CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206769Orig1s000

MEDICAL REVIEW(S)

FILE MEMORANDUM

Memo Date:	September 30, 2014
To NDA:	206769
Submission Date:	February 28, 2014
FDA Received Date:	February 28, 2014
EDR Location:	\\CDSESUB1\evsprod\NDA206769\206769.enx
Non-Clinical:	Christopher Sheth, Ph.D.
Clinical Pharmacology:	Young-Jin Moon, Ph.D.
Product Quality:	William Adams, Ph.D.
Microbiology:	Jessica Cole, Ph.D.
From:	Hyon-Zu Lee, Pharm.D., Clinical Reviewer; Division of Hematology Products (DHP)
Subject:	Argatroban
Via:	Virginia Kwitkowski, MS, RN, ACNP-BC, Clinical Team Leader, DHP

ISSUE: N/A

ACTIONS RECOMMENDED: Tentative approval

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

Background:

This is a 505(b)(2) application submitted by Teva Pharmaceuticals USA. The reference drug product is Sandoz Inc.'s Argatroban Injection (in 0.9% Sodium Chloride), 125 mg/125 mL (NDA 22485). The marketed drug product by Sandoz Inc. is supplied in a package containing two single-use clear glass vials for intravenous administration. Teva's proposed drug product, Argatroban Injection, 250 mg/250 mL (1 mg/mL), has the same proposed indications, active and inactive ingredients, strength, dosage form and route of administration as the reference listed drug. The proposed drug product differs from the reference listed drug in total drug content per container and packaging components. Teva's drug product is supplied in a (b) (4) bag containing 250 mL of Argatroban Injection (1 mg/mL).

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

/s/

HYON-ZU LEE
09/30/2014

VIRGINIA E KWITKOWSKI
09/30/2014
Concur.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 206769 **Applicant:** Teva Pharmaceutical Industries LTD **Stamp Date:** February 28, 2014

Drug Name: Argatroban Injection **NDA/BLA Type:** 505(b)(2)

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			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?			X	No clinical data were submitted to support this application.
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			
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			Module 1.14
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	No clinical data were submitted to support this application.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	No clinical data were submitted to support this application.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Module 1.12.11
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	X			505(b)(2)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?	X			NDA 022485 Argatroban Injection 125 mg/125 mL
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?			X	Module 1.12.11 and 1.12.12
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSE					
16.	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:			X	

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	Sample Size: Arms: Location in submission:				
EFFICACY					
17.	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	
18.	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	
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
21.	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	
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
24.	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	
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	

[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

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27.	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	
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	No clinical trials were requested
30.	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					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	Not seeking approval for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	No clinical data were submitted to support this application.
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	No clinical data were submitted to support this application.
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	No clinical data were submitted to support this application.
37.	Are all datasets to support the critical safety analyses available and complete?			X	No clinical data were submitted to support this application.
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	No clinical data were submitted to support this application.
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and			X	

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

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	Content Parameter	Yes	No	NA	Comment
	adverse dropouts)?				
40.	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	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?			X	
GOOD CLINICAL PRACTICE					
42.	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	

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Electronic stamp

Reviewing Medical Officer Date

Electronic stamp

Clinical Team Leader Date

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

/s/

ADAM N GEORGE
04/23/2014

VIRGINIA E KWITKOWSKI
04/23/2014