CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206769Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 206769 SUPPL # HFD #

Trade Name

Generic Name Argatroban Injection

Applicant Name Teva Pharmaceuticals USA

Approval Date, If Known December 15, 3014

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) - SE5

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.

No clinical or bioequivalence studies were conducted by the Applicant to bridge their product with the reference listed product. In support of a waiver of in vivo bioequivalence (BE), the applicant conducted an in vitro bridging study to assess in vitro equivalence of the anticoagulant pharmacodynamic (PD) activity between Teva's product and the RLD, Sandoz Argartroban Injection, NDA 22485. PD effects were measured by determining the prothrombin time (PT), the activated partial thromboplastin time (aPTT), and the thrombin time (TT) in human plasma spiked with clinically relevant concentrations of Teva's or Sandoz's argatroban product. An in vitro evaluation (study report) was also submitted.

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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?

N/A

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

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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#	022485	Sandoz, Argatroban in Sodium Chloride, 125 mg/125 ml
NDA#	022434	Eagle Pharmaceuticals, Argatroban in Sodium Chloride, 50 mg/50ml
NDA#	020882	Pfizer, Acova 250 mg/2.5 ml
NDA#	203049	Hikma Pharma Co Ltd., Argatroban 250 mg/ 2.5 ml

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

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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.

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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:

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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 !

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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: Natasha Kormanik
Title: Regulatory Health Project Manager
Date: December 15, 2014

Reference ID: 3672641

Name of Office/Division Director signing form: Edvardas Kaminskas, MD
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

NATASHA L KORMANIK
12/15/2014

EDVARDAS KAMINSKAS
12/15/2014

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 206769 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DHP PDUFA Goal Date: 12/28/14 Stamp Date: 2/28/2014

Proprietary Name: N/A

Established/Generic Name: Argatroban Injection

Dosage Form: 250 mg/ 250 mL

Applicant/Sponsor: Teva Pharmaceuticals USA

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):____
(Attach a completed Pediatric Page for each indication in current application.)

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

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☒ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

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

/s/

NATASHA L KORMANIK
04/23/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 206769	NDA Supplement #	If NDA, Efficacy Supplement Type: N/A *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: N/A Established/Proper Name: Argatroban Injection Dosage Form: Injectable		Applicant: Teva Pharmaceuticals USA Agent for Applicant (if applicable):
RPM: Natasha Kormanik		Division: Division of Hematology Products

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

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check: December 1, 2014

Note: 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: December 15, 2014 • User Fee Goal Date is December 28, 2014	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ 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[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] 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.

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Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 5 New Formulation
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy 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
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ 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
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

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

Reference ID: 3672772

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval December 15, 2014
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)*	☐ Included
• Original applicant-proposed labeling	☒ Included February 28, 2014
❖ 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)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ 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	☒ Included DATE
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	N/A
❖ Labeling reviews *(indicate dates of reviews)*	RPM: May 20, 2014 DMEPA: October 2, 2014 DMPP/PLT (DRISK): ☒ None OPDP: November 6, 2014 SEALD: ☒ None CSS: ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	RPM Filing Review 05/02/2014 Cleared by Clearance Committee: 10/28/2014 505(b)(2) Assessment Form: 12/15/14 ☐ Not a (b)(2)
❖ 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

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ 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: **Indication is with adult patients and a waiver was granted by FDA. According to the Pediatric Page, no PREA needed because this application is not a NEW active ingredient, indication, dosage form, dosing regimen, or route of administration**	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	12/04/2014; 10/30/2014; 10/08/2014; 09/25/2014; 09/23/2014; 07/01/2014; 05/20/2014; 05/14/2014; 05/02/2014; 03/10/2014
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	N/A
❖ Minutes of Meetings	
• 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)*	June 4, 2013
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	December 4, 2014
Cross-Discipline Team Leader Review *(indicate date for each review)*	December 1, 2014
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review Co-signed 09/30/2014 review
• Clinical review(s) *(indicate date for each review)*	Review September 30, 2014 Filing April 23, 2014
• 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)*	N/A This application is a 505(b)(2) and does not have any clinical data.

