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APPLICATION NUMBER:

209552Orig1s000

CLINICAL REVIEW(S)

Clinical Review of 505(b)(2) Application

Submission Date:	05/29/2018
NDA #	209552
SD#	17
Applicant	Aurobindo
Drug Name: non-proprietary (Proprietary, if appl.)	Argatroban
Indication(s) Sought	Heparin Induced Thrombocytopenia
Clinical Reviewer	Laurel Menapace
Clinical Team Leader	Virginia Kwitkowski

Actions Recommended: Approval

Background of Application:

NDA 209552 is a proposed 505(b)(2) for Argatroban Injection, 50 mg/mL and was initially submitted on 07/28/16. The listed drug referenced by the Applicant is Argatroban by Sandoz, NDA 22485.

DHP conducted labeling negotiations during that first cycle and sent revised labeling to them on 02/28/17 and on 04/13/17. Dr. George Shashaty completed a Clinical Review of the first Application on 04/13/17; there were no clinical issues for this application at that time. That application was issued a CR letter on 05/24/17 based upon facility deficiencies at (b) (4) and Aurobindo Pharma Limited (b) (4) (FEI 3008461619).

The Applicant submitted a Class 2/Resubmission on 09/19/17. We also conducted labeling negotiations during that cycle. On 12/29/17, this reviewer archived the Clinical Review of that application; no clinical issues were identified during my review. On 03/16/18, this application received a Complete Response letter. The CR was issued based upon facility deficiencies for Aurobindo Pharma Limited, (b) (4) (FEI 3008461619).

This application constitutes a response to the CR issued 03/16/18. In the cover letter, the Applicant states that the manufacturing facility (mentioned previously) has received a copy of the FDA Establishment Inspection Report (dated May 18, 2018) which indicates that the inspection is considered "closed". The Applicant provided a copy of this letter in the application and is requesting approval of this NDA.

In module 5.3.5, the Applicant submitted a Safety Update Report.

Summary of Review Findings:

The EIR (included in the Application) does state that the inspection received a VAI classification (Voluntary Action Indicated).

Reviewer Comment: Clinical defers to the CMC team as to whether the facility is now acceptable.

The Applicant conducted a PubMed database and Reactions Weekly search for new safety information that would alter the safety profile for argatroban injection. Eighty-eight citations were found, but no new findings were identified. This argatroban product is not marketed anywhere in the world, so no new post-marketing safety data is available.

Reviewer Comment: This reviewer also conducted a PubMed database search for recent publications regarding argatroban safety, and no new issues were identified.

Orange Book Status/Outstanding Exclusivities:

For NDA 22485 (the LD) there are no outstanding patents or exclusivities listed in the Orange Book.

There are 8 other NDAs (besides the Listed Drug), and there are no outstanding exclusivities for these NDAs either.

There are outstanding patent numbers 7589106 (method of treating thrombosis) and 7687516 (method of treating an argatroban treatable condition) for NDA 22434 that expire on 09/26/2027.

Labeling:

The labeling submitted was previously negotiated with the Sponsor and is in PLR and PLLR format. We conducted one labeling meeting on 08/02/18 for this resubmission. We recommended some revisions based upon guidances published since the last labeling negotiations and based upon revisions made to previously approved Argatroban products. That revised labeling should be communicated to the Applicant.

Regulatory Conclusion:

NDA 209552 is recommended for approval from the clinical perspective. There are no clinical PMRs or PMCs for this argatroban application.

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/s/

VIRGINIA E KWITKOWSKI on behalf of LAUREL A MENAPACE
08/27/2018

VIRGINIA E KWITKOWSKI
08/27/2018

Clinical Memo
Division of Hematology Products

Application Type: 505(b)(2)
Application Number(s): 209552
Priority or Standard: Standard
PDUFA Goal Date: May 28, 2017
Division/Office: Division of Hematology Products (DHP)
Reviewer Name: Laurel A. Menapace, MD
Team Lead: Gini Kwitkowski, MS, ACNP-BC
Review Completion Date: December 28, 2017

Established Name: Argatroban
(Proposed) Trade Name: Argatroban Injection
Applicant: Aurobindo Pharma LTD
Formulation(s): 50 mg/50 mL (1 mg/mL)
Dosing Regimen: Intravenous weight-based administration
Proposed Indication: Heparin-induced thrombocytopenia

Intended Population(s):

For prophylaxis or treatment of thrombosis in adult patients with heparin- induced thrombocytopenia (HIT) and

As an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI)

Clinical Memo:

NDA 209552 is a 505b2 application for Argatroban Injection, 50 mg/mL; the listed drug is Argatroban by Sandoz (NDA 22485).

