

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206769Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

NDA	206769
Submission Type	Original, 505(b)(2)
Submission Date	2/28/14
Brand Name	Argatroban Injection, (b) (4) mg/mL
Generic Name	Argatroban
Indication	An anticoagulant 1) for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT/ (b) (4)); 2) in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI)
Formulation	An intravenous solution containing (b) (4) of argatroban (each (b) (4) vial contains (b) (4) of argatroban)
Dosing Regimen	1) HIT/ (b) (4): 2 µg/kg/min as a continuous infusion then adjusted to steady-state aPTT being 1.5 - 3 times baseline 2) PCI: 25 µg/kg/min and a bolus of 350 µg/kg administered over 3 to 5 minutes then adjusted based on activated clotting time
Sponsor	TEVA Pharmaceuticals USA
OCP Reviewer	Young Jin Moon, Ph.D.
OCP Team Leader	Bahru Habtemariam, Pharm.D.
OCPB Division	Division of Clinical Pharmacology V
ORM Division	Division of Hematology Products

1 EXECUTIVE SUMMARY

This 505(b)(2) application submitted by Teva Pharmaceuticals USA is for Argatroban Injection, 250 mg/250 mL (1 mg/mL) in single-dose vials. The Teva Argatroban Injection has the same proposed indications, active and inactive ingredient, dosage form, strength, and route of administration as the innovator drug approved by the FDA under NDA 22485 (Sandoz Inc.). The innovator's ARGATROBAN Injection is the reference listed drug (RLD) for this 505(b)(2) application. The proposed drug product differs from the reference listed drug in total drug content per container and package components. Teva's drug product is supplied in a (b) (4) bag containing 250 mL of Argatroban Injection (1 mg/mL).

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 and Sandoz'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 Teva's or Sandoz's argatroban product. The 90% confidence intervals (CI₉₀) of the ratios of geometric means between Teva and the RLD for observed aPTT, PT, and TT at clinically relevant argatroban concentrations were within the pre-specified confidence bound of 90 to 110%.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology V considers this NDA acceptable from a clinical pharmacology perspective.

Error! Reference source not found.

1.2 PHASE 4 REQUIREMENT

None.

1.3 SIGNATURES

Young Jin Moon, Ph.D.
Reviewer
Division of Clinical Pharmacology V

Bahru Habtemariam, Pharm.D.
Acting Team Leader
Division of Clinical Pharmacology V

Cc: DHP: CSO - N Kormanik ; MTL - V Kwitkowski; MO - H-Z Lee
DCP-V: Reviewers - Y Moon; TL - B Habtemariam; DDD - B Booth
DD - A Rahman

1.4 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

Argatroban is a synthetic small molecule direct thrombin inhibitor. ARGATROBAN Injection, the RLD for this 505(b)(2) application, was approved by the FDA under 22485 (Sandoz Inc.) for the following indications:

- as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT/ (b) (4));
- as an anticoagulant in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI)

In support of a waiver of *in vivo* BE, an *in vitro* "bridge" study (Study No. 6000133) was conducted to assess the equivalence of the anticoagulant (PD) activity between Teva's Argatroban Injection to the RLD. The PD effects were measured by determining aPTT, PT, and TT in pooled donor human plasma (N=6) spiked with clinically relevant concentrations of argatroban from either the Teva or RLD product. Briefly, blood samples were collected from 3 male and 3 female subjects. The spiking solutions of either the RLD or Teva's product were prepared at 50 µg/mL using saline. An aliquot of each pooled human plasma was spiked with spiking solutions of each product, or the Reference items (vehicle for the RLD and the proposed argatroban product). Five plasma concentrations of argatroban at 0.25, 0.5, 1, 3 and 5 µg/mL were prepared and tested for PT and aPTT. Concentrations up to 1 µg/mL were tested for TT. Concentrations of argatroban in plasma were determined by a validated LC/MS/MS method.

The results (Table 1) show that the 90% confidence intervals (CI₉₀) of the ratios of geometric means between Teva and the RLD for observed aPTT, PT, and TT at clinically relevant argatroban concentrations were within the range between 90 and 110.

