CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209360Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 209360; Angiotensin II Injection

Integrated Quality Review

Recommendation: Approval

Drug Name/Dosage Form	Angiotensin II Injection
Strength	2.5 mg /vial (2.5 mg/mL) and 5 mg /vial (2.5 mg/mL)
Route of Administration	Parenteral (IV infusion)
Rx/OTC Dispensed	Rx
Applicant	La Jolla Pharmaceutical Company
Submissions (s) Reviewed	NDA 209360, and all the submitted CMC amendments

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Raymond Frankewich	ONDP/DNDPI/NDPBI
Drug Product/Environmental Assessment (EA)	Kambhampati Rao	ONDP/DNDPI/NDPBI
Process	Yahong Wang	OPQ/OPF/DPAI/PABI
Facility	Jonathan Swoboda,	OPF/DIA/IABI
Biopharmaceutics	Gerlie Gieser	ONDP/DB/BBI
Microbiology	Jianli Xue	OPQ/OPF/DMA/MABII
RBPM	Grafton Adams	OPRO DRBPMI/RBPMBI
Application Technical Lead	Mohan Sapru	ONDP/DNDPI/NDPBI

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 209360 (Angiotensin II Injection for Intravenous Infusion) is recommended for approval. Product shelf-life of 18 months is approved for the product when stored at 2°C – 8°C in the proposed commercial container closure system.

B. Recommendation on Post-Marketing Commitments (PMCs), Agreements, and/or Risk Management Steps, if Applicable

Not applicable.

II. Application, and Quality Assessment Summary

The applicant, La Jolla Pharmaceutical Company, has sought U.S. marketing approval for Tradename (Angiotensin II) Injection for intravenous infusion in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act and Section 314.50. Severe hypotension is a frequently fatal condition resulting from an underlying cause such as septic shock, inflammation, or severe drug reactions. Generally, those patients who require excessive doses of vasopressors have a high rate of mortality. The proposed product Angiotensin II Injection (LJPC-501) is a parenteral formulation of synthetic human angiotensin II, which is indicated for the treatment of hypotension in adults with distributive or vasodilatory shock who remain hypotensive despite fluid and vasopressor therapy (arguably referred to as catecholamine resistant hypotension, or CRH). Angiotensin II acetate (human sequence, 5-isoleucine [Ile5]-angiotensin II), which is not approved for marketing in the United States, has been designated as the New Molecular Entity (NME). For the approval of this NDA, the applicant mainly relies on the findings of the conducted Phase 3 clinical trial, *in vivo* animal hERG and CV Safety (GLP pharmacology) studies, *in vitro* pharmacodynamics bridging and comparative analytical assessments, in addition to the submitted published literature for supportive efficacy and safety, nonclinical and clinical pharmacology information. From product quality perspective, the proposed control strategies are adequate to ensure consistent product quality with regard to identity, strength, purity, sterility, potency, and stability.

A. Drug Substance (Angiotensin II Acetate) Quality Summary

The drug substance is the acetate salt of synthetic angiotensin II, an octapeptide identical to endogenous human angiotensin II. The active pharmaceutical product, a synthetic Ile5-angiotensin II acetate [human sequence]) of the proposed product has been classified as a New Molecular Entity (NME) because it does not have exactly the same amino acid sequence, chemical form and origin as the previously marketed Hypertensin® (synthetic Val5-angiotensin-II amide [bovine]; NDA 12-791]. Both the N- and the C-terminus of the sequence are unmodified. Acetate salt; the counter ion acetate is present in a non-stoichiometric ratio. (b) (4)

All chiral centers are of predefined stereochemistry. The CMC details concerning structural characterization, manufacturing, control of impurity levels, method validations, stability, and control strategies i.e., control of critical synthetic steps, and release specification are adequate. 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; peptide sequencing and amino acid analysis. The acceptance limit for purity (by HPLC) is set at ≥ (b) (4)% area. Since the ICH Q3A(R2) guidelines for new drug substances excludes peptides from consideration, the proposed limits for reporting, identification and qualification of peptide-related impurities have been justified based on Ph. Eur. Monograph 2034 guidelines that are widely cited as a reference to support establishment of specification limits for peptide related impurities. The elemental impurity content of the drug substance is determined by inductively coupled plasma mass spectrometry as per USP <233>. The bacterial endotoxins and microbial enumeration are controlled as per USP <85> and USP <61>, respectively. Angiotensin II acetate drug substance is packaged in (b) (4) The container closure system is (b) (4) (b) (4) (b) (4) The proposed retest period of (b) (4) months for the drug substance is supported by the primary stability data.

