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APPLICATION NUMBER:

203049Orig1s000

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

Clinical Pharmacology Review

NDA	203049
Submission Type	Original, 505(b)(2)
Submission Date	18 March 2011, 8 July, 2011
Brand Name	Argatroban Injection, 100 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 1mg/mL of argatroban (each 125 mL vial contains 125 mg 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	Exela Pharma Sciences, Inc.
OCP Reviewer	Young Jin Moon, Ph.D.
OCP Team Leader	Julie Bullock, Pharm.D.
OCPB Division	Division of Clinical Pharmacology 5
ORM Division	Division of Hematology Products

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1 EXECUTIVE SUMMARY

This 505(b)(2) application submitted by Exela Pharma Sciences, Inc. is for Argatroban Injection, 1 mg/mL in single-dose vials. The Exela Argatroban Injection has the same active ingredient, dosage form, strength, route of administration, and conditions of use as the innovator drug approved by the FDA under NDA 20-883 (Pfizer). The innovator's ARGATROBAN Injection is the reference listed drug (RLD) for this 505(b)(2) application.

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 Exela's and Pfizer's products. PD effects were measured by determining the activated partial thromboplastin time (aPTT), the prothrombin time (PT), and the thrombin time (TT) in pooled donor human plasma spiked with clinically relevant concentrations of Exela's or Pfizer's argatroban product.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 considers this NDA acceptable from a clinical pharmacology perspective.

For labeling recommendations, please refer to Section 3.

1.2 PHASE 4 REQUIREMENT

None.

1.3 SIGNATURES

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

Julie Bullock, Pharm.D.
Team Leader
Division of Clinical Pharmacology 5

Cc: DDOP: CSO - L Akinsanya; MTL - V Kwitkowski; MO - R Alvandi
DCP-5: Reviewers - Y Moon; TL - J Bullock; 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 NDA 20-883 (Pfizer) for the following indications:

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

The RLD is a sterile solution and available in 250 mg in 2.5 mL (100 mg/mL) single-use vials. The injection solution (100 mg/mL) needs to be diluted in 0.9% Sodium Chloride for Injection, 5% Dextrose for Injection, or Lactated Ringer's for Injection to a final concentration of 1 mg/mL prior to infusion.

Exela's proposed drug product contains a different quality and quantity of excipients than the RLD. The formulation change has been made to the (b) (4). In Exela's formulation, propylene glycol replaces D-sorbitol (b) (4). See Table 1 for the formulation comparison between Exela's product and Pfizer's RLD product. The applicant is seeking approval for all the RLD indications.

Table 1. Formulation Comparison Between Exela's Argatroban Injection and RLD ARGATROBAN Injection

Ingredients	Exela's Formulation	Pfizer's Formulation ¹
Each vial contains: (in mg)		
Argatroban	250	250
Dehydrated Alcohol, USP	800	1000
D-Sorbitol USP		750
Propylene Glycol, USP	1300	
(b) (4)		

In support of a waiver of *in vivo* BE, an *in vitro* "bridge" study (Study No. 024188) was conducted to assess the equivalence of the anticoagulant (PD) activity between Exela's Argatroban Injection to the RLD. The PD effects were measured by determining aPTT, PT, and TT in pooled donor human plasma spiked with clinically relevant concentrations of argatroban from either the Exela or RLD product. The results of the data analyses show that most of the 90% confidence intervals (CI₉₀) of the ratios of geometric means between Exela and the RLD for observed aPTT, PT, and TT at clinically relevant argatroban concentrations were within the range between 90 and 110% except at 0.2 µg/mL (aPTT ratio (Exela/RLD) of 104.3% (CI₉₀: 96.8-112.3), at 1 µg/mL (PT ratio of 93.7% (CI₉₀: 88.8-98.9)) and at 0.2 µg/mL TT ratio of 105.9% (CI₉₀: 100.9-111.1). Since these values are marginally above or below the limit, the results are acceptable.