Table 1. Ratios and 90% Confidence Intervals of PD Parameters Between Teva's Product and the RLD

Conc (µg/mL)	APP/ RLD Ratio (CI ₉₀)	
	PT	aPTT
0.25	101.4 (101.0-101.8)	99.26 (98.1-100.4)
0.5	100.1 (99.2-101.0)	99.46 (97.6-101.3)
1	101.5 (99.7-103.3)	102.1 (100.9-103.2)
3	99.11 (97.6-100.6)	98.85 (97.8 – 99.9)
5	99.20 (92.3 – 106.1)	99.58 (98.4 – 100.7)
	TT	
0.25	99.05 (98.4-99.7)	
0.5	99.35 (96.6-102.1)	
1	N.A. (Analysis failed since the TT was prolonged over the valid measurement range)	

The submitted *in vitro* PD activity evaluation results indicate the Teva product and the RLD have similar PT, aPTT, and TT properties as shown by the relatively tight 90% confidence bound (Table 1).

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/s/

YOUNG J MOON
11/18/2014

BAHRU A HABTEMARIAM
11/19/2014

BIOPHARMACEUTICS REVIEW			
Office of New Drug Quality Assessment			
Application No.:	NDA 206-769	Reviewer:	
Division:	DHP	Houda Mahayni, Ph.D.	
Applicant:	TEVA Pharmaceuticals USA	Team Leader:	
Trade Name:	---	Angelica Dorantes, Ph.D.	
Generic Name:	Argatroban Injection	Acting Supervisor:	
Indication:	-for prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT) -an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI)	Date Assigned:	March 4, 2014
Formulation/strength	Injection, 250 mg/250 mL (1 mg/mL)	Date of Review:	November 14, 2014
Route of Administration	Intravenous		
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission Date:	GRMP Date	PDUFA Date	
February 28, 2014	November 23, 2014	December 28, 2014	
Type of Submission	505 (b) (2)		
Key review point	Evaluation of the Biowaiver request		

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I) SUMMARY OF BIOPHARMACEUTICS FINDINGS

Submission:

NDA 206769 was submitted in accordance with Section 505(b) (2) of the FDC Act. To support the approval of the proposed product, Argatroban Injection 250 mg/250 mL, the Applicant is relying on FDA's previous finding of safety and effectiveness for the Listed Drug (LD) (Sandoz's approved drug product Argatroban Injection (in 0.9% Sodium Chloride), 125 mg/125mL, NDA 022485).

The Applicant described the differences between the proposed drug product and the LD as follows:

1) The total drug content per container (strength)

The LD Argatroban Injection (in 0.9% Sodium Chloride), 125 mg/125 mL, has a total drug content per container (strength) of 125 mg/125mL. The proposed product has total drug content per container (strength) of 250 mg/250 mL. The proposed drug product will have the same concentration, 1 mg/mL, as the LD product, but will be packaged as a different strength (total drug content per container) of 250 mg/ 250 mL.

2) Packaging components

The LD is packaged in a single-use vial, while the proposed drug product is packaged in a (b) (4) bag. The Applicant stated that the use of a (b) (4) bag is more suited for the proposed drug product because the total fill volume of the drug product solution would be two times that of the LD product, Sandoz's Injection (in 0.9% Sodium Chloride), 125 mg/125 mL.

Biowaiver:

The Applicant requested a waiver of *in vivo* bioavailability/bioequivalence (BA/BE) requirements for Argatroban for Injection based on 21 CFR § 320.22 (b).

The Applicant stated that the proposed changes in the drug product strength (total drug content per container) and packaging components do not pose questions of safety or efficacy because the formulation, the indications, the doses, and the route of administration of the proposed drug product are the same as those of the LD.

