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APPLICATION NUMBER:

211215Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review: NDA 211215

Date	16-July-2019
From	Mohan Sapru, M.S., Ph.D. CMC Lead for Cardiovascular and Renal Products
Through	Norman Stockbridge, M.D., Ph.D. Director, Division of Cardiovascular and Renal Products
Subject	Cross-Discipline Team Leader Review
NDA	211215 {Angiomax RTU (Bivalirudin) Injection}
Type of Application	505(b)(2)
Applicant	Maia Pharmaceuticals, Inc.
Date of Receipt	27-September-2018
PDUFA Goal Date	27-July-2019
Established/Proper Name	Angiomax RTU (Bivalirudin) Injection
Dosage forms; Strength	Parenteral; 5 mg/mL (250 mg/50 mL)
Route of Administration	Intravenous Infusion
Proposed Indication(s)	The proposed product is a direct-thrombin-binding anticoagulant indicated for use in patients undergoing percutaneous coronary intervention (PCI), including patients with heparin-induced thrombocytopenia and heparin-induced thrombocytopenia and thrombosis syndrome
Recommendation on Regulatory Action	**Approval**

This cross-discipline team leader review is based on the primary reviews, memos and documented review input, as listed below:

Material Reviewed/Consulted	**Review Team**
Integrated Quality Review (PANORAMA dated 16-June-2019)	Raymond Frankewich, Kambhampati Rao, Kumar Janoria, Gerlie Gieser, Denise Miller, and Mohan Sapru (Application Technical Lead)
Non-Clinical Review (DARRTS, dated 20-February-2019)	Elizabeth Hausner, and Xuan Chi
Immunogenicity Consult Review, DARRTS, dated 22-May-2019).	Haoheng Yan, and Bazarragchaa Damdinsuren
Clinical Review Memo (DARRTS, dated 15-February-2019	Rekha Kambhampati, and Aliza Thompson
DMEPA Reviews (DARRTS, dated 25-February 2019, and 18-March-2019)	Sarah Thomas, and Chi-Ming (Alice) Tu
OPDP Labeling Consult Review (DARRTS, dated 22-May-2019)	Zarna Patel, James Dvorsky

1. Background

The applicant, MAIA Pharmaceuticals, Inc., has sought U.S. marketing approval for Angiomax RTU (Bivalirudin) Injection, 5 mg/mL for intravenous infusion in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Angiomax RTU is a direct-thrombin-binding anticoagulant and is indicated for use in patients undergoing percutaneous coronary intervention (PCI). The proposed Bivalirudin Injection (5mg/mL) is supplied as a refrigerated, ready-to-use (RTU), sterile solution in single-dose, 50 mL glass vials. It is noted that the applicant does not rely upon NDA 208374 (Bivalirudin in 0.9% Sodium Chloride Injection) for seeking approval for this NDA. Instead, this NDA for Bivalirudin Injection relies for approval, in part, on the FDA's findings of efficacy and safety for the Listed Drug (LD), Angiomax® (Lyophilized Powder) for Injection (NDA 020873). The LD is a lyophilized drug product that is first reconstituted in Water for Injection (nominal concentration of 50 mg/mL), and subsequently diluted in either 0.9% Sodium Chloride Injection or 5% Dextrose Injection (nominal concentration of 5 mg/mL) prior to use. Regarding mode of action, bivalirudin binds both circulating and clot-bound thrombin. *In vivo*, bivalirudin increases activated partial thromboplastin time (aPTT), thrombin time (TT), and prothrombin time (PT) in a dose-dependent manner. The recommended clinical dose and dosage regimen for Angiomax RTU (Bivalirudin) Injection is identical to the LD i.e., a bolus injection (0.75 mg/kg) followed by a continuous intravenous infusion (1.75 mg/kg/h) for the duration of the PCI procedure and up to 4 hours post-procedure.