On September 19th, AuroMedics submitted a Class 2 resubmission in response to a CR letter that was issued on 5/24/17. The CR was issued for deficiencies identified in the manufacturing facilities, (b) (4) and Aurobindo Pharma Limited. No clinical issues arose during the initial review.

The Applicant now states that the manufacturer received a copy of their FDA Establishment Inspection Report (dated August 17, 2017) which indicates that the inspection is considered "closed." The Applicant states that it is their understanding is that the compliance status of the drug product manufacturer Aurobindo Pharma Limited (b) (4) (FEI 3008461619), is currently acceptable. Accordingly, they request approval of this NDA. Clinical defers to CMC regarding the inspectional findings.

Dr. George Shashaty completed a Clinical Filing Review for this NDA on September 19, 2016 and Clinical Review of the application on April 13, 2017. Labeling comments have been sent to the sponsor.

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/s/

LAUREL A MENAPACE
12/29/2017

VIRGINIA E KWITKOWSKI
12/29/2017

1

CLINICAL REVIEW

Application Type	505(b)(2)
Application Number(s)	209552
Priority or Standard	Standard
Submit Date(s)	July 28, 2016
Received Date(s)	July 28, 2016
PDUFA Goal Date	May 28, 2017
Division/Office	Division of Hematology Products (DHP)
Reviewer Name(s)	George Shashaty
Review Completion Date	March 25, 2017
Established Name	Argatroban
(Proposed) Trade Name	Argatroban Injection
Applicant	Aurobindo Pharma LTD
Formulation(s)	50 mg/50 mL (1 mg/mL)
Dosing Regimen	Intravenous weight-based administration
Proposed Indication(s)	Heparin-induced thrombocytopenia
Intended Population(s)	• For prophylaxis or treatment of thrombosis in adult patients with heparin- induced thrombocytopenia (HIT) and • As an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI)
Recommendation on Regulatory Action	No clinical data have been submitted to this NDA. Approval will require a determination of “sameness” with the reference listed drug. Approval should be denied if “sameness” is not established
Recommended Indication	Identical to the Reference Listed drug, as noted above

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101 **Glossary**

102	AC	advisory committee
103	AE	adverse event
104	BLA	biologics license application
105	BPCA	Best Pharmaceuticals for Children Act
106	BRF	Benefit Risk Framework
107	CBER	Center for Biologics Evaluation and Research
108	CDER	Center for Drug Evaluation and Research
109	CDRH	Center for Devices and Radiological Health
110	CDTL	Cross-Discipline Team Leader
111	CFR	Code of Federal Regulations
112	CMC	chemistry, manufacturing, and controls
113	COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
114	CRF	case report form
115	CRO	contract research organization
116	CRT	clinical review template
117	CSR	clinical study report
118	CSS	Controlled Substance Staff
119	DMC	data monitoring committee
120	ECG	electrocardiogram
121	eCTD	electronic common technical document
122	ETASU	elements to assure safe use
123	FDA	Food and Drug Administration
124	FDAAA	Food and Drug Administration Amendments Act of 2007
125	FDASIA	Food and Drug Administration Safety and Innovation Act
126	GCP	good clinical practice
127	GRMP	good review management practice
128	ICH	International Conference on Harmonization
129	IND	Investigational New Drug
130	ISE	integrated summary of effectiveness
131	ISS	integrated summary of safety
132	ITT	intent to treat
133	MedDRA	Medical Dictionary for Regulatory Activities
134	mITT	modified intent to treat
135	NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
136	NDA	new drug application
137	NME	new molecular entity
138	OCS	Office of Computational Science
139	OPQ	Office of Pharmaceutical Quality

