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APPLICATION NUMBER:

212593Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader (CDTL) Review: NDA 212593 (Vasopressin Injection)

Date	03-August-2020
From	Mohan Sapru, M.S., Ph.D. CMC Lead, Division of Cardiology and Nephrology (DCN)
Through	Norman Stockbridge, M.D., Ph.D. Director, Division of Cardiology and Nephrology
Subject	Cross-Discipline Team Leader Review
NDA	NDA 212593 (Vasopressin Injection)
Type of Application	505(b)(2)
Applicant	American Regent, Inc.
Date of Receipt of the Resubmission	06-June-2020
PDUFA Goal Date	04 August, 2020
Established/Proper Name	Vasopressin Injection
Dosage forms; Dosing Regimen	Intravenous infusion (b) (4) The starting dose is: Post-cardiotomy shock: 0.03 units/minute Septic shock: 0.01 units/minute Titrate up by 0.005 units/minute at 10- to 15-minute intervals until the target blood pressure is reached
Route of Administration	Intravenous Infusion
Proposed Indication(s)	Vasopressin Injection is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines
Recommendation on Regulatory Action	**Final Approval**

This cross-discipline team leader review #2 is based on the primary reviews, memos and documented review input, as listed below:

Material Reviewed/Consulted	**Review Team**
Integrated Quality Review NDA 212593 ORIG-1-RESUB-25 (DARRTS, 01-August-2020)	Dhanalakshmi Kasi, Upasana Sahu, and Mohan Sapru (Application Technical Lead)
DMEPA Review (DARRTS, 23-July- 2020)	Maximilian Straka

1. Background

Because final approval of NDA 212593, under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)], could not be granted before expiration of a period of patent protection and/or exclusivity, the original NDA was granted tentative approval on January 28, 2020 (for details, refer to CDTL Review, and Tentative

Approval Letter; DARRTS, dated January 28, 2020). It is noted that this application does not rely on Vasostrict NDA 204485 products 003 and 004 because these were approved on April 15, 20, i.e., after submission of original NDA 212593 under 505(b)(2) pathway.

2. NDA 212593 ORIG-1-RESUB-25 (Vasopressin Injection)

On June 4, 2020, the applicant, American Regent, Inc., submitted request that the FDA issue final approval for NDA 212593, and submitted Class1 resubmission to support stability/labeling updates. Based on the original NDA submission, a shelf-life of 24 months was approved for the product when stored at 2°C and 8°C (36°F and 46°F) in the proposed commercial container closure system. In the current Class1 resubmission, the applicant provided stability data to support the storage condition of 12 months at room temperature storage conditions (20 to 25°C [68 to 77°F], USP Controlled Room Temperature), in addition to 12 months at 2°C and 8°C (36°F and 46°F), to match the shelf-life of the Listed Drug, Vasostrict®. Evaluation of these stability data reveal that the product assay levels fall slightly while the levels of some impurities significantly increase at room temperature. However, these changed assay and impurity levels are within the drug product stability specification limits.

Revised Label and Labeling**:** The updated stability data support the following label claim concerning product storage and handling:

Unopened Refrigerated 2°C to 8°C (36°F to 46°F)	Unopened Room Temperature 20°C to 25°C (68°F to 77°F)
Until manufacturer expiration date	12 months or until manufacturer expiration date, whichever is earlier

Based on updated stability data, the applicant's revised container label and carton labeling and Prescribing Information (PI) are acceptable.

3. Assessment of Manufacturing Facilities

Based on the inspection history, manufacturing experience and acceptable compliant status, the Office of Pharmaceutical Manufacturing Assessment (OPMA) has recommended an overall approval for all the currently listed manufacturing and testing facilities concerning this NDA.

4. Expiration Date and Storage Conditions

A shelf-life of 24 months is approved for the product when stored at long-term storage conditions of 2°C and 8°C (36°F and 46°F) in the proposed commercial container closure system. In addition, product storage is permitted for up to 12 months at controlled room temperature (USP) 20 to 25°C (68 to 77°F) within the expiry date.

5. Quality Review Conclusion

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 212593 (Vasopressin Injection) is recommended for final approval (for details, refer to Integrated Quality Review; DARRTS, dated January 27, 2020; and Integrated Quality Review NDA 212593 ORIG-1-RESUB-25; DARRTS, 01-August-2020).