This Biopharmaceutics review evaluated the acceptability of the biowaiver request and found the Applicant's justification acceptable. The supportive *in vitro* study No. 6000133 assessing the equivalence of the anticoagulant pharmacodynamics (PD) activity between the proposed Argatroban product and the LD product in human citrated plasma using PT, PTT, and TT was evaluated and found acceptable by the Clinical Pharmacology Reviewer, Dr. Young Jin Moon*. Therefore, the biowaiver request for Argatroban Injection, 250 mg/250 mL (1 mg/mL) is granted.

*For specific information on the *in vitro* PK study No. 6000133, refer to the Clinical Pharmacology review dated 11/19/14 in DARRTS.

Risk Evaluation:

Risk Assessment Table

Initial Risk Assessment			Final Risk Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation approach	Risk Evaluation	Lifecycle Considerations/ Comments
Osmolality	None identified	L	Similar osmolality values were obtained comparing the osmolality of the LD and the proposed product	Acceptable	Osmolality test and limits are included in the finished product specification table
pH	None identified	L	Similar pH values were obtained comparing the pH of the LD and the proposed product	Acceptable	pH test and limits are included in the finished product specification table

II) RECOMMENDATION

The information provided to support the approval of the biowaiver request is acceptable and therefore the BE waiver for Argatroban Injection is granted.

From the Biopharmaceutics perspective, NDA 206-769 for Argatroban Injection, 250 mg/250 mL (1 mg/mL) is recommended for APPROVAL.

Signed on Behalf of Dr. Mahayni

**Angelica
Dorantes -S**

Digitally signed by Angelica Dorantes -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300070843,
cn=Angelica Dorantes -S
Date: 2014.11.21 14:41:59 -05'00'

Houda Mahayni, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

**Angelica
Dorantes -S**

Digitally signed by Angelica Dorantes -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300070843,
cn=Angelica Dorantes -S
Date: 2014.11.21 14:42:38 -05'00'

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

III) BIOPHARMACEUTICS ASSESSMENT-QUESTION BASED REVIEW APPROACH

A) GENERAL ATTRIBUTES

- a. *What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility)?*

Argatroban is very soluble in acetic acid, sparingly soluble in ethanol, very slightly soluble in water, practically insoluble in acetone, ethyl acetate, chloroform and diethylether. Also, Argatroban is non-hygroscopic and has (b) (4).

- b. *What is the route of administration? How is the product being administered?*

The proposed drug product is supplied in 250 mL (b) (4) bag with single port, closed by stopper and cap, placed into aluminum foil overpouch with clear window. Argatroban Injection, 250 mg/250 mL is administered as intravenous infusion. The drug product should not be diluted prior to administration.

- c. *Does the drug product include a delivery device?*

No.

B) DRUG PRODUCT FORMULATION

- d. *What is the formulation?*

The components and composition of the drug product are shown in table 1 below.

Table 1: Unit Composition for Argatroban Injection, 250 mg /250 mL (1 mg/mL)
(source: Module 2.3. Quality Overall Summary Part C)

Components	Concentration (mg/mL)	Each 250 mL bag contains ²⁾ (mg)	Function	Reference to quality standard
Argatroban (as Argatroban monohydrate)	1.0 (1.035)	250.0 (258.75)	Active ingredient	In-house
Sorbitol	3.0	750.0	(b) (4)	NF
Sodium chloride	9.0	2250.0	(b) (4)	USP
Water for Injections	Ad to 1 mL ¹⁾	Ad to 250 mL ¹⁾	(b) (4)	USP

e. What are the highlights of the drug product formulation development?

The proposed drug product differs from the LD in total drug content per container and packaging components. The LD is supplied as two single use vials in a package, each vial containing 125 mL of Argatroban Injection (1 mg/mL). The proposed presentation is a bag product containing 250 mL of Argatroban Injection (1 mg/mL).

C) SUPPORTIVE INFORMATION

f. What data are available to support the approval of the proposed product?

NDA 206769 was submitted in accordance with Section 505(b) (2) of the FDC Act. To support the approval of the proposed product, Argatroban Injection 250 mg/250 mL, the Applicant is relying on FDA's previous finding of safety and effectiveness for the Listed Drug (LD) (Sandoz's approved drug product Argatroban Injection (in 0.9% Sodium Chloride), 125 mg/125mL, NDA 022485).

