b) (4) and were emailed to Ruth Stevens, Exela PharmSci (b) (4) contact, on November 26, 2008.

Sponsor Questions and FDA Response:

1. *Is the Agency in agreement with the 505(b)(2) regulatory pathway for the Exela's Argatroban product?*

   FDA Response

   The Division agrees that the sponsor should consider the 505(b)(2) regulatory pathway. Sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 C.F.R. 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at http://www.fda.gov/cder/guidance/guidance.htm.

In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the agency's interpretation of this statutory provision. See Dockets 2001P-0323, 2002P-0447, and 2003P-0408.

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for a listed drug, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug. In this case, you should establish a "bridge" between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is appropriate. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

For example, an *in vitro* measurement of the effect of your drug product compared to that of the RLD upon the proposed laboratory tests (aPTT, PT and TT) on pooled human plasma may be acceptable as a bridge to demonstrate sufficient similarity (21 CFR 320.22(d)(3)) if the *in vitro* test has been correlated with *in vivo* data. This determination is a review issue. In addition, the effects of the other excipients in both products on coagulation parameters should be separately determined to ensure that none of the *in vitro* effects are caused by a change in excipients. A clinical PD study to support the *in vitro* study is recommended and may be required depending on the findings of the CMC review and the *in vitro* data.

2. *Does the Agency concur that for Exela's Argatroban product, the appropriate Reference Listed Drug (RLD) is Argatroban (NDA #20-883) injection?*

FDA Response

This appears acceptable.

3. *Does the FDA agree that the pharmacokinetics, efficacy and safety data in the public domain and from the approved labeling of Argatroban (NDA #20-883) support the efficacy and safety of Exela's Argatroban for the same indications?*

FDA Response

Please see the FDA response to question #1. Please note that you cannot reference the summary basis of approval to support the safety and efficacy of your product.
We noted your statement that the concentration of propylene glycol in Exela's Argatroban (b) (4) (b) (4) than the concentration of propylene glycol in at least one drug product already approved by CDER. However, propylene glycol exposure at high enough levels can be toxic and safety in regards to the maximum daily dose and duration of propylene glycol administration was not properly addressed in this pre-IND submission.

In your 505(b)(2) submission, please justify the safety of propylene glycol in terms of maximum daily dose and duration of exposure with the available preclinical and clinical (i.e., is the use of propylene glycol already approved at a higher dose and a longer duration than that proposed by Exela) data. You may find an article on propylene glycol toxicity by Wilson et al., (*Chest* 128:1674-1681, 2005) useful in this matter.

Lastly, you should refer to ICH Q3A and ICH Q3B in regards to impurities and/or degradation products, respectively.

4. *Exela does not plan to submit pharmacokinetic studies or clinical studies to demonstrate the efficacy and safety of its Argatroban formulation for the thrombocytopenia indications. Is the Division in agreement with this proposal?*

FDA Response

Please see the FDA response to question #1. Please note that you cannot reference the summary basis of approval to support the safety and efficacy of your product.

5. *Does the FDA agree that no pediatric studies will be required and that PREA has been addressed?*

FDA Response

The Pediatric Use Section in the current label for the RLD states that:

> **"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. Check the aPTT two hours after the initiation of the Argatroban infusion and adjust the dose to achieve the target aPTT. 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. 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."

If approved under 505(b)(2), we anticipate similar wording will apply to your product. However, you must submit a document that describes your Pediatric plan. Please consider the role of the propylene glycol in your drug.

6. *Because Exela's Argatroban product will be therapeutically equivalent and pharmaceutically equivalent, does the Agency agree that Exela's product will be rated as "AP" to Encysive's Argatroban product?*

FDA Response

Internal discussions are on going regarding the "AP" rating and FDA will get back to Exela regarding this issue.

Additional FDA Comments

Clinical Pharmacology

The following comments should be addressed during development:

- We recommend that you validate the analytical method(s) used to measure the parent drug and any active metabolites according to the principles described in the Guidance for Industry entitled "Bioanalytical Method Validation."
- We recommend that you validate the analytical method(s) used to measure efficacy (e.g., aPTT, PT, TT, etc.). Literature from the manufacturer of the method would generally not be considered sufficient to demonstrate validation. The precision, accuracy and reproducibility evaluations of the laboratory that will be performing the coagulation

testing (Include results for reagents, equipment and personnel) will be considered important to demonstrating validity.