2 QUESTION BASED REVIEW

Refer to ARGATROBAN Inject original NDA 20-883 (Approval Date: 30-June-2000) and the February 25, 1998, OCP review by Michael Fossler & K. Garry Barnette for the Clinical Pharmacology related issues. For brevity only QBR questions related to the current NDA submission are addressed below.

2.5 GENEARL BIOPHARMACEUTICS

2.5.1 What is the composition of the to-be-marketed formulation?

Exela's Argatroban is available in 2.5 mL solution in single-use vials at the concentration of 100 mg/mL. The list of ingredients, their pharmaceutical functions and amount per unit basis are presented in Table 2.

Table 2. Unit Composition for Argatroban Injection

Ingredients	Function of Components	Concentration (mg/mL)	Content per vial (mg/Vial)
Argatroban	Active Pharmaceutical Ingredient	100	250
Propylene Glycol, USP	(b) (4)	520	1300
Dehydrated Alcohol, USP	(b) (4)	320	800
(b) (4)			

Refer to Section 1.4 for the quantitative and qualitative comparisons between Exela's to-be-marketed product and the RLD. The active ingredient, dosage form, and route of administration for Exela's product are the same as the RLD.

2.5.2 What data support or do not support a waiver of in vivo BE data?

In support of the waiver of *in vivo* BE, Exela conducted an *in vitro* "bridge" study (Study No. 286) to assess the equivalence of the anticoagulant (PD) activity between the Exela's product and the RLD.

Briefly, blood samples were collected from 40 healthy subjects and were pooled. The spiking solutions of either the RLD or Exela's product were prepared at 1 mg/mL using saline. An aliquot of each pooled human plasma was spiked with spiking solutions of each product, or propylene glycol alone. Five plasma concentrations of argatroban at 0.05, 0.1, 0.2, 0.3, 0.5, 1, 2, 4, and 8 µg/mL were prepared and tested for PT and aPTT. Concentrations up to 0.5 µg/mL were tested for TT. Concentrations of argatroban in plasma were determined by a validated LC/MS/MS method (see Section 2.6).

Results

In vitro comparison of the anticoagulation effect of Exela's Product to RLD

The results indicate that the CI₉₀ of the ratios of geometric means for the PD parameters between the Exela's product and the RLD fell within the acceptance criteria of (b) (4) for equivalence except aPTT at 0.2 µM/mL, PT at 1 µM/mL, and TT at 0.2 µM/mL which are marginally above or below the limit (Table 3).

Table 3. Ratios and 90% Confidence Intervals of PD Parameters Between Exela’s Product and the RLD

Conc (µg/mL)	Exela/RLD Ratio (CI ₉₀)	
	aPTT	PT
0.05	96.3 (92.1-100.7)	98.7 (95.1-102.5)
0.1	102.6 (98.0-107.4)	96.9 (94.9-99.0)
0.2	104.3 (96.8-112.3)	96.9 (95.8-98.1)
0.3	103.6 (98.3-109.2)	98.6 (95.5-101.7)
0.5	98.5 (95.6-101.6)	98.2 (95.5-101.7)
1	98.5 (95.6-101.6)	93.7 (88.8-98.9)
2	100.5 (96.6-104.6)	100.2 (98.0-102.5)
4	99.6 (95.4-104.0)	103.1 (97.3-109.2)
8	102.3 (99.0-105.6)	102.8 (97.9-108.0)
	TT	
0.05	101.8 (95.8-108.2)	
0.1	98.6 (93.4-104.1)	
0.2	105.9 (100.9-111.1)	
0.3	104.2 (99.9-108.7)	
0.5	102.0 (97.9-106.3)	

The effect of excipient on PT, aPTT, and TT for Exela versus RLD

To evaluate the excipient effect on the PD parameters, the CI_{90%} of the geometric mean ratios between the propylene glycol and the blank control sample were calculated. The results indicate that the anticoagulant effects of the Exela’s excipients are equivalent to that of the group containing no excipient for PT, aPTT, and TT.