6. Non-Clinical Pharmacology/Toxicology

No stand-alone pharmacology or toxicology studies have been conducted by the applicant. The Agency previously agreed that the available information in the published literature is enough and no nonclinical studies with Vasopressin Injection are required

7. Clinical Pharmacology

N/A

8. Statistical-Evaluation

N/A

9. Safety

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

10. Advisory Committee Meeting

N/A

11. Pediatrics

Safety and effectiveness of Vasopressin Injection in pediatric patients with vasodilatory shock have not been established. There are no data on the presence of administered vasopressin in either human or animal milk. There is no information available about any potential effects of administered vasopressin on the breastfed infant, or milk production.

12. Other Relevant Regulatory Issues

N/A

13. Labeling

FDA's multidisciplinary recommendations and edits have been incorporated by the applicant in the most recent version of the label and labeling. 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.

14. Risk Benefit Assessment

The current NDA relies on FDA's previous finding of safety and efficacy for the Listed Drug (LD), Vasostrict (NDA 204485). The proposed product Vasopressin Injection, 20 Units/1 mL 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 proposed product Vasopressin Injection are identical to those for the LD. The evaluation of the recent published literature concerning vasopressin safety 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.

15. Recommended Regulatory Action

Based on multidisciplinary review and resolution of all identified deficiencies, Vasopressin Injection (NDA 212593) has been recommended for approval. I agree with this assessment and recommend a final approval regulatory action for this NDA.

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/s/

MOHAN K SAPRU
08/03/2020 09:23:44 AM

NORMAN L STOCKBRIDGE
08/03/2020 09:46:41 AM

Cross-Discipline Team Leader Review: NDA 212593 (Vasopressin Injection)

Date	27-January-2020
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	NDA 212593 (Vasopressin Injection)
Type of Application	505(b)(2)
Applicant	American Regent, Inc.
Date of Receipt	29-March-2019
PDUFA Goal Date	29-January-2020
Established/Proper Name	Vasopressin Injection
Dosage forms; Dosing Regimen	Intravenous infusion titrated (b) (4) The starting dose is: Post-cardiotomy shock: 0.03 units/minute Septic shock: 0.01 units/minute Titrate up by 0.005 units/minute at 10- to 15-minute intervals until the target blood pressure is reached.
Route of Administration	Intravenous Infusion
Proposed Indication(s)	Vasopressin Injection is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines
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 (DARRTS, 27-January-2020)	Monica Cooper, Grace Chiou, Upasana Sahu, Parnali Chatterjee, Valerie Huse, and Mohan Sapru (Application Technical Lead)
DMEPA Reviews (DARRTS, 15-January- 2020, and 27-November-2019)	Sarah Thomas, and Chi-Ming (Alice) Tu
Clinical Review (DARRTS, 02-December-2019)	Charu Gandotra
Division of Pediatric and Maternal Health (DPMH) Review (DARRTS, 13-December-2019)	Christos Mastroyannis
Non-Clinical Review (DARRTS, 18-November-2019)	Jagadeesh, Gowra
OPDP Labeling Review (DARRTS, 18-December-2019)	David Foss, James Dvorsky

1. Background

Vasopressin injection is an unapproved product that has been marketed in the United States by American Regent (formerly Luitpold Inc.) from September 1993. It has also been used off-label for the treatment of esophageal varices, gastrointestinal hemorrhage, cardiac arrest, septic shock, and vasodilatory shock. In June 2006, the FDA announced a new drug safety initiative to remove unapproved drugs from the market. In response to this initiative, NDA 204485 for Vasostrict (Vasopressin Injection) was submitted, which was approved on April 17, 2014. Vasostrict is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines. Currently, the applicant, American Regent, Inc. has sought U.S. marketing approval for Vasopressin Injection in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act and Section 314.50. For the approval of this NDA, the applicant relies on the Agency's determination of safety and effectiveness for the Listed Drug (LD) i.e., Vasostrict (NDA 204485), which is manufactured by Par Sterile Products LLC (Par).