B. Drug Product (Angiotensin II Injection for Intravenous Infusion) Quality Summary

Angiotensin II injection for intravenous infusion (LJPC-501) drug product is a sterile, aqueous solution containing 2.5 mg/mL angiotensin II and 25 mg/mL mannitol in water, adjusted to pH 5.5, and is supplied in single-dose vials. LJPC-501 drug product is supplied in two strengths: 2.5 mg angiotensin II/vial (2.5 mg/mL) and 5 mg angiotensin II/vial (2.5 mg/mL). There are no differences in the formulation or container closure system used for packaging for the two strengths. LJPC-501 drug product is diluted in 0.9% (v/v) sodium chloride solution prior to administration by intravenous infusion and is titrated to effect. All excipients utilized in the LJPC-501 drug product formulation are compendial. 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 critical quality attributes are controlled by product specification. In compliance with the Agency recommendation communicated via teleconference on December 1, 2017, the applicant revised drug product specification by including the second identification test (mass spectrometry) for the drug product. This second identification test utilizes the same validated method that is used for drug substance testing as per drug substance specifications. The acceptance limits of ≤ (b) (4)% w/w for the degradant (b) (4) is mainly based on lot history. This degradation product ha remained within specification through 18 months of storage at the long-term temperature (5 ± 3°C). All the analytical methods have been adequately validated. LJPC-501 drug product registration lots demonstrate that the controls in place for the drug substance and excipients are sufficient to minimize elemental impurities to acceptable limits in the finished drug product.

Manufacturing: The manufacturing process is (b) (4) The process steps used to manufacture the drug product include: (b) (4) Based on the control strategy, including in-process controls, and environmental controls, the manufacturing process is adequately controlled.

Microbiological Aspects: Given that the angiotensin II peptide [redacted] The validated process [redacted] The applicant has performed in-use study to evaluate the in-use microbiological stability of LJPC-501 drug product and the ability of LJPC-501 to support microbiological growth. The results of the microbiological in-use study support a 24-hour hold period at 25°C/60% RH.

Biopharmaceutics Aspects: The proposed to-be-marketed drug product has the same formulation, concentration (2.5 mg/mL), presentation (5 mg/2 mL vial), API supplier, and manufacturing process steps as the 5 lots that have been evaluated for efficacy, safety, and PK/PD in the pivotal Phase 3 clinical trial and for (registration) stability. Thus, bridging data per se with respect to the LJPC-501 formulation are not required. A biowaiver request has not been submitted nor is it required. Based on prior agreement with the Agency, bridging to the literature drug products (including those with different amino acid sequence and origin) has been justified mainly using comparative *in vitro* functional and receptor binding data, which are evaluated by Pharmacology/ Toxicology review team. In summary, biopharmaceutics information provided is adequate.

Container Closure System: The container closure system for LJPC-501 drug product consists of a clear 3 mL USP/Ph. Eur. Type [redacted] glass vial with a 13 mm elastomeric stopper, sealed with an aluminum closure and a plastic flip-off cap. The same container closure system is used for LJPC-501 drug product in the 2.5 mg/vial (2.5 mg/mL) strength and 5 mg/vial (2.5 mg/mL) strength with the exception of the cap color. 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.