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❖ 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)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(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
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review Co-signed 11/18/2014 review
Clinical Pharmacology review(s) *(indicate date for each review)*	Review November 18, 2014; Filing April 25, 2014
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review Co-signed 5/25/2014 review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	May 25, 2014
❖ 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
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

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Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ No separate review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ No separate review Co-signed 11/24/2014 review
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	Review: November 24, 2014; November 21, 2014; November 18, 2014; August 18, 2014 Filing April 22, 2014; April 12, 2014
❖ 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)*	Review August 19, 2014 Filing April 23, 2014
❖ 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)*	See page 77 of November 18, 2014 Product Quality Review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; 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[5])*	Date completed: September 24, 2014 ☒ 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)

[5] 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.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	N/A
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

Reference ID: 3672772

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/s/

NATASHA L KORMANIK
12/15/2014

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Thursday, December 04, 2014 7:32 AM
To: scott.tomsky@tevapharm.com
Subject: NDA 206769 Argatroban Injection Labels
Attachments: Argatroban Injection Final-pi clean.doc; Argatroban Injection Final bag clean.doc; Argatroban Final carton clean.doc

Dear Mr. Tomsky,

Please refer to your New Drug Application (NDA) dated February 28, 2014, received February 28, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Argatroban Injection, 250 mg/ 250 mL.

We have completed our labeling review of this application. Attached you will find the final agreed-upon labeling documents.

Please feel free to contact me with any questions.

Kind Regards,
Natasha Kormanik, RN, BSN, OCN®
LT, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue, Room 2389
Silver Spring, MD 20903
(o) 240-402-4227
Natasha.Kormanik@fda.hhs.gov

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

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/s/

NATASHA L KORMANIK
12/04/2014

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Thursday, October 30, 2014 11:33 AM
To: scott.tomsky@tevapharm.com
Subject: NDA 206769 Argatroban Injection Labeling Comments for Package Insert

Dear Mr. Tomsky,

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Argatroban Injection. Below you will find comments to the draft package insert submitted in the amendment dated October 8, 2014.

Comments for the Draft Package Insert:

1. In section 2: Dosage and Administration, revise line one to use the term "polyolefin bag" instead of (b) (4) (b) (4).
2. In section 11: Description, revise the typographical error in the molecular formula (from "O5S" to "O_5S").
3. In section 16: How Supplied/Storage and Handling, the second paragraph refers to a (b) (4) containing 5 bags and the third paragraph states that the bags are to be retained in the original "carton". Since that container is actually a carton, we recommend that the second paragraph be revised to use the term "carton".

Please review the recommendations and address the comments directly to the package insert. We ask that if you make any additional changes, make them in tracked changes.

After you have made the changes, please e-mail the revised labels (in tracked changes word document) by **November 6, 2014 at 1:00 PM (ET) .** Please also follow up with a formal submission.

Please confirm receipt of this message by e-mail and feel free to contact me with any questions.

Kind Regards,
Natasha Kormanik, RN, BSN, OCN®
LT, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue, Room 2389
Silver Spring, MD 20903
(o) 240-402-4227
Natasha.Kormanik@fda.hhs.gov

Reference ID: 3650858

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/s/

NATASHA L KORMANIK
10/30/2014

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Friday, October 03, 2014 1:41 PM
To: scott.tomsky@tevapharm.com
Subject: NDA 206769 Argatroban Injection Container Label and Carton Label

Dear Mr. Tomsky,

Please find below the FDA recommendations for NDA 206769/ Argatroban Injection regarding the Container Label and Carton Label.

Recommendations for the Container Label and Carton Labeling:

A. Container Label

1. Bold the "For Intravenous Infusion Only" statement on the principal display panel, to increase prominence of this important safety information.
2. Decrease the prominence of the statement, "Do not use if solution is cloudy or contains a precipitate" by decapitalizing the letters and by use of lower case letters, as this information in not unique to this product and takes away attention from more important information such as the name, and route of administration of the product. For example: "Do not use if solution is cloudy or contains…."
3. Consider revising administration statement to "Do not dilute" because phrase (b) (4) [redacted] " could be confusing.
4. Consider bolding, revised "Do not dilute" statement.

B. Carton Labeling

1. See A1. – A.4 and revise carton labeling accordingly.

Please review the recommendations and address the comments directly to the both the Container Label and Carton Label. We ask that if you make any additional changes, make them in tracked changes.

After you have made the changes, please e-mail the revised labels (in tracked changes word document) by **October 9, 2014 at 3:00 PM (EDT) .**

Please confirm receipt of this message by e-mail. Please feel free to contact me if you have any questions.