2. Clinical

NDA 212593 submission refers to the literature, published between April 14, 2014 (date of Vasostrict approval) and September 17, 2018, to identify any new data that may be inconsistent with FDA's previous findings of safety and efficacy for Vasostrict. The applicant submitted 35 studies to support efficacy and safety, 5 studies to support safety, 4 systematic literature reviews, and 15 case reports. The clinical review team concluded that the published literature continues to support FDA's previous findings of safety and efficacy for the use of vasopressin. A new safety signal of development of transient diabetes insipidus after discontinuation of vasopressin infusion has been identified based on case reports. However, most cases of diabetes insipidus resolve within 24 hours with treatment comprised of intravenous fluids, re-initiation of vasopressin infusion, and/or Desmopressin. This finding does not change the overall benefit-risk profile for vasopressin. Vasopressin Injection is contraindicated in patients with known allergy or hypersensitivity to 8-Larginine vasopressin or chlorobutanol. From a clinical perspective, the review team has recommended NDA approval.

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

3.1. Summary of Quality Assessments

The proposed to-be-marketed drug product is to be made available as a 20 USP units/mL sterile solution for intravenous injection and is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines. Based on the known physicochemical attributes of the LD, USP monograph, and data from multiple laboratory batches, the applicant has adequately defined the quality target product profile (QTPP) for the proposed formulation. From quality perspective, the proposed control strategies are adequate to ensure consistent product quality with regard to identity, strength, purity, sterility, potency, and stability.

3.2. Drug Substance (Vasopressin, USP)

Vasopressin is a cyclic peptide, which consists of nine amino acids with a disulfide bridge linking the side chains of two cysteine amino acids. All 9 amino acids are present in their natural L-form, and the C-terminal Gly is present in its amide form. No side-chain or N-terminal modification is present. There are no polymorphic forms known. All CMC information for the drug substance has been referenced to DMF (b) (4) , which has been reviewed and found adequate (Review #2, 13-Nov-2019; M. Cooper). Briefly, structural characterization of vasopressin drug substance using appropriate validated analytical procedures is adequate. Specifically, Fourier Transform- Ion Cyclotron Resonance – Mass Spectrometry (FT-

ICR MS) technique has been used to confirm the presence of the disulfide bond. As documented in pre-NDA 212593 meeting minutes, FDA recommended that structural characterization of the drug substance should include the one-time demonstration of sufficient correlation between a bioassay test and the proposed HPLC assay. Based on information provided in the NDA, the applicant has adequately demonstrated that bioactivities determined for 3 vasopressin batches using the bioassay method are well correlated with the content values determined via the HPLC assay. Thus, the HPLC assay is sufficient for batch release testing of the vasopressin drug substance and a routine bioassay test is not needed for release or stability testing. The applicant has used the well-established (b) (4) for manufacture of the drug substance. Specifically, the identity, quality and purity of each batch of the drug substance are assessed and confirmed as per the specification, which includes testing for identification by mass spectrometry and HPLC; amino acid analysis, and determination of vasopressin (assay; (b) (4)) content and peptide-related impurities. The bacterial endotoxins and microbial enumeration are controlled as per USP <85> and USP <61>, respectively.

3.3. Drug Product (Vasopressin Injection)

3.3.1. Product Design, and Release Specification: The proposed product, Vasopressin Injection, USP, 20 Units/1 mL in a single-dose 2 mL glass vial, is to be administered by intravenous infusion following dilution with normal saline (0.9% sodium chloride) or 5% dextrose in water. The drug product is formulated in water with chlorobutanol (a preservative) and sodium chloride and acetic acid, (b) (4). There are no novel excipients and no excipients of human or animal origin. It is noted that the use of chlorobutanol as (b) (4); however, presence of chlorobutanol in the formulation does not pose any risk to product quality, safety or efficacy. All the product critical quality attributes are controlled by product specification. Specifically, the product release specification includes testing for appearance, identity, assay, degradants, volume of solution, particulate matter, pH, chlorobutanol, (b) (4) endotoxins (USP<85>) and sterility (USP<71>). The level of each excipient used in the manufacture of the drug product is at or below levels typically found in other parenteral products as per the FDA's inactive ingredient database. All the analytical methods have been adequately validated. Based on the risk assessment and testing performed in compliance with ICH Q3D, USP <232>, and USP<233>, no routine release testing of elemental impurities and/or additional controls ~~are~~ is required.