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140	OSE	Office of Surveillance and Epidemiology
141	OSI	Office of Scientific Investigation
142	PBRER	Periodic Benefit-Risk Evaluation Report
143	PD	pharmacodynamics
144	PI	prescribing information
145	PK	pharmacokinetics
146	PMC	postmarketing commitment
147	PMR	postmarketing requirement
148	PP	per protocol
149	PPI	patient package insert
150	PREA	Pediatric Research Equity Act
151	PRO	patient reported outcome
152	PSUR	Periodic Safety Update report
153	RLD	Reference listed drug
154	REMS	risk evaluation and mitigation strategy
155	SAE	serious adverse event
156	SAP	statistical analysis plan
157	SEALD	Study Endpoints and Labeling Development
158	SGE	special government employee
159	SOC	standard of care
160	TEAE	treatment emergent adverse event

161 **1 Executive Summary**

163 **1.1. Product Introduction**

164 Argatroban Injection is a parenterally administered direct thrombin inhibitor whose proposed
165 indications are:
166

- 167 • For prophylaxis or treatment of thrombosis in adult patients with heparin- induced
- 168 thrombocytopenia (HIT)
- 169 • As an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous
- 170 coronary intervention (PCI)

171
172 The sponsor's presentation is as a single dose vial containing 50 mg/50mL (1 mg/mL). The
173 proposed dose is the same for Argatroban Injection as it is for Argatroban (Sandoz, NDA 22485),
174 the Reference Listed Drug (RLD). The comparison between the proposed drug and the RLD is
175 shown in the following table.

176
177 **Table 1. Comparison Between the Proposed Drug and the Reference Listed Drug^a**
178

Parameters	Proposed Drug Product [505(b)(2) Application]	Reference Listed Drug
Condition of Use	Argatroban is a direct thrombin inhibitor indicated: • For prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT). • As an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI).	Argatroban is a direct thrombin inhibitor indicated: • For prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT). • As an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI).
Active Ingredient	Argatroban	Argatroban
Inactive Ingredient(s)	Sodium Chloride USP Sorbitol USNF Water for Injection USP	Sodium Chloride, USP Sorbitol, NF Water for Injection, USP
Route(s) of Administration	Intravenous	Intravenous
Dosage Form	Injection	Injection
Strength(s)*	50 mg/50 mL (1 mg/mL)	125 mg/125 mL (1 mg/mL)

179 Pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, the Proposed
180 New Drug Application for Argatroban Injection in 0.9% Sodium Chloride differs in
181 strength from Reference Listed Drug (S a n d o z I n c , NDA # 022485) Argatroban
182 Injection. However, the Indications, Active Ingredient, Inactive Ingredients, Route of
183 Administration, Dosage Form and Concentration are same as Reference Listed Drug NDA #
184 022485.

185 ^aSource. Sponsor submission 1.12.12

186

187 **Conclusions on the Substantial Evidence of Effectiveness**

188 The sponsor has submitted this application as a 505(b)(2) NDA under the Federal Food, Drug
189 and Cosmetic Act. No additional or independent clinical studies were performed or submitted
190 by the sponsor in support of the application. The sponsor has based its conclusions of
191 effectiveness and safety of Argatroban Injection on the data already submitted and available to
192 FDA pertinent to the determination of the efficacy and safety of the reference listed drug,
193 Argatroban (NDA 22485), and has requested that FDA rely on those data to support the
194 approval of Argatroban Injection. The sponsor for Argatroban Injection has requested a waiver
195 from the need to perform bioequivalence (BE) or bioavailability (BA) studies because it states
196 that the drug will be given intravenously. The sponsor has submitted data for Argatroban
197 Injection that it maintains assures the “sameness” of the drug for subcutaneous use. Those
198 data are being evaluated by FDA Biopharmaceutics and Chemistry, Manufacturing and Controls
199 (CMC) reviews.

200

201

202

203 **1.2. Benefit-Risk Assessment**

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Benefit-Risk Summary and Assessment

The analysis of benefit and risk for the use of Argatroban Injection is based on the benefit and risk of Argatroban (NDA 22485), the RLD.

During review of NDA 22485, the efficacy and safety of the use of Argatroban in patients with heparin-induced thrombocytopenia were assessed based on clinical data from 2 clinical trials characterized as follows:

- The total patient population in the 2 studies included 568 adults with a clinical diagnosis of HIT or HITTS (heparin-induced thrombocytopenia with thrombosis) compared to a historical population of 193 adults with the same diagnoses. Patients with actual or potential bleeding disorders were excluded. The primary efficacy endpoint was a composite of death from all causes, amputations or new thromboses through day 37 from the beginning of therapy. Compared to the control population, there was a statistically significant decrease for the composite endpoint in patients treated with argatroban.