The proposed drug product differs from the LD in total drug content per container and packaging components. The LD is supplied as two single use vials in a package, each vial containing 125 mL of Argatroban Injection (1 mg/mL). The proposed presentation is a bag product containing 250 mL of Argatroban Injection (1 mg/mL).

According to the Applicant the proposed drug product meets the waiver criteria for the following reasons:

1. Argatroban Injection, 250 mg/ 250 mL (1 mg/ mL), is a parenteral drug product intended for administration by injection.
2. The proposed drug product contains the same active and inactive ingredients in the same concentration as LD.
3. An in vitro bridging study demonstrated in vitro equivalence of the anticoagulant pharmacodynamics (PD) activity between LD and the proposed product.

Reviewer's Comment:

This reviewer confirmed that the Clinical Pharmacology Reviewer, Dr. Young-Jin Moon, is reviewing the in vitro PD No. 6000133, which assessed the equivalence of the anticoagulant pharmacodynamics (PD) activity between the proposed Argatroban product and the LD product in human citrated plasma using PT, PTT, and TT.

g. Does the Applicant rely on the safety and/or efficacy of a reference product?

Yes, the Applicant is relying on FDA's previous finding of safety and effectiveness for the Listed Drug (LD) (Sandoz's approved drug product Argatroban Injection (in 0.9% Sodium Chloride), 125 mg/125mL, NDA 022485).

h. Was a bioequivalence study conducted? If yes, is a Biopharmaceutics Review needed for the submission?

No, the Applicant did not conduct any in vivo studies to support their product. However, the Applicant conducted in vitro bridging study (Study No. 6000133) to demonstrate the in vitro equivalence of the anticoagulant pharmacodynamics (PD) activity between the LD and the proposed product.

D) BIOWAIVER

i. Is there a waiver request for the submission of in vivo BA/BE data (biowaiver)?

Yes, the Applicant is requesting a biowaiver from the requirements for submission of *in vivo* bioavailability or bioequivalence data. The justification for the biowaiver request is provided under (f) above.

j. What is the purpose of the biowaiver request?

Pursuant to 21 CFR § 320.22(b) (1), the Applicant requests a waiver from the requirements for submission of *in vivo* bioavailability or bioequivalence data. The proposed drug product contains the same active and inactive ingredients in the same concentration, route of administration and conditions of use as the LD.

k. What information supports the biowaiver request?

According to the Applicant the proposed drug product meets the waiver criteria for the following reasons:

1. Argatroban Injection, 250 mg/ 250 mL (1 mg/ mL), is a parenteral drug product intended for administration by injection.
2. The proposed drug product contains the same active and inactive ingredients in the same concentration as LD. A comparative side-by-side table listing the components and composition of the LD product and the proposed drug product is provided in Table 2. The pH and osmolarity values for each are provided in Table 3.
3. An in vitro bridging study demonstrated in vitro equivalence of the anticoagulant pharmacodynamics (PD) activity between LD and the proposed product.

Table 2: Components and Composition Comparison of the RLD and Teva's Argatroban Injection, 250 mg/250 mL (Source: Module 2.3 Quality Overall Summary Part C)

Components	Innovator Product: Argatroban Injection in 0.9% Sodium chloride, 125 mg/125 mL (1 mg/mL)		TEVA product: Argatroban Injection, 250 mg/250 mL (1 mg/mL)	
	Concentration / 1.0 mL	Concentration /125.0 mL	Concentration /1.0 mL	Concentration /250.0 mL
Argatroban (as Argatroban monohydrate)	1.0 mg (1.035 mg)	125.0 mg (129.38 mg)	1.0 mg (1.035 mg)	250.0 mg (258.75mg)
Sorbitol	3.0 mg	375.0 mg	3.0 mg	750.0 mg
Sodium chloride	9.0 mg	1125.0 mg	9.0 mg	2250.0 mg
Water for injections	ad 1.0 mL	ad 125.0 mL	ad 1.0 mL	ad 250.0 mL