Table 4. Effect of Propylene Glycol on PT, aPTT, & TT

Coagulation Parameter	Excipient Dose	Average Difference Between Excipient Dose and 0 Dose	Original Scale Upper 90% Confidence Limit	Original Scale Lower 90% Confidence Limit
APTT	2.5 uL	-0.03247	1.032598	0.907534
APTT	5.1 uL	-0.03153	1.035013	0.907135
APTT	10 uL	-0.02619	1.040552	0.911989
APTT	40 uL	0.003273	1.070177	0.940562
PT	2.5 uL	-0.0192	1.008062	0.954636
PT	5.1 uL	-0.00255	1.025609	0.970065
PT	10 uL	0.00711	1.035567	0.979484
PT	40 uL	0.01339	1.041455	0.986259
TT	2.5 uL	-0.00145	1.022469	0.975192
TT	5.1 uL	0.000233	1.024737	0.976315
TT	10 uL	0.004498	1.029117	0.980489
TT	40 uL	-0.00816	1.015632	0.968671

Conclusion

Exela’s product met the criteria for the PD equivalence to the RLD.

2.6 ANALYTICAL SECTION

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Argatroban concentrations in plasma were determined by a validated high performance liquid chromatography - tandem mass spectrometry (HPLC/MS/MS) assay. Validation summary is presented in Table 7.

Table 5. Validation Summary

Analyte	Argatroban
Internal standard (IS)	Nitrazepam
Method description	LC-MS/MS
Limit of quantization (ng/mL)	50.0 ng/mL
Average recovery of Argatroban (%) (Low, Med, High QC)	52.3%, 50.6%, and 52.0%
Average Recovery of IS (% Mean)	50.4%
Standard curve concentrations (ng/mL)	50.0-1000 ng/mL
QC concentrations (ng/mL)	150, 1500, and 7500 ng/mL
QC intra-assay precision range (% CV)	2.2 to 4.7
QC intra-assay accuracy range (% bias)	0.1 to 17.4
QC inter-assay precision range (% CV)	3.4 to 6.8
QC inter-assay accuracy range (% bias)	-2.8 to 4.7
Bench-top stability (hours)	18 hours @ ambient temperature
Processed stability (hours)	119 hours @ room temperature
Freeze-thaw stability (freeze-thaw cycles)	3 freeze-thaw cycles @ -80°C
Long-term storage stability (days)	20 days @ -80°C

With respect to the coagulation assays, the accuracy, precision, and stability of the quality control samples are summarized in Table 8.

Table 6. Validation Parameters for Coagulation Assays using Amax Destiny Plus autoanalyzer

	PT	aPTT	TT
*Accuracy (% of the nominal concentrations range) Intra-Assay Inter-Assay	N/A		
Precision range (% CV) *Intra-Assay *Inter-Assay	0.81% 0.85%	1.43% 3.66%	5.10% N/A
Refrigerator stability (@ 2 - 8° C)	4 hours	4 hours	4 hours
Bench-top stability (ambient temperature)	2 hours	2 hours	2 hours
Freeze-thaw stability (freeze-thaw cycles)	1	1	N/A
Long-term storage stability (@ - 20° C)	46 days	46 days	6 days

*Note

- The accuracy is not required for instrument validation per the manufacturer. Assay standards are not available to determine accuracy.
- Precision Intra-assay performed at instrument or assay installation
- Precision Inter-assay performed at control lot installation (Trinicheck C1 control lot W099046)

3 DETAILED LABELING RECOMMENDATIONS

Only relevant Clinical Pharmacology sections of the applicant's proposed PLR format package insert is reproduced. The contents added by the agency are in **Red** and strikethroughs in **Blue** indicate content taken out by the agency.