Product Stability and In-Use Studies: While there is a trend for gradual increase of degradation impurity [redacted] under long-term conditions (2°C – 8°C), its levels go out of specification following [redacted] storage under accelerated conditions (25 ± 2°C; 60 ± 5% RH). Overall, the stability results demonstrate that the product is stable for 18 months under long-term conditions and [redacted] under accelerated conditions. Furthermore, the applicant has performed an in-use study to evaluate the compatibility of the drug product with the normal saline (0.9% sodium chloride) solution and administration components. Specifically, compatibility of LJPC-501 drug product has been assessed using normal saline, IV infusion bags and IV infusion administration tubing sets at a concentration of 5,000 ng angiotensin II/mL (equivalent to 1 mL LJPC-501 drug product in 500 mL IV bag) and a concentration of 10,000 ng angiotensin II/mL (equivalent to 1 mL LJPC-501 drug product in 250 mL IV bag) for [redacted] hours. Results from this in-use study demonstrate that LJPC-501 drug product is stable and compatible when diluted in normal saline IV bags of both the PVC and non-PVC bag types for [redacted] hours at 25°C. The two concentrations tested support the range of expected clinical administration concentrations. The [redacted] holding time of 24 hours (at 25°C/60% RH) for the diluted drug product.

Expiration Date & Storage Conditions: ***The current stability data support a shelf-life of 18 months for the product when stored at 2°C – 8°C in the proposed commercial container closure system.*** Given that LJPC-501 drug product is diluted in normal saline solution prior to administration by intravenous infusion, the diluted drug product solution needs to be stored at room

temperature or refrigerated. Unused diluted LJPC-501 drug product solution needs to be discarded after 24 hours.

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

III. Summary of Drug Product and Intended Use

Proprietary Name of the Drug Product	To be decided
Non Proprietary Name of the Drug Product	Angiotensin II Injection
Active ingredient	Angiotensin II
Route of Administration	Intravenous Infusion
Strength(s)	2.5 mg /vial (2.5 mg/mL) and 5 mg /vial (2.5 mg/mL)
Proposed Indication(s)	The product is indicated for the treatment of hypotension in adults with distributive or vasodilatory shock who remain hypotensive despite fluid and vasopressor therapy (also referred to as catecholamine resistant hypotension).
Maximum Daily Dose/ Duration of Treatment	For dosage and administration: The product must be administered as an intravenous (IV) infusion, (b) (4) Start intravenously at 20 nomograms (ng)/kg/min. Titrate as frequently as every five minutes by increments of up to 15 ng/kg/min as needed to maintain target blood pressure. During the first 3 hours, the maximum dose should not exceed 80 ng/kg/min. Maintenance dose should not exceed 40 ng/kg/min.
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

1. BCS Designation: The proposed drug product is an injectable solution, and the applicant has not request an official BCS designation,

2. Biowaivers/Biostudies: A biowaiver request has not been submitted and is not required,

3. IVIVC: N/A.

E. Any Special Product Quality Labeling Recommendations: In compliance with the Agency recommendation communicated via teleconference on December 6, 2017, the applicant revised the drug product labeling (indicated below by representative container carton label) by replacing the (b) (4) with the term "single -dose", and including an equivalency statement that states that each mL contains 2.5 mg angiotensin II equivalent to an average of 2.9 mg angiotensin II acetate per mL of the product.

OPQ's all labeling recommendations are reflected in the most recent version of the product labeling.

Final Risk Assessment on the next page

F. Life Cycle Knowledge Information

NDA 209360 (Angiotensin II Injection for Infusion)

Final Risk Assessment-

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors Affecting CQA**	**Initial Risk Ranking**	**Risk Mitigation**	**Final Risk Evaluation**	**Comments**
Sterility	Formulation Container Closure Process Parameters Scale/Equipment/ Site	**H (High)**	(b) (4)	Acceptable	Given that the product sterility is the high risk attribute, any proposed changes in (b) (4) manufacturing process or microbiological testing-related product specification may need to be carefully evaluated.
Endotoxin Pyrogen	Formulation Container Closure Process Parameters Scale/equipment/ Site	**M (Moderate)**		Acceptable	Any proposed changes concerning acceptance limits for endotoxin levels will need to be evaluated based on the maximum total daily dose.
Assay (API), Stability	Formulation Container Closure Raw Materials Process Parameters Scale/Equipment/ Site	L (Low)		Acceptable	
Uniformity of Dose – Fill/ deliverable Volume	Formulation Container Closure Process Parameters Scale/equipment/ site	L (Low))		Acceptable	