Chemistry Manufacturing Control

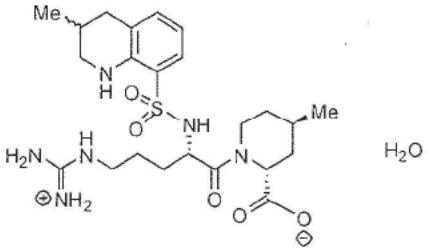
- Provide identification of the source for the Argatroban API and Argatroban drug product. Include information on manufacturers, CGMP site status, and availability of manufacturing information such as in a DMF or NDA.
- Provide the general plan for the submission of the stability data for both API and drug product.
- Comparative stability data of the reference listed product and your product in the final injectable dosage form after dilution. The stability studies should include but not be limited to Argatroban assay, related compounds/degradants, pH, particulate matter (visible/subvisible) and microbiological attributes.
- Labeling recommendations:

  a. The name of Argatroban API should account for the presence of all four chiral centers and for the guanidinium moiety as follows:

  IUPAC nomenclature: (2*R*,4*R*)-1-[(*S*)-5-amino(iminio)methylamino)-2-((*R*,*S*)-3-methyl-1,2,3,4-tetrahydroquinoline-8-sulfonamido)pentanoyl]-4-methylpiperidine-2-carboxylate monohydrate; **Common**: (2*R*,4*R*)-4-methyl-1-N^2-[[(*R*,*S*)-1,2,3,4-tetrahydro-3-methyl-8-quinolinyl]sulfonyl]-L-arginyl]pipecolic acid monohydrate.

  b. To capitalize "Argatroban" when referring to the drug substance. This is considered a designated name for the 65:35 mixture of the *R* and *S* stereoisomers.

  c. The preferred structural formula for Argatroban monohydrate is the one reflecting its zwitterionic form as shown below:



  d. The name of the dosage form for the drug product should be "Argatroban for Injection" to indicate the product must be diluted prior to i.v. administration. Also, the label should state, below the dosage form information, that the product is "not intended for direct administration".

Linked Applications	Sponsor Name	Drug Name / Subject
IND (b) (4)	(b) (4)	ARGATROBAN

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

/s/

EBLA ALI IBRAHIM
12/19/2008

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Monday, October 24, 2011 11:37 AM
To: 'Jonathan Sterling'
Cc: Akinsanya, Lara
Subject: Information Request - Clinical Microbiology: NDA 203049 - DUE 10/28/2011

Dear Jonathan,

Please respond to the information request below:

(b) (4)

Please respond by **Friday, October 28, 2011**.

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

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

/s/

MONSURAT O AKINSANYA
10/24/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203049 **INFORMATION REQUEST**

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Hikma Pharmaceuticals Co. Ltd
c/o Exela Pharma Sciences, LLC.
Attention: Jonathan Sterling
Director of Quality, Regulatory & Product Development
1325 William White Place
Lenoir, NC 28645

Dear Mr. Sterling:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Argatroban Injection, 100 mg/mL.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).[1] The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or "prep" run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or "prep" runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is

[1] These violations include studies conducted by (b) (4)

searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Janet Jamison, Regulatory Project Manager, at (301) 796-2313.

Sincerely,

{See appended electronic signature page}

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

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
09/16/2011

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Friday, August 12, 2011 8:41 AM
To: 'Jonathan Sterling'
Cc: Akinsanya, Lara
Subject: Information Request - Microbiology: NDA 203049 - DUE by September 30, 2011

Dear Jonathan,

Please respond to the information request below:

1) Regarding the endotoxin testing.

(b) (4)

(b) (4)

(b) (4)

3) The hold time study (b) (4) Provide this information.

Please respond by **September 30, 2011**.

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

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

/s/

LARA M AKINSANYA
08/12/2011

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Tuesday, August 16, 2011 12:20 PM
To: 'Jonathan Sterling'
Cc: Akinsanya, Lara
Subject: Information Request - Clinical Pharmacology: NDA 203049 - DUE by August 30, 2011

Dear Jonathan,

Please respond to the information request below:

Provide us with these two tables:

Table 1. Validation summary for the LC/MS/MS assay used to determine the concentration of argatroban in plasma

