

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208374Orig1s000

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

CLINICAL PHARMACOLOGY MEMORANDUM

NDA, SDN	208374, SDN 2
Submission Date	02/28/2017
Submission Type	505(b)(2)
Generic name	Bivalirudin
Brand name	Bivalirudin in 0.9% Sodium Chloride Injection
Applicant	Celerity Pharmaceuticals LLC
Dosage form/Strengths	Sterile solution for injection/infusion, 250 mg/50 mL and 500 mg/100 mL
Route of Administration	Intravenous infusion
Indications	Direct thrombin inhibitor indicated for use as an anticoagulant in patients 1) [REDACTED] (b) (4) 2) undergoing percutaneous coronary intervention (PCI) [REDACTED] (b) (4) 3) [REDACTED] (b) (4)
Associated IND	126428
OCP Division	Division of Clinical Pharmacology-1 (DCP-1)
OND Division	Division of Cardiovascular and Renal Products (DCRP)
Reviewer	Snehal Samant, PhD
Secondary Reviewer	Martina Sahre, PhD

Celerity Pharmaceuticals LLC. (Celerity) has submitted a New Drug Application for BIVALIRUDIN in 0.9% Sodium Chloride Injection (Bivalirudin) under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The application relies on the Agency's safety and efficacy findings for the listed drug, Angiomax[®], approved as NDA 020873. The applicant is seeking approval for the following indications [REDACTED] (b) (4)

Direct thrombin inhibitor indicated for use as an anticoagulant in patients:

- [REDACTED] (b) (4)
- undergoing percutaneous coronary intervention (PCI) [REDACTED] (b) (4)
- [REDACTED] (b) (4)

Bivalirudin in 0.9% sodium chloride injection is a frozen, iso-osmotic, sterile, non-pyrogenic, premixed 50 mL or 100 mL solution containing 250 mg or 500 mg bivalirudin, respectively. Angiomax is a lyophilized powder for reconstitution and injection. The applicant requested a waiver for the requirement to submit in vivo bioavailability/bioequivalence (BA/BE) study data based on 21 CFR 320.22(a) and (b)(1)(i) and (ii). The applicant conducted an in vitro assessment of the clotting effects of different lots of a test pre-mixed frozen formulation of bivalirudin (Celerity Pharmaceuticals, LLC) and the lyophilized powder formulation of bivalirudin (Angiomax[®], The Medicines Company) as measured by activated partial thromboplastin time (aPTT), prothrombin time (PT), and thrombin time (TT) using pooled plasma from human adult male subjects. In vitro assessments were reviewed by Office of New Drug Products (ONDP) within the Office of Product Quality (OPQ). OPQ did not identify any issues in the in vitro assessments that needed OCP review.

The Office of Clinical Pharmacology/DCP-1 recommends modification of the current proposed label for dosing in (b) (4) patients to give a clear actionable instruction for (b) (4).

The label proposed by the applicant:

(b) (4)

Labelling recommendation by Office of Clinical Pharmacology/DCP-1:

2.2. Dosing in Renal Impairment

...In patients with creatinine clearance less than 30 mL/min (by Cockcroft Gault equation), reduce the infusion rate to 1 mg/kg/h.

The recommendation will be conveyed to the Applicant via labeling comments.