Final Risk Assessment (continued, next page)

QUALITY ASSESSMENT

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors Affecting CQA**	**Initial Risk Ranking**	**Risk Mitigation**	**Final Risk Evaluation**	**Comments**
Osmolality	Formulation Raw materials Process parameters Scale/equipment/ site	L (Low)	(b) (4)	Acceptable	
pH (High)	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)		Acceptable	
Particulate Matter	Formulation Container Closure Process Parameters Scale/equipment/ site	**M (Moderate)**		Acceptable	
Leachable Extracts	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)		Acceptable	There is some low risk of (b) (4) on storage beyond the currently granted expiration period Therefore, during the lifecycle management of this product; the vials/product may need to be monitored for (b) (4)
Appearance	Formulation Raw materials Process Parameters Scale/equipment/ site	L (Low)		Acceptable	

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead (ATL) Assessment and Signature:

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 209360 (Angiotensin II Injection) is recommended for approval.

Mohan Sapru, M.S., Ph.D.
Application Technical Lead (ATL)
CMC Lead for Cardiovascular and Renal Products (Actg)
ONDP/DNDPI/NDPBI

Mohan K. Sapru -S

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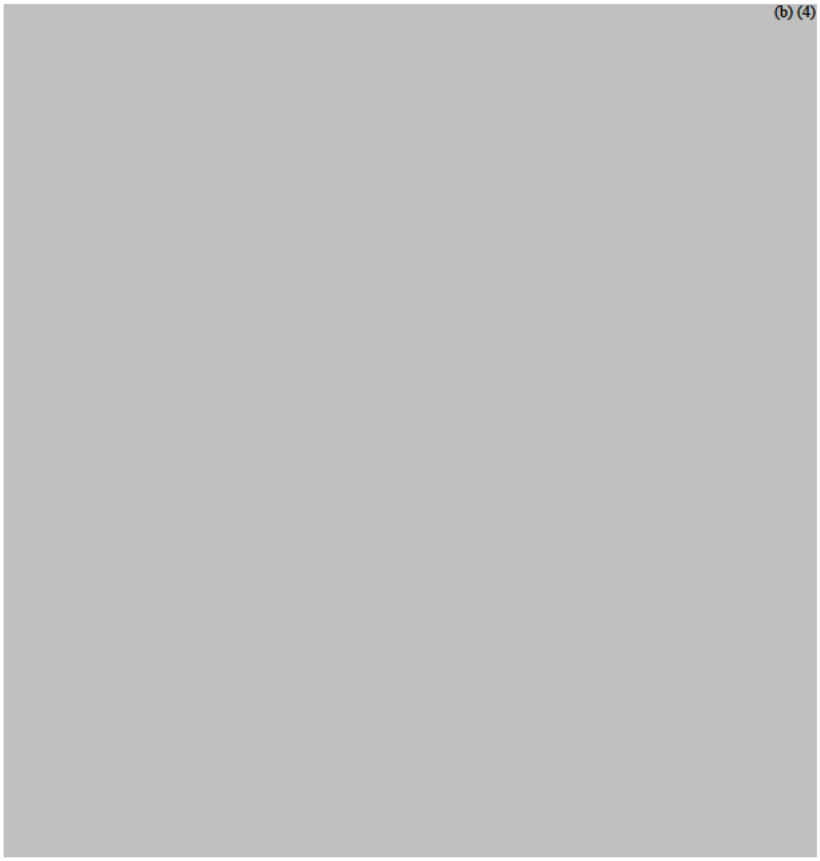
LABELING

R Regional Information

1.14 Labeling

Immediate Container Labels

The applicant proposed to market 2.5 (b) (4) and 5 (b) (4) strength vials but both contain the same drug concentration (2.5 mg/mL). In the initial NDA submission, the applicant provided the following sample immediate container labels:



Not to scale: estimate 2.0" x 0.625" L x H

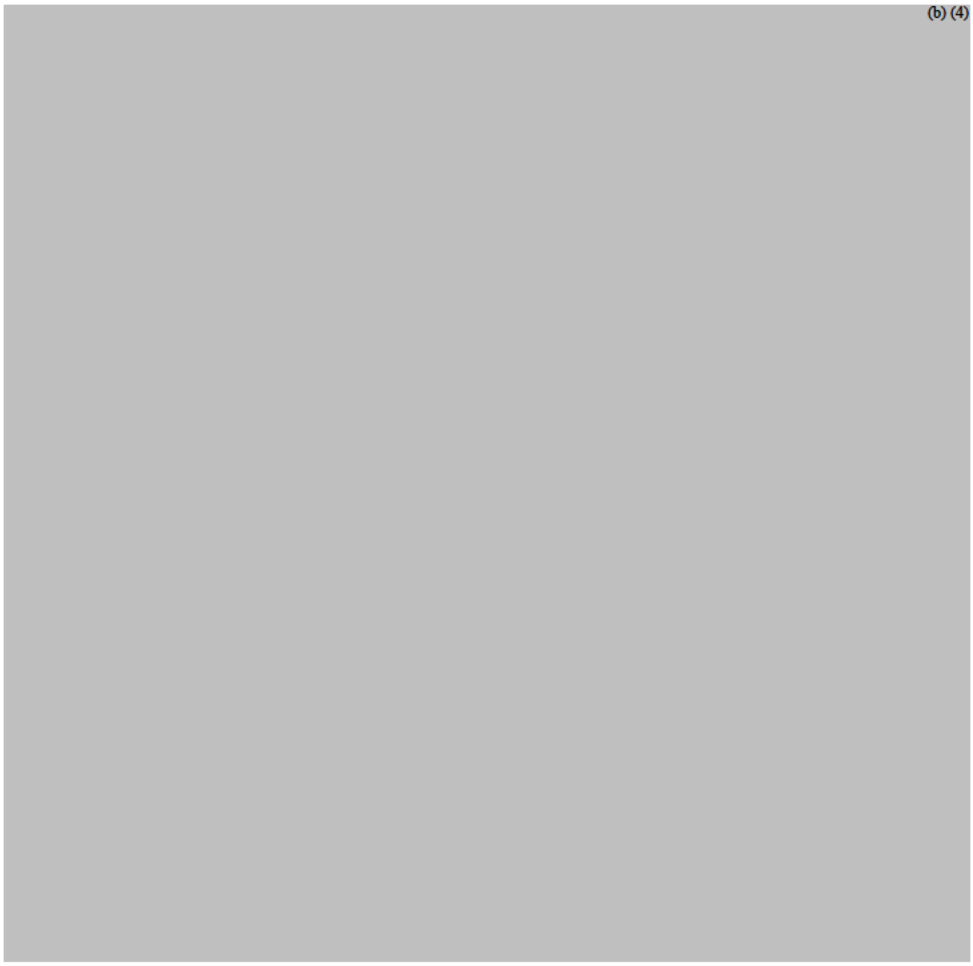
Reviewer's Assessment: The above sample container labels contain most of the required information and they are acceptable after the following recommended changes are incorporated into the final container labels:

1) **Since the tradename "(b) (4)" is not acceptable to DMEPA, it should be changed to a mutually agreeable name.**