The efficacy and safety of the use of argatroban for patients with a current or previous clinical diagnosis of HIT or heparin-dependent antibodies who were undergoing percutaneous coronary intervention were assessed based on 3 studies that were similar to each other and characterized as follows:

- The total patient population in the 3 studies was 91 adults. All subjects received aspirin and seven also received glycoprotein IIb/IIIa inhibitors. Acute procedural success was defined as lack of death, emergent coronary artery bypass graft surgery or Q-wave infarction. In subjects treated with argatroban, acute procedural success was achieved in 98.2% compared to a success rate of 94.3% in a historical control population anticoagulated with heparin.

Argatroban (RLD) remains a marketed drug in the U.S. Therefore, if Argatroban Injection is deemed to be the “same” as Argatroban, the efficacy and safety of the use of Argatroban Injection for the same indications can be assumed.

Dimension	Evidence and Uncertainties	Conclusions and Reasons

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	HIT and HITT occur not uncommonly amongst patients who have been treated with heparin, and are related to the development of platelet Factor 4-heparin dependent antibodies in such patients. Because there is an increased incidence of symptomatic thromboembolism in patients with HIT or HITT, there is a need for alternative anticoagulation. Additionally, patients who have a history of HIT or HITT are generally regarded as having a relative contraindication to future administration of heparin and, in the event of needing to undergo a procedure in which an anticoagulant is considered standard of care, should receive a non-heparin anticoagulant.	In patients who develop HIT or HITT, there is a need for alternative, non-heparin anticoagulation. The selection of available drugs is limited. Argatroban appears to be useful for the treatment of this disorder.
Current Treatment Options	Bivalirudin is approved for use as an anticoagulant in patients with HIT or HITT who are undergoing PCI, but not for the treatment of HIT or HITT alone. Argatroban is the only drug that is approved both for patients with HIT or HITT who are undergoing PCI, and for the prevention and treatment of thromboembolism in patients with HIT or HITT. Lepirudin (Refludan, NDA 20807) is approved as an anticoagulant for patients with HIT/HITT, but not for patients with HIT/HITT undergoing PCI. However, the sponsor for lepirudin discontinued marketing of the drug in the U.S. in 2016.	Anticoagulant therapy for the treatment of patients with HIT/HITT is limited to Argatroban alone. For patients with HIT/HITT who are undergoing PCI, bivalirudin is also an approved drug. Current treatment options for these indications are quite limited.
Benefit	As noted above, Argatroban, the RLD, has demonstrated effectiveness in patients with HIT/HITT compared to a historical patient population in the prevention of a composite endpoint of recurrent thrombosis, need for amputation and death. In the U.S., it has been customary for patients undergoing PCI to be anticoagulated during the procedure, but there are no adequate and well-controlled trials of the use of placebo compared to heparin for such an indication. The frequency of successful PCI in patients with HIT/HITT anticoagulated with Argatroban was comparable to a historical patient cohort treated with heparin, and this was accepted to be non-inferior to “standard of care”.	The role of argatroban in patients with HIT/HITT is to prevent further thrombotic/embolic events since such patients are believed to be considerably more prone to these problems than are patients who do not have HIT/HITT. Persons with HIT/HITT are generally considered to have a relative contraindication to the use of heparin when undergoing PCI.

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 Argatroban Injection

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	The main adverse event associated with the administration of Argatroban is hemorrhage, which is secondary to its mechanism of action.	The risk of bleeding appears to be similar to that associated with the use of heparin.
Risk Management	None.	None.

207 **2 Therapeutic Context**

208 **2.1. Analysis of Condition**

209 Anticoagulant therapy is employed in a large proportion of the American population. For
210 example, in one study, approximately 41% of all patients admitted to a large hospital received
211 unfractionated heparin (Smythe, MA et al. 2007. The incidence of recognized heparin-induced
212 thrombocytopenia in a large, tertiary care teaching hospital. Chest. 13:1644-1649). This
213 therapy, which has been available since the time of the discovery of heparin in the 1930's, is
214 used in medical conditions in which there is a presumption that local or systemic activation of
215 the coagulation system induces clotting and subsequent thrombosis and/or embolization in the
216 interaction between the vascular endothelium and the circulating components of the blood
217 (particularly platelets and coagulation factors).