(b) (4)



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/s/

YOUNG J MOON
10/31/2011

JULIE M BULLOCK
11/03/2011

BIOPHARMACEUTICS FILING REVIEW
Office of New Drugs Quality Assessment

Application No.:	NDA 203049	Reviewer: Deepika Arora Lakhani, PhD	
Submission Date:	March 21, 2011	Team Lead: Angelica Dorantes, PhD	
Division:	Division of Medical Imaging and Hematology Products	Supervisor: Patrick Marroum, PhD	
Sponsor:	Exela Pharma Sciences	Date Assigned:	May 6, 2011
Trade Name:	Argatroban Injection	Date of Review:	May 16, 2011
Generic Name:	Argatroban Injection	Type of Submission: Supplemental New Drug Application	
Indication:	Prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia; for heparin induced thrombocytopenia undergoing percutaneous coronary intervention (PCI)		
Formulation/ strengths	Injection, 100 mg/mL		
Route of Administration	Intravenous, Infusion		

SUBMISSION:

The 505(b)(2) application is for Exela's proposed drug product that has the same active ingredient, dosage form, strength, route of administration, and conditions of use as Pfizer's Argatroban Injection. However, the proposed drug product contains a formulation change (b)(4), where in, propylene glycol has replaced the D-sorbitol (used in Pfizer's drug product) as the (b)(4) (b)(4) dehydrated alcohol (b)(4)

BIOPHARMACEUTICS:

The Biopharmaceutics review for this submission will be focused on the evaluation of the biowaiver requests for in vivo BA/BE study (ies).

RECOMMENDATION:

The ONDQA/Biopharmaceutics team upon review of NDA 203049 for filing purposes, found the application to be fileable, from Biopharmaceutics perspective. The grant of Biowaiver will be a review issue.

Deepika Arora Lakhani, Ph.D.
 Biopharmaceutics Reviewer
 Office of New Drugs Quality Assessment

Angelica Dorantes, Ph.D.
 Biopharmaceutics Team Leader or Supervisor
 Office of New Drugs Quality Assessment

cc: P. Marroum

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/s/

DEEPIKA LAKHANI

05/18/2011

The NDA is fileable, from Biopharmaceutics perspective.

PATRICK J MARROUM

05/19/2011

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	203-049	Brand Name	Argatroban Injection, 100 mg/mL
OCP Division (I, II, III, IV, V)	V	Generic Name	Argatroban
Medical Division	OND/OODP/DHP	Drug Class	A synthetic direct thrombin inhibitor
OCP Reviewer	Young-Jin Moon, Ph.D.	Indication(s)	As an anticoagulant for <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 Team Leader	Julie Bullock, Pharm.D.	Dosage Form	An intravenous solution containing 100 mg/mL of argatroban (each 2.5-mL vial contains 250 mg of argatroban) which must be diluted 100-fold prior to infusion
Pharmacometrics Reviewer	N/A	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
Date of Submission	18-March-2011	Route of Administration	IV
Estimated Due Date of OCP Review		Sponsor	Exela Pharma Sciences, Inc.
Medical Division Due Date		Priority Classification	Standard
PDUFA Due Date	19-January-2012		

Clin. Pharm. and Biopharm. Information

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies				
HPK Summary				
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
In vitro PD bridge study		1	1	
Literature References				
Total Number of Studies				

Reviewer's comment:

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 Pfizer under the approved NDA20-883. The Exela's product has the same active ingredient, dosage form, strength, route of administration of use as the RLD. However, Exela's product contains a different (b)(4) than the RLD. The (b)(4) dehydrated alcohol in Exela's formulation is 800 mg/vial (b)(4), whereas the (b)(4) RLD is 1000 mg/vial (b)(4). Also, in Exela's formulation, propylene glycol replaces D-sorbitol (b)(4).

Based on the Pre-IND meeting (held on 12/2/08) and written responses for PIND (b)(4) an *in vitro* "bridge" study (Study No. 024188) was conducted to assess the equivalence of the anticoagulant (PD)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

activity between the Exela's product and the RLD formulation. Using PT, aPTT, and TT assays, the *in vitro* anticoagulant effect of Exela's product was compared to the RLD formulation in human plasma.

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					

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

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** _____

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

Young-Jin Moon, Ph.D	05-May-11
Reviewing Clinical Pharmacologist	Date
<hr/>	
Julie Bullock, Pharm. D.	05-May-11
Team Leader/Supervisor	Date

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/s/

YOUNG J MOON
05/10/2011

JULIE M BULLOCK
05/17/2011