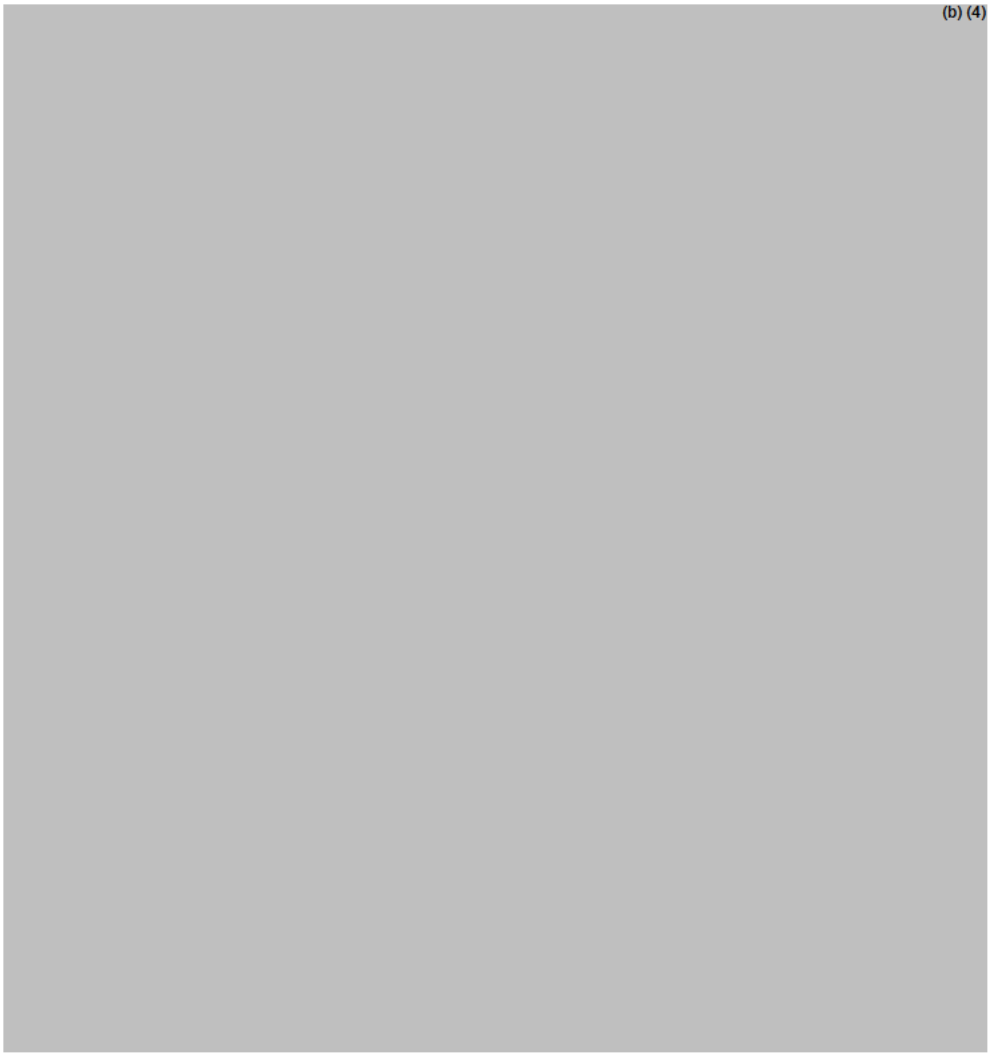
2) Strength should be expressed by providing the total quantity per total volume followed by the concentration per mL, therefore, strength should be changed to as follows:
   Remove "(b) (4)" and replace it with "2.5 mg/mL".
   Remove "(b) (4) and replace it with "5 mg/2mL (2.5 mg/mL)".
3) Prominence of the established name "angiotensin II" should be at least 50% of the tradename.
4) Storage statement should also include foreign height units, therefore, the statement should be changed to "Store at 2° to 8°C (36° to 46°F)".
5) Since the drug product solution is made by using angiotensin II acetate salt, a free base equivalency statement should be included.

Carton Labeling: *Sample carton labels were provided for the 2.5 (b) (4) and 5 (b) (4) strength vials.*

Carton of the 2.5 (b) (4) strength vial:



Carton of the 5 (b) (4) Strength Vial:



Reviewer's Assessment: The above sample carton labels contain most of the required information and they are acceptable after the following recommended changes are incorporated into the final carton labels:

1) **Since the tradename "(b) (4)" is not acceptable to DMEPA, it should be changed to a mutually agreeable name.**
2) **Strength should be expressed by providing the total quantity per total volume followed by the concentration per mL, therefore, strength should be changed to as follows:**
   Remove "(b) (4))" and replace it with "2.5 mg/mL".
   Remove "(b) (4)" and replace it with "5 mg/2mL (2.5 mg/mL)".
3) **Prominence of the established name "angiotensin II" should be at least 50% of the tradename.**
4) **Since the drug product solution is made by using angiotensin II acetate salt, a free base equivalency statement should be included.**