218
219 Instrumentation of the vascular tree to enhance blood flow and thereby improve organ
220 function is a frequent medical therapy that is performed primarily to open blood vessels
221 narrowed by atherosclerosis. Beginning with the earliest instrumental procedures, it became
222 standardized practice to use heparin to reduce the likelihood of clot formation within vessels
223 that had been instrumented and, therefore, more prone to the accumulation of platelets and
224 fibrin in the instrumented areas. Heparin, either in its original unfractionated form or, as a
225 fractionated product, became the most commonly used parenteral anticoagulant because of its
226 availability and the belief in its efficacy. Heparin interacts with anti-thrombin III, a serine
227 protease inhibitor, to diminish thrombosis by preventing the conversion of several coagulation
228 factors into their active forms, thereby reducing the risk of vascular obstruction.

229
230 There are several adverse events that are causally related to the administration of heparin. As
231 an anticoagulant, the most common adverse reaction is the induction of hemorrhage. Another
232 important adverse reaction related to its use is the development of heparin-induced
233 thrombocytopenia (HIT), sometimes with the development of thrombosis (HITT). HIT/HITT is
234 due to the induction of heparin-platelet factor 4 antibodies in a significant proportion of
235 patients administered heparin that not only reduces the platelet count but may lead to clinically
236 important thrombotic/embolic events.

237
238 Patients who have suspected or known HIT/HITT generally require a non-heparin anticoagulant
239 when the clinical need arises. There are several alternative anticoagulants that have been
240 approved for indications similar to those for heparin. Bivalirudin (Angiomax[®]) is a direct
241 thrombin inhibitor that is approved for use in patients undergoing PCI/PTCA (percutaneous
242 transluminal coronary angioplasty) as well as for use during PCI in patients with HIT/HITT.

243 Argatroban, the RLD for this application, is approved for use in patients with HIT/HITT, and for
244 patients with HIT/HITT who are undergoing PCI. Although not approved, fractionated (low
245 molecular weight) heparin (LMWH) is used by some physicians because LMWH may have a
246 lesser risk of inducing further thrombocytopenia or thrombosis in these patients.

247
248 A comparison between the RLD and the proposed drug product for this application is shown in
249 the table below. The only difference is in the strength of the two drugs.

251 **Table 2. Comparison between the Proposed Drug and the Reference Listed Drug**
252

Parameters	Proposed Drug Product [505(b)(2) Application]	Reference Listed Drug
Condition of Use	Argatroban is a direct thrombin inhibitor indicated: • For prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT). • As an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI).	Argatroban is a direct thrombin inhibitor indicated: • For prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT). • As an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI).
Active Ingredient	Argatroban	Argatroban
Inactive Ingredient(s)	Sodium Chloride USP Sorbitol USNF Water for Injection USP	Sodium Chloride, USP Sorbitol, NF Water for Injection, USP
Route(s) of Administration	Intravenous	Intravenous
Dosage Form	Injection	Injection
Strength(s)*	50 mg/50 mL (1 mg/mL)	125 mg/125 mL (1 mg/mL)

253
254 * The Proposed New Drug Application, pursuant to section 505(b)(2) of the Federal
255 Food, Drug, and Cosmetic Act for Argatroban Injection in 0.9% Sodium Chloride
256 [505(b)(2) Application] differs in strength from Reference Listed Drug NDA # 022485
257 Argatroban Injection in 0.9% Sodium Chloride of Sandoz Inc. However, the
258 Indications, Active Ingredient, Inactive Ingredients, Route of Administration, Dosage
259 Form and Concentration are same as Reference Listed Drug NDA # 022485.
260

261 **2.2. Analysis of Current Treatment Options**

262 There are two approved agents for the indication of the anticoagulant for use during PCI in
263 patients with, or likely to have, HIT/HITT. These include bivalirudin and argatroban. In
264 addition, bivalirudin is also approved for use as an anticoagulant in patients undergoing
265 PCI/PTCA even though HIT/HITT is not a factor. The latter indication is not approved for
266 argatroban. In contrast, argatroban is approved for use in patients with HITT to treat and
267 prevent thromboses whereas bivalirudin lacks a similar approval. There are no other drugs
268 approved for the PCI/PTCA indication. For the HIT/HITT indication, the only other approved
269 drug is lepirudin (Refludan), which was withdrawn from marketing in the U.S. by its sponsor on
270 April 27, 2016. Information for these drugs is summarized in the following table.