Kind Regards,
Natasha Kormanik, RN, BSN, OCN®
LT, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue, Room 2389
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(o) 240-402-4227
Natasha.Kormanik@fda.hhs.gov

Reference ID: 3640860

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/s/

NATASHA L KORMANIK
10/08/2014

Stephen Dobkowski

From: Baird, Amy [Amy.Baird@fda.hhs.gov]
Sent: Friday, October 04, 2013 6:03 PM
To: (b) (4); FDA SharedMailbox; FDASharedMailboxForwarding
Subject: IND (b) (4) Argatroban - FDA Responses

Sunni,

Please refer to Teva's submission dated June 4, 2013, wherein a meeting is requested to discuss a proposed 505(b)(2) application for Argatroban. We also refer to the questions you posed in the meeting request.

Below are the FDA responses to these questions.

Please do not hesitate to contact me should you have any questions.

Pre-Clinical

Our proposed drug product has the same concentration, dosage form, route of administration and is intended for the same indications as Sandoz's Argatroban Injection (in Sodium Chloride), 125 mg/125 mL. Therefore, in accordance with Section 505(b)(2) of the Act, Teva does not intend to conduct toxicological studies, since we may rely on the Agency's prior finding of safety for Sandoz's Argatroban Injection (in 0.9% Sodium Chloride), 125 mg/125 mL. Does the agency agree that the toxicological studies are not necessary?

FDA Response:
Your approach is acceptable if the formulation of your drug product will be identical to that of Sandoz.

Clinical

1. **Teva's proposed drug product is parenteral solution intended solely for administration by injection, and contains the same active ingredient as the reference listed drug, Sandoz's Argatroban Injection (in 0.9% Sodium Chloride), 125 mg/125 mL. Additionally, our proposed drug product has the same inactive ingredients in the same concentration as that of Sandoz's Argatroban Injection (in 0.9% Sodium Chloride), 125 mg/125 mL. Furthermore, our drug product is intended (in 0.9% Sodium Chloride), 125 mg/125mL. Therefore, in accordance with Section 505(b)(2) of the Act, Teva does not intend to conduct bioequivalence or other clinical studies, since we may rely on the Agency's prior finding of efficacy for Sandoz's Argatroban Injection (in 0.9% Sodium Chloride), 125 mg/125 mL Does the agency agree that the bioequivalence or other clinical studies are not necessary?**

FDA Response:

From a clinical standpoint, no additional studies are required.

With respect to Biopharmaceutics and based on the information presented in the Briefing Package, you may request FDA to waive the requirement for the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence of your product by submitting a request for a waiver with the application. In support of the waiver request you should provide data from an in vitro bridging study assessing the in vitro equivalence of the anticoagulant pharmacodynamic (PD) activity between the Reference Listed Drug (RLD) product and your proposed product. Also, provide a comparative side-by-side table listing the components and composition of the RLD and your product including the pH and osmolarity values for each.

Chemistry, Manufacturing and Controls (CMC)

2. **The maximum daily dose of drug product used in establishing the drug substance and drug product impurities specifications was calculated based upon (b) (4) maximal dosing in patients with Heparin-Induced Thrombocytopenia (as referenced in the RLD's label) and the average adult human body weight of 70 kg (according to the Center for Disease Control and Prevention, clinical growth charts) as follows:**

(b) (4)

The identification and qualification thresholds corresponding to the calculated maximum daily dose of (b) (4) that were used in setting our drug substance and drug products impurities specifications inline with the ICH Q3A (R2) and ICH Q3B (R2) guidelines are indicated in the table below:

Reference ID: 3676303

	Identification Threshold	Qualification Threshold
Drug Substance	(b) (4)	
Drug Product		

Although the reference listed drug insert labeling uses the body weight range of 50 kg to 140 kg in the illustration of the recommended dosage of Argatroban Injection, Teva decided to use the generally accepted industry average adult human body standard weight of 70 kg based on the Center for Disease Control and Prevention, clinical growth charts in the calculation of the maximum daily dose used in establishing the drug substance and drug product impurities specifications. Does the Agency agree with Teva's approach to setting the drug substance and drug product impurities specifications?

FDA Response:
Your proposal to use 70 kg as the body weight is reasonable. Impurities above the levels present in the listed drug should be qualified or their levels be adequately justified. The final decision on the acceptability of the specifications will be made during the NDA review.

Additional comment:

Please note that the qualification threshold described in ICH Q3A for daily intake of ≤ 2 g is 0.15%, not (b) (4)% as currently presented in your briefing package.