2. Product Quality/Chemistry, Manufacturing and Controls (CMC)

2.1. Summary of Quality Assessments

The proposed to-be-marketed drug product Angiomax RTU (Bivalirudin) Injection has the same active ingredient as the LD, with the same trifluoroacetate salt content. However, the proposed to-be-marketed product is not quantitatively and qualitatively the same as the LD Angiomax® for Injection (NDA 20873). The differences from the LD include replacement of inactive ingredient mannitol with polyethylene glycol 400 (b) (4) higher osmolality, and relatively higher level of degradant impurities at end-of-shelf-life in the proposed product. The scientific bridge between the LD and the proposed Angiomax RTU (Bivalirudin) Injection has been established based on applicant's studies that demonstrate equivalence in terms of *in vitro* anticoagulant activities, *in vitro* hemolytic potential, and *in vivo* animal systemic toxicity profiles, as well as the FDA's evaluation of submitted medical and nonclinical literature. From a quality perspective, the proposed control strategies are adequate to ensure consistent product quality with regard to identity, strength, purity, sterility, potency, and stability.

2.2. Drug Substance (Bivalirudin)

Bivalirudin is a single chain linear 20-amino acid peptide analog of hirudin (a naturally occurring peptide in the salivary glands of blood-sucking leeches that has blood anticoagulant property) consisting of the hirudin active site-binding domain and the fibrinogen-binding domain linked together with a linker containing four glycine residues. All amino acid residues except the achiral Gly and the N-terminal D-Phe are in the L-configuration. All CMC information, including structural characterization, manufacturing, batch analysis and stability data have been cross-referenced to DMF (b) (4) held by (b) (4) The DMF (b) (4) has been reviewed in support of this NDA and found adequate. Based on CMC information provided in the NDA, the drug substance, available as a trifluoroacetate salt (range of trifluoroacetic acid composition of 1.7 to 2.6 equivalents), is very hygroscopic and freely soluble in water. Bivalirudin is manufactured by (b) (4) under GMP controls. The drug substance is controlled for its identity using three methods (IR, ESI-MS and Amino acid analysis), potency (Assay) and impurities. Other attributes that are tested at release include description, appearance of solution, thrombin inhibition, trifluoroacetic acid

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content, water content, microbial count and residual (b) (4) solvents. As appropriate for a drug substance intended for use in a parenteral product, bivalirudin is also controlled for endotoxin level at NMT (b) (4) EU/mg, well below the target limit for the drug product. The combined data from HPLC RT, ESI-MS, Amino Acid Analysis, Thrombin Inhibition Activity by UV-V provide adequate information about API identification, including sequence confirmation. The proposed drug substance specification is adequate. The analytical procedures have been adequately validated.

2.3. Drug Product (Bivalirudin Injection)

2.3.1. Product Design, and Release Specification: Angiomax RTU (Bivalirudin) Injection is a sterile, ready-to use formulation of bivalirudin. Each milliliter of Bivalirudin Injection contains 5 mg of bivalirudin (equivalent to an average of 5.5 mg bivalirudin trifluoroacetate) and the following inactive ingredients: 0.8 mg sodium acetate (trihydrate), 100 mg polyethylene glycol 400, and Water for Injection, q.s to 1 mL, and sodium hydroxide (NF)/glacial acetic acid (NF) for pH adjustment. All proposed excipients are compendial grade. No novel or human/animal origin excipients are used in the proposed formulation. All the inactive ingredients are below the permitted listed levels in Inactive Ingredients Database (IID) maintained by FDA. Polyethylene glycol 400 (b) (4)) is used as (b) (4) in this formulation. The Inactive Ingredients Database lists the use of PEG 400 as high as 75.58% for solution, injection and it is controlled in the to-be marketed formulation as per the USP-NF monograph. Critical material attributes of the excipients employed in the formulation are controlled as per the relevant USP/NF monographs. The product release specification, involving testing of product critical quality attributes such as identity, pH, osmolality, particulate matter, sterility, elemental impurities (per USP <232>/ICH Q3D requirements), bacterial endotoxins, and bivalirudin related substances (organic impurities), is adequate. The analytical procedures have been adequately validated.

2.3.2. Manufacturing: The manufacturing process is (b) (4) The applicant has demonstrated that the drug product batches can be manufactured with consistent quality and purity. Based on the control strategy, including in-process controls, and environmental controls, the manufacturing process is adequately controlled.

2.3.3. Microbiological Aspects: The manufacturing of the drug product is adequately controlled for microbiological attributes (b) (4) (b) (4) . Process validation, including validation of: (b) (4) container closure package integrity, is adequate. The drug product is tested for sterility and is controlled for endotoxins against an acceptable limit of NMT (b) (4) EU/mg of bivalirudin. The applicant has demonstrated the container closure package integrity of Bivalirudin Injection, 5 mg/mL, packaged in 50 mL clear glass (b) (4) vial. Testing for bacterial endotoxins is appropriately performed according to USP <85>, and Total Viable Aerobic Count (TVAC) testing complies to USP <61>.