271 **Table 3. Drugs Approved for the Indications**
272

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments [Combine by Pharmacologic Class, if relevant]						
Bivalirudin (Angiomax, NDA20873)	Anticoagulant during PCI in HIT/HITTS	2000	0.75 mg/kg bolus, then 1.75 mg/kg/hour	Uncontrolled trial in patients with HIT/HITT undergoing PCI. Success rate was 98%	Bleeding, MI when used in STEMI	
Lepirudin (Refludan, NDA 20807)	Anticoagulation in patients with HIT and thromboembolic disease to prevent further thromboembolic complications	1998	Starting dose is 0.4 mg/kg bolus, followed by 0.15 mg/kg as a continuous IV infusion for 2-10 days, adjusted by monitoring aPTT (1.5-2.5)	Reduction in risk of thromboembolic events in 198 patients with HIT/HITT compared to historical controls in two trials	Bleeding, fever, abnormal LFTs, allergic reactions	Not currently marketed in the U.S. NDA withdrawn 4/27/2016

273

274 **3 Regulatory Background**

275 **3.1. U.S. Regulatory Actions and Marketing History**

276 Regulatory activities between FDA and the sponsor prior to the submission of the NDA did not

277 occur. The product is not approved for use in the U.S. or in any country in the world. The
278 sponsor is basing its NDA application entirely on the RLD, which was approved in 2000. The
279 sponsor states that the only difference between Argatroban Injection and the RLD is in strength
280 (Argatroban Injection is 50 mg/50mL and the RLD is 125 mg/125mL).

281 **3.2. Summary of Presubmission/Submission Regulatory Activity**

282 There were no regulatory activities between FDA and the sponsor prior to submission of the
283 NDA. The sponsor has submitted the required User Fee. The sponsor has requested a waiver
284 of bioavailability/bioequivalence studies of Argatroban Injection because it has the same active
285 ingredient, inactive ingredients, dosage form, concentration, indications and route of
286 administration as the RLD. For similar reasons, the sponsor has requested a waiver for the
287 need to fulfill any PREA requirements.

288
289 **3.3 Foreign Regulatory Actions and Marketing History**

290 Argatroban Injection is not approved in any country in the world.

291 **4 Significant Issues from Other Review Disciplines Pertinent to Clinical**
292 **Conclusions on Efficacy and Safety**

294 **4.1. Office of Scientific Investigations (OSI)**

295 The Office of Scientific Investigations was not involved in the review of this NDA. No clinical
296 studies were submitted.
297

298 **4.2. Product Quality**

299 The NDA refers to the DMF for argatroban as indicated in the following table.
300

DMF #	Drug Substance	DMF holder / Manufacturer address	FEI / DUNS
(b) (4)*	Argatroban		(b) (4)

301 * The Type II DMF Letter of Authorization is enclosed in Module 1.4.2.
302

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303 The details of the facility used for manufacturing, testing and packaging of the drug product
304 Argatroban Injection in 0.9% Sodium Chloride, 50 mg/50 mL (1 mg/mL) are as follows:

305

Facility Details	FEI / DUNS	Status
Aurobindo Pharma Limited, (b) (4) Hyderabad, Telangana - 502307, INDIA	FEI # 3008461619 DUNS # 650498244	Operations are in compliance with cGMP requirements listed in 21 CFR § 210 and 211. Facility classified as acceptable per inspection during the period (b) (4) by US FDA.

306
307 The CMC aspects of the application are under review by CMC.

308 4.3. Clinical Microbiology

309 The proposed drug is a parenterally administered product. Therefore, the NDA should be
310 reviewed by Microbiology for sterility and infection risk.

311 4.4. Nonclinical Pharmacology/Toxicology

312
313 The sponsor has not submitted any data from Nonclinical Pharmacology/Toxicology studies.
314 The sponsor requests that FDA review Non-Clinical studies for the RLD to assess the Nonclinical
315 Pharmacology/Toxicology for Argatroban Injection. Please refer to the
316 Pharmacology/Toxicology review.