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/s/

SNEHAL N SAMANT
11/07/2017

MARTINA D SAHRE
11/07/2017

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	208374	SDN	0000
Applicant	Celerity Pharmaceuticals LLC	Submission Date	02/28/2017
Generic Name	Bivalirudin		
Drug Class	Anticoagulant-direct thrombin inhibitor		
Background	<p>Celerity Pharmaceuticals, LLC has submitted a 505(b)(2) application for a new formulation of bivalirudin. The reference drug is ANGIOMAX[®] (bivalirudin) for injection (NDA 20873), which is a lyophilized powder for reconstitution and injection. The test formulation is Bivalirudin in 0.9% sodium chloride injection as a frozen, iso-osmotic, sterile, non-pyrogenic premixed 50 mL or 100 mL solution containing 250 mg or 500 mg, respectively, as bivalirudin. The applicant conducted an in vitro assessment of the in vitro clotting effects of different lots of a test pre-mixed frozen formulation of bivalirudin (Celerity Pharmaceuticals, LLC) and the lyophilized powder formulation of bivalirudin (Angiomax[®], The Medicines Company) as measured by activated partial thromboplastin time (aPTT), prothrombin time (PT), and thrombin time (TT) using pooled plasma from human adult male subjects. Per an MOU between the Office of Clinical Pharmacology (OCP) and the Office of New Drug Products (ONDP) within the Office of Product Quality (OPQ), in vitro assessments that are meant to ensure quality of the drug product will be reviewed by ONDP, unless issues that need OCP review are identified.</p>		
Indication	<p>Direct thrombin inhibitor indicated for use as an anticoagulant in patients:</p> <p align="right">(b) (4)</p> <p>Undergoing percutaneous coronary intervention (PCI)</p> <p align="right">(b) (4)</p>		
Dosage Regimen	<p align="right">(b) (4)</p> <p align="right">(b) (4)</p> <p>PCI: 0.75 mg/kg intravenous bolus dose followed immediately by a 1.75 mg/kg/h intravenous infusion for the duration of the procedure.</p>		
Dosage Form	Solution for injection	Route of Administration	Intravenous
OCP Division	DCP 1	OND Division	Division of Cardiovascular and Renal Products
OCP Review Team	Primary Reviewer(s)		Secondary Reviewer/ Team Leader
Division	Snehal Samant		Martina Sahre
Pharmacometrics	--		--
Genomics	--		--
Review Classification	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Expedited		
Filing Date	4/29/2017	74-Day Letter Date	5/13/2017
Review Due Date	10/28/2017	PDUFA Goal Date	12/28/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

Yes No

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

Yes No

Is there a need for clinical trial(s) inspection?

Yes No

Clinical Pharmacology Package

Tabular Listing of All Human Studies Yes No Clinical Pharmacology Summary Yes No
 Bioanalytical and Analytical Methods Yes No Labeling Yes No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
<input type="checkbox"/> Metabolism Characterization	0	
<input type="checkbox"/> Transporter Characterization	0	
<input type="checkbox"/> Distribution	0	
<input type="checkbox"/> Drug-Drug Interaction	0	
<input checked="" type="checkbox"/> In vitro PD activity	1	
In Vivo Studies		
Biopharmaceutics		
<input type="checkbox"/> Absolute Bioavailability	0	
<input type="checkbox"/> Relative Bioavailability	0	
<input type="checkbox"/> Bioequivalence	0	
<input type="checkbox"/> Food Effect	0	
<input type="checkbox"/> Other	0	
Human Pharmacokinetics		
Healthy Subjects	<input type="checkbox"/> Single Dose	0
	<input type="checkbox"/> Multiple Dose	0
Patients	<input type="checkbox"/> Single Dose	0
	<input type="checkbox"/> Multiple Dose	0
<input type="checkbox"/> Mass Balance Study	0	
<input type="checkbox"/> Other (e.g. dose proportionality)	0	
Intrinsic Factors		
<input type="checkbox"/> Race	0	
<input type="checkbox"/> Sex	0	
<input type="checkbox"/> Geriatrics	0	
<input type="checkbox"/> Pediatrics	0	
<input type="checkbox"/> Hepatic Impairment	0	
<input type="checkbox"/> Renal Impairment	0	

<input type="checkbox"/> Genetics	0				
Extrinsic Factors					
<input type="checkbox"/> Effects on Primary Drug	0				
<input type="checkbox"/> Effects of Primary Drug	0				
Pharmacodynamics					
<input type="checkbox"/> Healthy Subjects	0				
<input type="checkbox"/> Patients	0				
Pharmacokinetics/Pharmacodynamics					
<input type="checkbox"/> Healthy Subjects	0				
<input type="checkbox"/> Patients	0				
<input type="checkbox"/> QT	0				
Pharmacometrics					
<input type="checkbox"/> Population Pharmacokinetics	0				
<input type="checkbox"/> Exposure-Efficacy	0				
<input type="checkbox"/> Exposure-Safety	0				
Total Number of Studies		In Vitro	1	In Vivo	0
Total Number of Studies to be Reviewed			0		0

Criteria for Refusal to File (RTF)		
RTF Parameter	Assessment	Comments
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	The applicant is requesting a biowaiver
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	Study previously conducted by the sponsor of the RLD
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	Waiver
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A	Applicant is requesting biowaiver
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	Quality and Clinical summary are submitted.
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
Complete Application 10. Did the applicant submit studies including study reports, analysis datasets, source code,	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	

input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?		
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
4. 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)?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
6. 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?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	

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/s/

SNEHAL N SAMANT
04/27/2017

MARTINA D SAHRE
04/27/2017