Regulatory

3. **The accelerated storage condition (40±2°C/NMT (b) (4)% RH), intermediate storage condition (30±2°C, 65±5% RH) and real-time (25±2°C/40±5% RH) stability studies on Teva's proposed drug product, Argatroban Injection, 250 mg/250 mL (1 mg/mL) are on-going and will be completed after a period of 6 months for the accelerated stability study, 12 months for the intermediate stability study and beyond the proposed expiration period is 24 months for the real-time stability study. All attributes used to confirm the quality of the finished drug product at batch release are evaluated during stability testing, with the exception of identity as this is not expected to change over time. The acceptance limits for these attributes remain the same as those used to confirm the quality of the finished drug product at batch release.**

Interim accelerated, intermediate and real time stability results for 3 months revealed no deviations from the product specifications. According to the available results (provided in the briefing information package), Argatroban Injection, 250 mg/250 mL (1 mg/mL) packaged in the proposed marketing container closure system is stable for 3 months at accelerated, intermediate and long-term conditions. All impurity levels were below ICH limits and the stability profile is comparable to that of the RLD. Based on this assessment, Teva would like to seek the Agency's pre-agreement with our proposal to submit the NDA with 6 months accelerated stability data and 6 months real-time stability data. The remaining real time stability data will be provided as it becomes available.

FDA Response:

No. Six months long-term drug product stability data is not acceptable. According to Guidance for Review Staff and Industry Good Review Management Principles and Practices for PDUFA Products (GRMPs), all NDAs are to be complete in the original submission. This includes all stability data and corresponding data summaries necessary to establish a shelf life. International Conference on Harmonization (ICH) Q1A (R2) states "long term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission".

Our proposed drug product does not contain a new active ingredient; and is not for a new indication, new dosing regimen, nor a new route of administration. Therefore, in accordance with 21 CFR 314.55(a) a pediatric study is not required. Does the Agency agree that a pediatric evaluation is not required?

FDA Response:

Yes. However, you are required to formally submit a pediatric waiver request with your application.

Regards,

Amy Baird

Reference ID: 3676303

Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 2122
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

Reference ID: 3676303

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Thursday, September 25, 2014 8:06 AM
To: scott.tomsky@tevapharm.com
Subject: NDA 206769 Argatroban Injection Label Revisions
Attachments: Argatroban draft-pi post Redlined FDA 9.23.14.doc

Dear Mr. Tomsky,

Please find the attached FDA revised version of the label for your review regarding NDA 206769/ Argatroban Injection.

Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with including all format/minor editorial changes
- Edit over the ones that you do not agree with **(do not reject any changes that the FDA proposed)**
- Please address the comments directly to the document in tracked changes

After you have made the changes, please e-mail a revised label (in tracked changes word document) by **3:00 PM (EDT) Wednesday, October 1, 2014**.

Please confirm receipt of this message by e-mail and feel free to contact me if you have any questions.

Kind Regards,
Natasha Kormanik, RN, BSN, OCN®
LT, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue, Room 2389
Silver Spring, MD 20903
(o) 240-402-4227
Natasha.Kormanik@fda.hhs.gov

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/s/

NATASHA L KORMANIK
09/25/2014

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Tuesday, September 23, 2014 11:57 AM
To: scott.tomsky@tevapharm.com
Subject: NDA 206469 Argatroban Information Request

Categories: Red Category

Dear Mr. Tomsky,

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Argatroban Injection.

We are reviewing your application and have the following requests:

Information Request

1. Regarding the proposed drug product manufacturing process:
   (a) Specify the procedure and target time for the solution [redacted] (b) (4) process.
   (b) Specify the target and acceptable range for final weight of bulk drug product solution.
   (c) Revise the description of the manufacturing process in NDA section 3.2.P.3.3. to indicate that the first [redacted] (b) (4) of bulk drug product solution [redacted] (b) (4). Product development discussion indicates this as a standard procedure, however it is not indicated in NDA section 3.2.P.3.3 or in the executed batch records.
   (d) Specify the [redacted] (b) (4)
   (e) Specify the rate at which [redacted] (b) (4) include a target and acceptable range.
   (f) Describe the analytical method and criterion for the in-process control for seal integrity. Also, specify the sample size and sampling frequency for this test.
   (g) Specify whether [redacted] (b) (4)
   (h) Explain why the in-process controls for bulk DP solution [redacted] (b) (4) do not include assay.

2. Regarding the excipient controls
   (a) Specify the tests that are routinely performed on each lot of sodium chloride [redacted] (b) (4) for acceptance.
   (b) Describe the procedure for supplier validation and how often a supplier is revalidated

3. Regarding the proposed release specification for drug product:
   (a) Revise the criterion for the Container Content test to include a target and acceptable range. Also, describe the analytical method.
   (b) Specify the target for pH. Also, justify the proposed range based on batch analysis data and the effect of pH on product quality.
   (c) Specify whether unit dose uniformity will be established for a commercial batch based on the in-process control results for fill weight or by sampling from the completed batch. If the former, then describe the sampling frequency and sample size. Also, describe how the proposed procedure meets the requirements of USP <905>.