317 4.5. Clinical Pharmacology

318 The sponsor has not submitted any Clinical Pharmacology data for Argatroban Injection.

319 4.5.1. Mechanism of Action

320 The sponsor has not submitted any information to elucidate the mechanism of action of
321 Argatroban Injection. Argatroban is a synthetic direct thrombin inhibitor.

322 4.5.2. Pharmacodynamics

323 No clinical pharmacodynamic studies of Argatroban Injection have been conducted.

324 4.5.3. Pharmacokinetics

325 No clinical pharmacokinetic studies of Argatroban Injection have been conducted.

326

327 **4.6. Devices and Companion Diagnostic Issues**

328 Not applicable.

329 **4.7. Consumer Study Reviews**

330 Not applicable.

331 **5 Sources of Clinical Data and Review Strategy**

332 **5.1. Table of Clinical Studies**

333 See Section 5.2. No clinical studies of Argatroban Injection were submitted to assess its
334 efficacy and safety. Argatroban Injection has not been administered to any person.

APPEARS THIS WAY ON ORIGINAL

336 **5.2. Review Strategy**

337 This is a 505(b)(2) NDA submission. The sponsor has not submitted any data from clinical trials
338 to support the efficacy or safety of the use of Argatroban Injection for the desired indications.
339 For effectiveness and safety, the sponsor is relying entirely on data submitted for NDA22485
340 (Argatroban, the reference listed drug) that led to Argatroban’s approval by FDA.

341 **6 Review of Relevant Individual Trials Used to Support Efficacy**

342 No clinical data were submitted by the sponsor. See 5.2, above.
345

APPEARS THIS WAY ON ORIGINAL

346 **7 Integrated Review of Effectiveness**

347 No clinical data were submitted by the sponsor. See 5.2, above.

349 **8 Review of Safety**

350 No clinical data were submitted by the sponsor. See 5.2, above.

351

352 8.7.3

353

354 The sponsor states that Argatroban Injection should be exempt from the Pediatric Research
355 Equity Act (PREA) (21 U.S.C. 355c), as the application does not propose any new active
356 ingredients, indications, dosage forms, dosing regimens, or routes of administration and, hence,
357 an assessment of the safety and effectiveness of the product in pediatric patients is not
358 applicable.

359 ***Reviewer Comments. The statement of the sponsor is correct and the application should be***
360 ***exempt from a requirement for pediatric studies.***

362 **9 Advisory Committee Meeting and Other External Consultations**

363 No Advisory Committee meeting or other external consultations were held or obtained.

364 **10 Labeling Recommendations**

365 10.1. **Prescribing Information**

366 The label content submitted by the sponsor is identical to that currently in use for the
367 Argatroban RLD except for the name of the drug, the differences in the inactive ingredients, and
368 company and product specific information.

369

370 10.2. **Patient Labeling**

371 Not applicable.

372

373 10.3. **Non-Prescription Labeling**

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374 Not applicable.

375

376

377 **11 Risk Evaluation and Mitigation Strategies (REMS)**

378 Given the known safety profile of Argatroban, there are no additional risk management
379 strategies required beyond the recommended labeling.

380 **12 Postmarketing Requirements and Commitments**

381 There are no proposed PMCs or PMRs for Argatroban Injection. At this time, there are no
382 outstanding PMCs or PMRs for Argatroban.

383 **13 Appendices**

384 13.1. **References**

385 None.

386 13.2. **Financial Disclosure**

387 Pursuant to Section 306(k) of the Federal Food, Drug and Cosmetic Act, as amended by the
388 Generic Drug Enforcement Act of 1992, Aurobindo Pharma Limited certifies that
389 Aurobindo Pharma Limited did not and will not use, in any capacity, the services of any person
390 debarred under subsections (a) or (b) of the Generic Drug Enforcement Act of 1992 in
391 connection with this New Drug Application (NDA). Aurobindo Pharma Limited further certifies
392 that, during the previous five years, it has not sustained a conviction that is described in
393 subsections (a) or (b) of the Generic Drug Enforcement Act of 1992. In addition, Aurobindo
394 Pharma certifies that Aurobindo Pharma Limited did not and will not use, in any capacity, the
395 services of any person convicted under subsections (a) or (b) of the Generic Drug Enforcement
396 Act of 1992 in connection with this New Drug Application (NDA).

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/s/

GEORGE G SHASHATY
04/13/2017

KATHY M ROBIE SUH
04/13/2017