Analyte	Argatroban
Internal standard (IS)	
Limit of quantization (μg/mL)	
Average recovery of Argatroban (%) (Low , Med, High QC)	
Average Recovery of IS (% Mean)	
Standard curve concentrations (μg/mL)	
QC concentrations (μg/mL)	
QC intra-assay precision range (% CV)	
QC intra-assay accuracy range (% bias)	
QC inter-assay precision range (% CV)	
QC inter-assay accuracy range (% bias)	
Bench-top stability (hours)	X hours @ ambient temperature

Processed stability (hours)	X hours @ 4^{oC}
Freeze-thaw stability (freeze-thaw cycles)	X freeze-thaw cycles
Long-term storage stability (days)	X days @ -80oC

Table 2. Validation parameters for coagulation assays

	PT	aPTT	TT
Accuracy (% of the nominal concentrations range) Intra-Assay Inter-Assay			
Precision range (% CV) Intra-Assay Inter-Assay			
Refrigerator stability (@ 2 - 8° C)			
Bench-top stability (ambient temperature)			
Freeze-thaw stability (freeze-thaw cycles)			
Long-term storage stability (@ - 20° C)			

Please respond by **August 30, 2011**.

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

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

/s/

LARA M AKINSANYA
08/16/2011

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Friday, August 05, 2011 10:53 AM
To: 'Jonathan Sterling'
Cc: Akinsanya, Lara
Subject: REQUEST: NDA 203049-: Argatroban/Exela Pharma/ Label (PI) Review

Attachments: PI.docx

Dear Jonathan Sterling,

Attached is the most current PI that I have on file for your application. It is still very different from the most recently approved Argatrobans and they need to exactly the same with the exception of your Chemistry sections.

PI.docx (234 KB)

Would you please look at the recently approved Argatobans on the FDA website and revise your PI accordingly?

Please email me your revised label by COB on Wednesday, August 10, 2011.

Thank You.
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

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

/s/

LARA M AKINSANYA
08/08/2011

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Friday, July 01, 2011 7:27 AM
To: 'Jonathan Sterling'
Cc: Akinsanya, Lara
Subject: Information Request - Clinical Pharmacology: NDA 203049 - DUE by July 11, 2011

Dear Jonathan,

Please respond to the information request below:

- **Please provide the raw data for Study 024188 as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file.**

Please respond by **July 11, 2011**.

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

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

/s/

LARA M AKINSANYA
07/01/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203049

FILING COMMUNICATION

Hikma Pharmaceuticals Co. Ltd
c/o Exela Pharma Sciences, LLC.
Attention: Jonathan Sterling
Director of Quality, Regulatory & Product Development
1325 William White Place
Lenoir, NC 28645

Dear Jonathan Sterling:

Please refer to your New Drug Application (NDA) dated March 18, 2011, received March 28, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Argatroban Injection, 100mg/mL.

We also refer to your submission dated May 04, 2011.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is January 28, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by December 31, 2011.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Lara Akinsanya, Regulatory Project Manager, at (301) 796-9634.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, M.D.
Acting Division Director
Division of Hematology Products
Office of Oncology Drug 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
05/31/2011

NDA/BLA Number: 203049	**Applicant: Hikma (Exela)**	**Stamp Date: 03/18/2011**
Drug Name: Argatroban	**NDA/BLA Type: 505(b)(2)**	FDSWA150\NONECTD\N203049\S 001\2011-03-18

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			FDSWA150\NONECTD\N203049\S 001\2011-03-18 Modules submitted as PDF files.
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?			X	PDF files
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?		X		The label has been requested in PLR format.
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			(Literature Review)

	Content Parameter	Yes	No	NA	Comment
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			Argatroban Injection (GSK; patent held by Encysive Pharmaceuticals)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:			X	505(b)(2)
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	505(b)(2)
16.	Do the endpoints in the			X	505(b)(2)

	Content Parameter	Yes	No	NA	Comment
	pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.				
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	505(b)(2)
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			X	505(b)(2)
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	505(b)(2)
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	505(b)(2)
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	505(b)(2)
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	505(b)(2)
23.	Has the applicant submitted the coding dictionary[2] used			X	505(b)(2)

