

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208374Orig1s000**

**CLINICAL REVIEW(S)**

## Cross-Discipline Team Leader Review

<b>Date</b>	November 28, 2017
<b>From</b>	Martina Sahre, PhD
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA#</b>	208374
<b>Applicant</b>	Celerity Pharmaceuticals LLC
<b>Date of Submission</b>	2/28/2017
<b>PDUFA Goal Date</b>	12/28/2017
<b>Proprietary Name / Established (USAN) names</b>	Bivalirudin in 0.9% Sodium Chloride Injection / Bivalirudin
<b>Dosage forms / Strength</b>	Sterile solution for injection, 250 mg in 50 mL or 500 mg in 100 mL (5 mg/mL)
<b>Proposed Indication(s)</b>	1. (b) (4) 2. Percutaneous Coronary Intervention (PCI), 3. (b) (4) 4. (b) (4)
<b>Recommended:</b>	<i>Approval of the revised indication (Section 12 of this review)</i>

### 1. Introduction

On February 28, 2017, Celerity Pharmaceuticals LLC submitted NDA 208374 for Bivalirudin under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The application relies on the finding of safety and efficacy of the reference listed drug (RLD) Angiomax® (NDA 20,873), which is approved for the following indications, concomitantly with aspirin:

1. Percutaneous Transluminal Coronary Angioplasty (PTCA),
2. Percutaneous Coronary Intervention (PCI),
3. Use with Aspirin, and
4. Limitation of Use in patients with ACS who are not undergoing PTCA or PCI.

The Applicant for NDA 208374 (b) (4) the reference drug.

#### Material Reviewed/Consulted

Office of Pharmaceutical Quality, Integrated Review (November 13, 2017)	Technical Lead: Mohan Sapru, MS, PhD Reviewers: Rajan Pragani, Dan Berger, Mark Johnson, Jonathan Swoboda, Banu Zolnik, Alifiya Ghadiyali
Clinical Pharmacology	Snehal Samant, PhD, Martina Sahre, PhD
DPMH	Christos Mastroyannis, MD, Tamara Johnson, MD, Lynne Yao, MD
Office of Prescription Drug Promotion (OPDP)	Zarna Patel, PharmD, James Dvorsky, PharmD
Division of Medication Error Prevention and Analysis (DMEPA)	Sara Thomas, PharmD, Chi-Ming (Alice) Tu, PharmD, BCPS

A review from OND explaining the rationale for changes to sections 1, 5, 6, and 14 is still outstanding.

## 2. Background

Bivalirudin belongs to the class of direct-thrombin-binding anticoagulants. It binds both circulating and clot-bound thrombin. In vivo, bivalirudin increases activated partial thromboplastin time (aPTT), thrombin time (TT), and prothrombin time (PT) dose dependently.

The RLD, Angiomax<sup>®</sup>, is marketed as a sterile, lyophilized powder for reconstitution. Currently, there is no ready-to-use solution available on the market. The formulation under review is bivalirudin in 0.9% sodium chloride, ready for injection after thawing.

## 3. CMC

OPQ recommends approval from the quality perspective. There are no post-marketing commitments recommended and no unresolved items.

### Drug Substance

Bivalirudin is a synthetic peptide 20 amino acids long. (b) (4)  
To support the drug substance CMC information, DMF (b) (4) was reviewed previously (7/26/2017, M. Ethirajan) and found acceptable. The sponsor is relying on an identification threshold of (b) (4)% and a qualification threshold of (b) (4)% for impurities, per European Pharmacopoeia, in the absence of applicable guidance by ICH Q3A. OPQ finds these acceptance limits acceptable based on prior experience with these impurities for the listed drug Angiomax<sup>®</sup>.

### Drug Product

Bivalirudin in 0.9% Sodium Chloride Injection is a frozen, isosmotic, sterile, nonpyrogenic solution available as 250 mg in 50 mL or 500 mg in 100 mL in a GALAXY (plastic) container. In addition to bivalirudin, the formulation contains the following excipients: sodium chloride and water for injection. Hydrochloric acid or sodium hydroxide are used for pH adjustment. The proposed product formulation was found to be acceptable by the drug product reviewer. Degradants include (b) (4), with acceptance limits of (b) (4)%, respectively, observed during manufacturing and throughout the shelf-life. The degradant levels for the proposed product are similar to those of the listed drug over a storage period of 12 months (frozen) or 24 h at room temperature. Therefore, the product reviewer found degradant and impurity levels acceptable.

### Stability/Shelf-life

Stability data support the proposed shelf-life of 12 months at -20 °C/-4 °F. Storage for 7 days under refrigerated conditions (5 °C/41 °F) or 24 h at room temperature (25 °C/77 °F) have also been supported with stability data. Adequate sterilization processes were established.

### Facilities review/inspection

OPQ has determined that facilities are acceptable based on prior inspection of manufacturing sites. No new inspections were conducted.

## 4. Nonclinical Pharmacology/Toxicology

The applicant did not submit new pharmacology/toxicology information. A pharmacology/toxicology review was not considered necessary by the relevant review division.

## 5. Biopharmaceutics/ Clinical Pharmacology

The applicant did not conduct in vivo studies, and has requested a waiver of in vivo studies based on 21 CFR 320.22 (a). The biopharmaceutics reviewer considered that the bridge to the RLD was established (21 CFR 320.24(b)(6)). While the listed drug Angiomax® contains mannitol, this is not thought to impact pharmacokinetic properties of the proposed drug product significantly, since the drug is injected intravenously. In addition, an in vitro comparison of listed drug to proposed drug product showed similar results for the coagulation markers aPTT, PT, and TT. Geometric mean ratios of test results fell within the 80-125% boundary typically accepted for bioequivalence assessment.

## 6. Clinical/Statistical- Efficacy

The applicant did not conduct new in vivo studies, and the in vitro potency study as well as the biowaiver based on based on 21 CFR 320.22 (a) provide the bridge to the RLD. A review was not considered necessary by the relevant division.

## 7. Safety

The application does not raise new issues regarding the safety of bivalirudin. Specific changes to safety sections of the label are discussed under "Labeling".

## 8. Advisory Committee Meeting

The application does not raise new significant issues regarding the safety or effectiveness of the drug. Therefore, no Advisory Committee Meeting was held.

## 9. Pediatrics

Because the proposed drug product is a new dosage form, the submission triggers PREA. As agreed with PeRC the requirement to conduct pediatric studies for the indications sought by the sponsor will be waived, because this is not an indication commonly observed in pediatric patients.

## 10. Other Relevant Regulatory Issues

None.

## 11. Labeling

The label was revised to update several sections of the label and update it to conform to contemporary labeling practices, including bringing the label to accordance with the PLLR. In addition, the sections mentioned below were edited for clarity and redundancies in indication and dosing statements were removed.

Key sections of labeling that were revised include the following:

1. Indications and Usage	 (b) (4)
2. Dosage and Administration	

5. Warnings and Precautions	(b) (4)
6. Adverse Reactions	
14. Clinical Studies	

## 12. Recommendations/Risk Benefit Assessment

### Recommended Regulatory Action

Approval for the following indication:

Bivalirudin Injection is an anticoagulant for use in patients undergoing percutaneous coronary intervention.

### Risk Benefit Assessment

The risk-benefit of this product is not expected to differ from that of the reference listed drug Angiomax.

### Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

### Recommendation for other Postmarketing Requirements and Commitments

None

### Recommended Comments to Applicant

None

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/s/  
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MARTINA D SAHRE  
12/15/2017

NORMAN L STOCKBRIDGE  
12/15/2017  
I concur.