4. Regarding the submitted packaging information:
   (a) Describe the tests which will be routinely performed on each lot of each packaging component.

Reference ID: 3632657

(b) Since the manufacturing process, and the quality and stability of the proposed drug product are very sensitive to the materials of construction, physicochemical attributes and dimension of the packaging components, a change of supplier should be qualified by testing per the proposed specification as well as appropriate qualification studies including biocompatibility studies. Since there is no protocol for change of packaging components, any change should be filed as an appropriate supplemental application.

5. After evaluation of the submitted stability study data, we have concluded that the data is only stuffiest to support an initial expiry period of (b) (4) months at the listed storage condition.

We request a response by September 29, 2013 at 3:00 PM (EDT). Please confirm receipt of this e-mail and follow-up with an official response submission to your NDA. Please do not hesitate to contact me with any questions.

Kind Regards,
Natasha Kormanik, RN, BSN, OCN®
LT, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue, Room 2389
Silver Spring, MD 20903
(o) 240-402-4227
Natasha.Kormanik@fda.hhs.gov

Reference ID: 3632657

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/s/

NATASHA L KORMANIK
09/23/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206769

INFORMATION REQUEST

Teva Pharmaceuticals USA
Attention: Scott D. Tomsky
Vice President, US Generics Regulatory Affairs
425 Privet Road
Horsham, PA 19044

Dear Mr. Tomsky:
Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Argatroban Injection, 250 mg/ 250 mL.

We also refer to your original NDA submission.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a written response by July 8, 2014, in order to continue our evaluation of your NDA.

Please provide the following information or a reference to its location in the subject submission.

1. We refer to the [redacted] (b) (4)
2. We refer to the [redacted] (b) (4)
3. We refer to the [redacted] (b) (4)
4. We refer to the [redacted] (b) (4)
5. Provide a description of the growth media used for environmental monitoring. Confirm that personnel monitoring plates are incubated at a minimum of 48 hours at 32.5±2.5°C or 72 hours at 22.5±2.5°C.
6. Describe the [redacted] (b) (4) strategy for the container closure system.

7. Provide the sterility test and endotoxin test method verification studies.

If you have any questions, please contact Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Ali H. Al Hakim, PhD
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

JANICE T BROWN
07/01/2014
Janice Brown for Ali Al-Hakim

Wright, Kevin

From: Cory Wohlbach <Cory.Wohlbach@tevapharm.com>
Sent: Friday, May 23, 2014 10:40 AM
To: Wright, Kevin; Scott Tomsky; FDA SharedMailbox; FDASharedMailboxForwarding
Cc: Kang, Sue; Kormanik, Natasha
Subject: RE: NDA 206769 Argatroban: Request for proprietary name

Follow Up Flag: Follow up
Flag Status: Flagged

Categories: DMEPA

Hello Kevin,

As a follow up to your below email, Teva does not intend to market this product (NDA 206769 argatroban) with a proprietary name.

Cory

Cory Wohlbach Director, Regulatory Affairs
Tel: (215) 293-6519 Cell: (b) (6) Fax: (215) 591-8812
Cory.Wohlbach@tevapharm.com www.tevapharm.com

From: Cory Wohlbach
Sent: Tuesday, May 20, 2014 10:43 PM
To: Wright, Kevin; Scott Tomsky; FDA SharedMailbox; FDASharedMailboxForwarding
Cc: Kang, Sue; Kormanik, Natasha
Subject: RE: NDA 206769 Argatroban: Request for proprietary name

Hello Kevin,

I confirm receipt of this email and we will submit a request for proprietary name if we intend to market this product with a proprietary name.

Cory

Cory Wohlbach Director, Regulatory Affairs
Tel: (215) 293-6519 Cell: (b) (6) Fax: (215) 591-8812
Cory.Wohlbach@tevapharm.com www.tevapharm.com

From: Wright, Kevin [mailto:Kevin.Wright@fda.hhs.gov]
Sent: Tuesday, May 20, 2014 3:30 PM
To: Scott Tomsky; FDA SharedMailbox; FDASharedMailboxForwarding
Cc: Kang, Sue; Kormanik, Natasha
Subject: NDA 206769 Argatroban: Request for proprietary name

Reference ID: 3514535

Hello Scott,

This email is to notify you that Division of Medication Error and Prevention Analysis (DMEPA) is requesting you submit a request for proprietary name review to NDA 206769 if you intend to market this product with a proprietary name.