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if

	Content Parameter	Yes	No	NA	Comment
	for mapping investigator verbatim terms to preferred terms?				
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	505(b)(2)
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	505(b)(2)
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?		X		Please see CMC filing check list entered into DARRTs 05/09/2011. Per CMC filing check list/reviewer: "*Agency requested comparative stability data of the reference listed product and your product in the final injectable dosage form after dilution. Comparative studies were not performed.*"
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Section 1.9.1 contains a Request for Waiver of Pediatric Studies. The applicant ,Exela (Hikma) states that "*Exela's proposed product has the same active ingredient, and the same indication, dosage form, dosing regimen, and route of administration as that of the reference drug, Pfizer's Argatroban Injection.*"
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	505(b)(2)
DATASETS					
31.	Has the applicant submitted			X	No clinical studies were conducted/no patient

it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
	datasets in a format to allow reasonable review of the patient data?				data was submitted. The pertinent material otherwise submitted is in a format to allow reasonable review.
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	No clinical studies were conducted
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	No clinical studies were conducted
34.	Are all datasets to support the critical safety analyses available and complete?			X	No clinical studies were conducted
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	No clinical studies were conducted
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	505(b)(2)
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	505(b)(2)
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			Financial Disclosure 1.3.4 listed as "Not Applicable". Not required because no clinical studies were conducted by the Applicant.
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	505(b)(2)

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

The application appears to be fileable from a clinical perspective.

There are no review issues to be forwarded to the Applicant for the 74-day letter.

Firoozeh Alvandi, MD Reviewing Medical Officer	05/10/2011 Date
Virginia Kwitkowski, MS, RN, ACNP-BC Clinical Team Leader	05/10/2011 Date

---

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

/s/

FIROOZEH ALVANDI
05/10/2011

VIRGINIA E KWITKOWSKI
05/11/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203049

RECEIPT OF USER FEES

Hikma Pharmaceuticals Co. Ltd
c/o Exela Pharma Sciences, LLC.
Attention: Jonathan Sterling
Director of Quality, Regulatory & Product Development
1325 William White Place
Lenoir, NC 28645

Dear Jonathan Sterling:

Please refer to your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for Argatroban Injection, 100mg/mL.

You were notified in our letter dated March 28, 2011, that your application was not accepted for filing due to non-payment of fees. This is to notify you that the Agency has received all fees owed and your application has been accepted as of March 28, 2011.

Unless we notify you within 60 days of the above date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 27, 2011 in accordance with 21 CFR 314.101(a).

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). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

Please cite the NDA 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

If you have any questions, contact Lara Akinsanya, Regulatory Project Manager, at (301) 796-9634.

Sincerely,

{See appended electronic signature page}

Janet Jamison, RN, CCRP
Chief, Project Management Staff
Division of Hematology Products
Office of Oncology Drug 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/

JANET K JAMISON
03/30/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203049 **UNACCEPTABLE FOR FILING**

Hikma Pharmaceuticals Co. Ltd
c/o Exela Pharma Sciences, LLC.
Attention: Jonathan Sterling
Director of Quality, Regulatory & Product Development
1325 William White Place
Lenoir, NC 28645

Dear Jonathan Sterling:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Argatroban Injection, 100mg/mL

Date of Application: March 18, 2011

Date of Receipt: March 21, 2011

Our Reference Number: NDA 203049

We have not received the appropriate user fee for this application. An application is considered incomplete and cannot be accepted for filing until all fees owed have been paid. Therefore, this application is not accepted for filing. We will not begin a review of this application's adequacy for filing until FDA has been notified that the appropriate fee has been paid. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 979107
St. Louis, MO 63197-9000

Checks sent by courier should be addressed to:

U.S. Bank
Attention: Government Lockbox 979107
1005 Convention Plaza
St. Louis, MO 63101

When submitting payment for an application fee, include the User Fee I.D. Number, the Application number, and a copy of the user fee coversheet (Form 3397) with your

application fee payment. When submitting payment for previously unpaid product and establishment fees, please include the Invoice Number(s) for the unpaid fees and the summary portion of the invoice(s) with your payment. The FDA P.O. Box number (P.O. Box 979107) should be included on any check you submit.

The receipt date for this submission (which begins the review for filability) will be the date the review division is notified that payment has been received by the bank.

Please cite the NDA 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

If you wish to send payment by wire transfer, or if you have any other questions, please call Bev Friedman or Mike Jones at 301-796-3602.

If you have any questions, contact Lara Akinsanya, Regulatory Project Manager, at (301) 796-9634.

Sincerely,

{See appended electronic signature page}

Janet Jamison, RN, CCRP
Chief, Project Management Staff
Division of Hematology Products
Office of Oncology Drug 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/

JANET K JAMISON
03/28/2011

7 Pages of Overview of the NDA/BLA application for filing has been removed, a duplicate of this Overview dated 5/11/12 can be found in this review.