Table 3: pH and Osmolarity Results of Teva's Argatroban Injection, 250 mg/250 mL and the RLD

Test	Method	Requirement	Results			
			Innovator product	TEVA product		
			Batch Number: CC2823	Batch number: K1151012	Batch number: K2871112	Batch number: K2881112
pH	USP<791>-DFA-241	3.2 – 7.5	6.1	5.6	6.0	6.4
Osmolarity	USP<785>-DFA-116	270-330 mOsmol/kg	309	315	313	312

The Biopharmaceutics review is evaluating the data provided in support of the biowaiver request.

It is noted that the pharmacodynamics (PD) in vitro bridging study (Study No. 6000133) performed to demonstrate the in vitro equivalence of the anticoagulant pharmacodynamics (PD) activity between LD and the proposed product was reviewed by OCP and found acceptable. For specific information on this PD study, refer to the Clinical Pharmacology review by Dr. Young Moon dated 11/19/14 in DARRTS.

Reviewer's Assessment: SATISFACTORY

The PD, pH, and osmolarity results comparing the LD to the proposed product are similar.

l. Are the CFR requirements for granting a biowaiver met? If not, are the provided justification and supportive data appropriate?

Yes.

m. Is the overall information supporting the biowaiver request acceptable?

The acceptability of the biowaiver request is pending the review outcome of the PD bridging study which is under review by the Office of Clinical Pharmacology.

n. Is the biowaiver granted?

Yes. The provided information supports the approval of the BE waiver request.

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

NDA/BLA Number:	206769/000	SDN:	1
Sponsor:	TEVA Pharmaceuticals, Inc.	Date of Submission	28-February-14
Brand Name:	Argatroban Injection, 250 mg/250 mL	Generic Name:	Argatroban
Drug Class:	A synthetic direct thrombin inhibitor		
Dosage Form:	Intravenous solution as a single use (b) (4) bag containing 250 mg argatroban in 250 mL aqueous sodium chloride solution (1 mg/mL)		
Dosing Regimen:	HIT, (b) (4): 2 µg/kg/min as a continuous infusion then adjusted to steady-state aPTT being 1.5 - 3 times baseline; PCI: 25 µg/kg/min and a bolus of 350 µg /kg administered over 3 to 5 minutes then adjusted based on activated clotting time		
Route of Administration:	Intravenous As an anticoagulant for		
Indication:	<ul style="list-style-type: none"> • prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT/ (b) (4)) • patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI) 		
OCP Division:	DCP5	OND Division:	DHP
OCP Reviewer:	Young Jin Moon, Ph.D.		
OCP Team Leader:	Gene Williams, Ph.D.		
PM Reviewer:			
PM Team Leader:			
GG Reviewer:			
GG Team Leader:			
Priority Classification:	<input type="checkbox"/> Standard <input type="checkbox"/> Priority		PDUFA Due Date
OCP Review Due Date:			OND Division Due Date:

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Critical Comments
Table of Contents present and sufficient to locate reports, tables, data, etc.	<input checked="" type="checkbox"/>		
Tabular Listing of All Human Studies	<input type="checkbox"/>		
Human PK Summary	<input type="checkbox"/>		
Labeling	<input checked="" type="checkbox"/>		
Bioanalytical and Analytical Methods	<input type="checkbox"/>		
I. Clinical Pharmacology			
Mass balance:	<input type="checkbox"/>		
Isozyme characterization:	<input type="checkbox"/>		
Blood/plasma ratio:	<input type="checkbox"/>		
Plasma protein binding:	<input type="checkbox"/>		
Pharmacokinetics (e.g., Phase I) - <i>Healthy Volunteers:</i>	<input type="checkbox"/>		
single dose:	<input type="checkbox"/>		
multiple dose:	<input type="checkbox"/>		
<i>Patients:</i>			
single dose:	<input type="checkbox"/>		
multiple dose:	<input type="checkbox"/>		
Dose proportionality -			
fasting / non-fasting single dose:	<input type="checkbox"/>		
fasting / non-fasting multiple dose:	<input type="checkbox"/>		