2.3.4. Biopharmaceutics Aspects: To establish the scientific bridge to the LD, data from comparative *in vitro* pharmacodynamic, nonclinical (repeat dose animal toxicity), and *in vitro* hemolysis studies, as well as

additional justification, have been provided in the submission. Specifically, the proposed product intentionally degraded (at 30 °C for 10 days) has demonstrated equivalence to the reconstituted/diluted LD in terms of prothrombin time (PT), activated partial thromboplastin time (aPTT), and thrombin time (TT) over the therapeutic bivalirudin concentration range. Based on prior agreement with the Agency, no *in vivo* bioequivalence studies have been performed. The Agency has previously agreed that a study to assess the equivalence of the pharmacodynamic activity between the proposed product and the LD can be used to support the approval of the biowaiver request. The data from applicant's two *in vitro* human plasma studies, to assess equivalence of the anticoagulant (pharmacodynamic) activity of the proposed product and the LD, are adequate. As expected, the applicant has not conducted clinical studies for bivalirudin. To supplement the known safety profile of bivalirudin from approved labeling for the LD, additional safety and tolerability information from recent published literature, including analysis of FAERS reports has been evaluated and found adequate.

2.3.5. Container Closure System: The drug product is packaged in a 50 mL clear (b) (4) glass vial with a 32-mm neck, stoppered with a 32-mm grey (b) (4) rubber stopper and sealed with a 32-mm aluminum seal with a (b) (4) flip-off button. Based on study of leachables and extractables, and pharmaceutical development studies, the applicant has demonstrated compatibility with the active ingredient, excipients, container and closure components, and dosing components. The product stability data also indicate suitability of the proposed container closure system for the intended use.

2.3.6. Product Stability. The applicant provided data from stability studies from three registration batches stored in the intended commercial packaging under long-term conditions (5±3°C) for up to 24 months and accelerated conditions (25±2°C) for 3 months.

Potential Impact of End-of-Shelf-Life Levels of Degradant Impurities on Product Quality and Safety:

- The applicant indicated presence of higher end-of-shelf-life levels of degradant impurities in the Bivalirudin Injection (ready-to-use product) compared to the LD (lyophilized powder).

- Based on a 14-day continuous infusion of intentionally heat-degraded Bivalirudin RTU Solution (worst-case scenario product degradation with a total level of degradants at (b) (4)%) in rats, there is no indication that the higher level of degradant impurities induces any new toxicities or exacerbate the known toxicities of bivalirudin.

- The Office of Biotechnology Products (OBP) review team had concerns because of potential immunogenicity risk that may be associated with the higher end-of-shelf-life levels of degradant impurities in the Bivalirudin Injection compared to the LD. To address these potential concerns, the applicant agreed to CMC-recommended mitigation strategy i.e., a): to revise the proposed drug product shelf-life specification by tightening the acceptance criteria for product impurities (b) (4) , b) to reduce the requested expiry period to 11 months, which is adequately supported by long-term stability data in conformity with revised/tightened shelf-life specification limits. (b) (4)

- Based on alleviation of immunogenicity concern due to applicant's tightening of the acceptance criteria for product impurities (b) (4) and shortening of the proposed shelf life to 11 months, the OBP review team has recommended approval for this NDA.

- Post-approval, [redacted]

- It is noted that the only degradant with a change in the primary sequence [redacted] is already controlled [redacted] and is below the level specified in the LD (less than [redacted]%) and is hence the degradant is unlikely to pose any additional risk from an immunogenicity standpoint.

- The applicant's proposal for post-approval [redacted] studies [redacted] has been reviewed by the OBP review team and Agency's recommendations regarding the design of these studies have been communicated to the applicant (General Advice Letter, DARRTS, dated 8-July-2019).

2.3.7. Expiration Date and Storage Conditions: Based on evaluation of long-term and accelerated stability data as per the revised/tightened shelf-life specification limits for product impurities, an expiration period of 11 months is granted for the product when stored in the commercial packaging at the long-term storage condition of 2 – 8°C (36 - 46°F). Product excursions are permitted to [redacted] Photostability of the proposed product has been demonstrated. Study of product stability under temperature cycling (Freeze – Thaw) conditions does not show any significant change with respect to all evaluated parameters. The post-approval stability commitments are appropriate to ensure the quality of the drug product over the proposed shelf-life.