3.3.2. Manufacturing: The manufacturing process is a standard (b) (4) process. The process steps used to manufacture the drug product include: (b) (4) The listed critical material and process parameters are adequate. Based on the control strategy, including in-process controls, and environmental controls, the manufacturing process is adequately controlled.

3.3.3. Microbiological Aspects: The validated process for (b) (4), and container closure integrity testing performed are adequate. Sterility and bacterial endotoxins tests are performed at release and on stability in accordance with USP <71> and USP <85>, respectively. The product specification meets regulatory expectations for a sterile and preserved drug product.

3.3.4. Biopharmaceutics Aspects: The proposed drug product has the same active moiety (vasopressin) and is considered to be the same dosage form that involves same route of administration [IV use] and indication as the listed drug (LD), Vasostrict® (vasopressin) for injection, 20 Units/1 mL (NDA 204485). However, the proposed product and the LD are different with regard~~s~~ to the excipients. Specifically, the proposed formulation contains chlorobutanol while the LD does not contain this preservative in the listed dosing configuration. Unlike

the LD, the proposed formulation involves the use of sodium chloride (b) (4). As the formulated drug product is (b) (4) In addition, acetic acid is used to adjust the pH of the drug product while the LD uses sodium acetate to adjust the pH. This difference is inconsequential as acetate ions are introduced in both the LD and the proposed formulation. Based on the supporting data from pH and osmolality comparisons, and literature information, differences in the inactive ingredients are not expected to affect the disposition kinetics (the sum of distribution and elimination rates) of vasopressin in the proposed drug product when administered via the IV route. Essentially, the disposition kinetics of vasopressin is expected to be similar after administration of either the proposed product or the LD. The data and information submitted in the application demonstrate that the proposed drug product has been adequately bridged to the LD; therefore, per 21 CFR 320.24(b)(6), an in vivo pharmacokinetic study is not needed.

3.3.6. Container Closure System: Vasopressin Injection, USP 20 units/mL will be packaged in 2-mL (b) (4) type (b) (4) glass vial with a 13 mm stopper, sealed with a (b) (4). The applicant has performed extractable/leachable testing that is compliant with USP <1663> and <1664>. Consistent with the LD, light protection for Vasopressin Injection, USP 20 units/mL is provided via packaging each clear glass vial in an opaque secondary container carton. The product stability data indicate suitability of the proposed container closure system for the intended use.

3.3.7. Expiration Date and Storage Conditions: The current stability data, which includes 18 months of long-term and 6 months of accelerated stability data, support a shelf-life of 24 months for the product when stored at 5°C ± 3°C in the proposed commercial container closure system. The unused diluted solution is to be discarded after 18 hours at room temperature or 24 hours under refrigeration.

3.3.8. Assessment of Manufacturing Facilities: Based on the inspection history, manufacturing experience and acceptable compliant status, the Office of Pharmaceutical Manufacturing Assessment (OPMA) has recommended an overall approval for all the currently listed manufacturing and testing facilities concerning this NDA.

3.3.9. Quality Review Conclusion: Based on OPQ's Integrated Quality Review, from quality perspective, Vasopressin Injection (NDA 212593) has been recommended for approval. Product shelf-life of 24 months is approved for the product when stored at 5°C ± 3°C in the proposed commercial container closure system.

4. Non-Clinical Pharmacology/Toxicology

No stand-alone pharmacology or toxicology studies have been conducted by the applicant. The Agency previously agreed that the available information in the published literature is enough and no nonclinical studies with Vasopressin Injection are required

5. Clinical Pharmacology

N/A

6. 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

Safety and effectiveness of Vasopressin Injection in pediatric patients with vasodilatory shock have not been established. There are no data on the presence of administered vasopressin in either human or animal milk. There is no information available about any potential effects of administered vasopressin on the breastfed infant, or milk production.

9. Other Relevant Regulatory Issues

N/A

10. Labeling

FDA's multidisciplinary recommendations and edits have been incorporated by the applicant in the most recent version of the label and labeling. 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, Vasostrict (NDA 204485). The proposed product Vasopressin Injection, USP, 20 Units/1 mL 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 proposed product Vasopressin Injection are identical to those for the LD. The evaluation of the recent published literature concerning vasopressin safety 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, Vasopressin Injection (NDA 212593) 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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