The request for proprietary name review should include FDA Form 356h, and a cover letter stating "REQUEST FOR PROPRIETARY NAME", on the first page of the submission. Also, this submission should contain the proposed labels and labeling or a reference to the submission containing the labels and labeling.

A complete request for proprietary name review should include the primary proprietary and where applicable the alternate proprietary name, intended pronunciation, derivation of proprietary name, and/or intended meaning of any modifiers (e.g. prefix, suffix) contained in the proprietary name.

Additionally, your request should include the following product characteristics: established name, prescription status, dosage form, product strength, proposed indication for use, route of administration, usual dosage, frequency of administration, dosing in specific populations, instructions for use, setting of use, storage requirements and the intended package configuration.

If you have any questions or comments regarding this email, please contact me.

Best regards,

Kevin Wright, PharmD

Safety Regulatory Project Manager | OSE | CDER | FDA | 301.796.3621 |kevin.wright@fda.hhs.gov

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THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PREDECISIONAL, PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW.

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/s/

KEVIN WRIGHT
05/29/2014

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Wednesday, May 14, 2014 1:53 PM
To: scott.tomsky@tevapharm.com
Subject: NDA 206769 Argatroban Injection Information Request

Dear Mr. Tomsky,

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Argatroban Injection.

We have reviewed your labeling format and identified the below issues. Please note that this review did not include a content review.

Labeling issues identified:

1. Based on labeling regulations (21 CFR 201.56 and 201.57) and guidances, Highlights need to be less than a half of page. Please request a waiver to permit the highlights being greater a half-page.
2. The initial U.S. Approval in Highlights indicates the approval year of 2000. Please revise to reflect "YYYY" as this product is not approved.
3. The revision date at the end of Highlights indicates a revised date of 12/2003. Please revise to reflect MM/YYYY as this product is not approved.
4. In the Table of Contents, the subsection headings for 2.1, 2.3, and 2.4, the preposition article "with" should not be capitalized.

We ask that you correct these deficiencies and resubmit the PI in Word format by June 4, 2014 (3:00 EDT). The resubmitted PI will be used for further labeling review.

Kind Regards,
Natasha Kormanik, RN, BSN, OCN®
LT, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue, Room 2389
Silver Spring, MD 20903
(o) 240-402-4227
Natasha.Kormanik@fda.hhs.gov

Reference ID: 3506664

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/s/

NATASHA L KORMANIK
05/14/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206769

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Teva Pharmaceuticals USA
Attention: Scott D. Tomsky
Vice President, US Generics Regulatory Affairs
425 Privet Road
Horsham, PA 19044

Dear Mr. Tomsky:

Please refer to your New Drug Application (NDA) dated February 28, 2014, received February 28, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Argatroban Injection, 250 mg/ 250 mL.

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**.

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, mid-cycle, 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 November 30, 2014.

During our filing review of your application, we identified the following potential review issues:

<u>Microbiology</u>

1. Module 3.2.P.3.3 indicates the bioburden sample will be collected (b) (4)

2. Justify the requalification (b) (4)

(b) (4)

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

1. Provide all the raw data used in study report 6000133 (*In vitro* evaluation of the equivalence of the anticoagulant PD activity between Argatroban Injection and a RLD in human citrated plasma using PT, aPTT and TT) in SAS transport file (*.xpt) format. Submit this requested information by May 7, 2014.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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

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

If you have any questions, call Natasha Kormanik, Regulatory Project Manager, at (240) 402-4227.

Sincerely,

{See appended electronic signature page}

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

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/s/

ANN T FARRELL
05/02/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206769

NDA ACKNOWLEDGMENT

Teva Pharmaceuticals USA
Attention: Scott D. Tomsky
Vice President, US Generics Regulatory Affairs
425 Privet Road
Horsham, PA 19044

Dear Mr. Tomsky:

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

Name of Drug Product: Argatroban Injection, 250 mg/ 250 mL

Date of Application: February 28, 2014

Date of Receipt: February 28, 2014

Our Reference Number: NDA 206769

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 29, 2014, 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.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (240) 402-4227.

Sincerely,

{See appended electronic signature page}

Natasha Kormanik, RN, BSN, OCN®
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

NATASHA L KORMANIK
03/10/2014