2.3.8. Assessment of Manufacturing Facilities: The office of Process and Facilities has recommended overall approval for all the currently listed manufacturing facilities concerning this NDA.

In conclusion, based on OPQ's Integrated Quality Review, from quality perspective, Angiomax RTU (Bivalirudin) Injection is recommended for approval.

3. Non-Clinical Pharmacology/Toxicology

Bivalirudin is catabolized extensively *in vivo* and approximately 20% of full length bivalirudin and some degradants are excreted in the urine. The initial *in vivo* degradation involves hydrolysis of the N-terminal dipeptide, producing [redacted], which is also a major degradant *in vitro*. Bivalirudin is also slowly hydrolyzed by thrombin and other circulating proteases at the Arg3-Pro4 bond. The primary metabolite of this is [redacted] which is reportedly not active due to loss of affinity for the catalytic activity site of thrombin. To qualify the systemic and local safety of the higher end-of-shelf-life levels of degradant impurities in the proposed product compared to the LD, a 14-day continuous infusion toxicity study in rats was carried out by the applicant. The repeat-dose animal toxicity study has evaluated up to 258 mg/kg/day continuous IV infusion doses of intentionally heat-degraded Bivalirudin RTU Solution (with total level of degradants at [redacted]%). This was aimed to simulate a worst-case-scenario of degradation at the end of product shelf-life. Based on the Pharmacology and Toxicology review, the continuous infusion study has produced no findings of toxicological significance. Additionally, no overt immunogenic reaction-related concerns are apparent based on hematology,

clinical chemistry and histopathology data from this study. From the nonclinical perspective, the NDA is recommended for approval.

4. Clinical Pharmacology

N/A

5. Statistical-Evaluation

N/A

6. Safety

This application primarily relies on the Agency's previous determination of safety for the LD.

7. Advisory Committee Meeting

N/A

8. Pediatrics

Because this NDA does not seek approval for a new active ingredient, new dosage form, new dosing regimen, or new route of administration; therefore, under Section 505B (a)(1) (A) of the Food, Drug, and Cosmetic Act, a pediatric assessment is not required. Per the Pre-NDA Meeting Minutes, the Agency has previously agreed that this application is exempt from Pediatric Research Equity Act (PREA) requirements.

9. Other Relevant Regulatory Issues

N/A

10. Labeling

Proprietary name, Angiomax RTU, has been found acceptable. As discussed with the applicant via teleconference on 7-10-2019, the applicant's storage statement i.e.., (b) (4) [redacted] " is not currently supported by available product stability/excursion data per revised shelf-life product specification. The recommended storage instructions are as follows: "Store Angiomax RTU vials in the refrigerator between 2° to 8°C (36°to 46°F). Excursions are permitted to 20° to 25°C (68 to 77°F) *[see Dosage and Administration (2.3)]*. Avoid excess heat". Based on multidisciplinary labeling reviews, including by the Office of Pharmaceutical Quality (OPQ), Division of Medication Error Prevention and Analysis (DMEPA) and the Office of Prescription Drug Promotion (OPDP), the revised labeling is acceptable.

11. Risk Benefit Assessment

The current NDA relies on FDA's previous finding of safety and efficacy for the LD, Angiomax® (Lyophilized Powder) for Injection. The applicant's proposed product is essentially similar to the LD, as it has the same active moiety and delivers the same amount of drug to the patient. The differences in inactive ingredients between the proposed product and the LD have been adequately justified by the applicant and are not expected to impact disposition, safety, or efficacy of the proposed drug product. The proposed indication, and recommended clinical dose and dosage regimen for Angiomax RTU (Bivalirudin) Injection are identical to those for the LD. The evaluation of the recent published literature for bivalirudin safety information has not identified any new safety information which would change the drug's known safety profile. Hence, the risk-benefit ratio with the proposed product is expected to be similar to that for the currently marketed LD.

12. Recommended Regulatory Action

Based on multidisciplinary review and resolution of all identified deficiencies, Angiomax RTU (Bivalirudin) Injection NDA 211215 has been recommended for approval. I agree with this assessment and recommend an approval regulatory action for this NDA.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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