Drug-drug interaction studies -		
In-vivo effects on primary drug:	<input type="checkbox"/>	
In-vivo effects of primary drug:	<input type="checkbox"/>	
Concomitant therapy:	<input type="checkbox"/>	
In-vitro:	<input type="checkbox"/>	
Subpopulation studies -		
ethnicity:	<input type="checkbox"/>	
gender:	<input type="checkbox"/>	
pediatrics:	<input type="checkbox"/>	
geriatrics:	<input type="checkbox"/>	
renal impairment:	<input type="checkbox"/>	
hepatic impairment:	<input type="checkbox"/>	
PD -		
Phase 2:	<input type="checkbox"/>	
Phase 3:	<input type="checkbox"/>	
PK/PD -		
Phase 1/2, proof of concept:	<input type="checkbox"/>	
Phase 3 clinical trial:	<input type="checkbox"/>	
Population Analyses -		
Data rich:	<input type="checkbox"/>	
Data sparse:	<input type="checkbox"/>	
QT evaluation:		
<input type="checkbox"/>		
II. Biopharmaceutics		
Absolute bioavailability:	<input type="checkbox"/>	
Relative bioavailability -		
solution as reference:	<input type="checkbox"/>	
alternate formulation as reference:	<input type="checkbox"/>	
Bioequivalence studies -		
traditional design:	<input type="checkbox"/>	
replicate design:	<input type="checkbox"/>	
Food-drug interaction studies:		
<input type="checkbox"/>		
Bio-waiver request based on BCS		
<input type="checkbox"/>		
BCS class		
<input type="checkbox"/>		
Alcohol induced dose-dumping		
<input type="checkbox"/>		
III. Other CPB Studies		
Genotype/phenotype studies	<input type="checkbox"/>	
Chronopharmacokinetics	<input type="checkbox"/>	
Pediatric development plan	<input type="checkbox"/>	
In vitro PD bridge study	<input checked="" type="checkbox"/>	1
Literature References	<input type="checkbox"/>	
Total Number of Studies		1

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?			X	
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?			X	
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?			X	
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			X	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

Is the Clinical Pharmacology Section of the Application Fileable?

- Yes
 No

If the NDA/BLA is not fileable from the clinical pharmacology 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.

None.

We have the following non-refuse-to-file comment:

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

Signatures:

Young Jin Moon, Ph.D.
Reviewer
Division of Clinical Pharmacology 5

Gene Williams, Ph.D.
Team Leader
Division of Clinical Pharmacology 5

Clinical Pharmacology - NDA Filing Memo

NDA: 206769/000 Original Submission **IND:** (b) (4)
Compound: Argatroban
Sponsor: TEVA PHARMACEUTICALS INC
Filing Date:
Reviewer: Young Jin Moon, Ph.D.

This is a 505(b)(2) application which relies on the FDA's finding of safety and/or effectiveness for the reference listed drug (RLD), Argatroban Injection marketed by Sandoz Inc. under the approved NDA22-485.

There are two differences between Sandoz's Argatroban Injection (in 0.9% Sodium Chloride) and Teva's proposed product.

- 1) The RLD has a total drug content per container of 125 mg/125 mL. Teva's proposed product will have a total drug content per container of 250 mg/250 mL.
- 2) The RLD is packaged in a single-use vial, while Teva's proposed drug product will be packaged in a (b) (4) bag.

Teva's proposed drug has the same active and inactive ingredients, strength, dosage form, route of administration, and conditions of use as the RLD.

An *in vitro* "bridge" study (Study No. 6000133) was conducted to assess the equivalence of the anticoagulant (PD) activity between the Teva's product and the RLD formulation. Using PT, aPTT, and TT assays, the *in vitro* anticoagulant effect of Teva's product was compared to the RLD formulation in human plasma.

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/s/

YOUNG J MOON
04/25/2014

GENE M WILLIAMS
04/25/2014