QUALITY ASSESSMENT

List of Deficiencies: None

Primary Labeling Reviewer Name and Date: Rao V. Kambhampati, Ph.D. 11/29/2017

Secondary Reviewer Name and Date: Wendy Wilson-Lee, Ph.D. 11/29/2017

Rao Kambhampati

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BIOPHARMACEUTICS

Product Background:

NDA 209360
NDA Type: 505 (b)(2), Priority; **Chemical Type:** New Molecular Entity

Drug Product Name / Strength: (b) (4) [LJPC-501 or Angiotensin II (A-II) Acetate] Injection; 2.5 mg/1 mL and 5 mg/2 mL (2.5 mg/mL as A-II peptide (b) (4) in vials for dilution with 0.9% NaCl Solution prior to use

Route of Administration: for IV Infusion
Proposed Indication: Treatment of hypotension in adults with distributive or vasodilatory shock who remain hypotensive despite fluid and vasopressor therapy
Proposed Dosage: Initially, 20 ng/kg/min. Then, titrate as frequently as every 5 min by increments of (b) (4) ng/kg/min as needed to maintain target blood pressure.

Applicant Name: La Jolla Pharmaceutical Co, Inc.

Background:
Angiotensin II is an 8-amino acid, endogenous peptide with hypertensive activity. The Angiotensin II acetate drug substance is soluble in water and pH 2 and pH 9 aqueous solutions, and slightly soluble in pH 7 aqueous solutions (b) (4) (LJPC-501 or Angiotensin II) Injection is an aqueous solution containing 2.5 mg/mL synthetic Ile^5-angiotensin II (human sequence) acetate, and 25 mg/mL mannitol in water, adjusted to pH 5.5.

This 505(b)(2) NDA relies mainly on the findings of the conducted Phase 3 clinical trial, *in vivo* animal hERG and CV Safety (GLP pharmacology) studies, *in vitro* pharmacodynamic (functional and receptor affinity) bridging and comparative analytical assessments, in addition to the submitted published literature for supportive efficacy and safety, nonclinical (toxicology/PK) and clinical pharmacology information. The API (synthetic Ile^5-angiotensin II acetate [human sequence]) of (b) (4) is being classified as a New Molecular Entity (NME) because it does not have exactly the same amino acid sequence, chemical form and origin as the previously marketed Hypertensin® (synthetic Val^5-angiotensin-II amide [bovine]; NDA 12-791].

Review Summary:

This Biopharmaceutics Review focused on the evaluation of the adequacy of information provided to bridge the clinical development formulations to the proposed to-be-marketed LJPC-501 drug product.

The proposed to-be-marketed drug product (b) (4) has the same formulation, solution concentration (2.5 mg/mL), presentation (5 mg/2 mL vial), API supplier, and manufacturing

process steps as the 5 lots (as well as the same manufacturing site as 2 of 5 lots) that were evaluated for efficacy, safety, and PK/PD in the pivotal Phase 3 clinical trial and for (registration) stability. Thus, bridging data *per se* with respect to the LJPC-501 formulation are not required.

Additionally, (as confirmed by the Drug Product Reviewer) stability bridging data support the addition of the 2.5 mg/1 mL vial presentation (to avoid waste, resulting in a larger headspace within the vial but with no difference in the formulation, solution concentration, and container closure system as compared to the 5 mg/2 mL vial).

A biowaiver request was not submitted nor required.

As previously agreed with FDA, bridging to the literature drug products (including those with different amino acid sequence and origin) was justified mainly using comparative in vitro functional and receptor binding data, which are evaluated by Pharmcology/ Toxicology review team.

Recommendation:
From the Biopharmaceutics perspective, NDA 209360 for (b) (4) (Angiotensin II) Acetate Injection is recommended for APPROVAL.

Bridging of LJPC-501 Formulations

Reviewer's Assessment: *NOT REQUIRED (for the Formulations)*

Bridging data *per se* for LJPC-501 Injection formulations are not needed because the formulation/concentration (2.5 mg/mL), manufacturer (b) (4) and process steps of the proposed to-be-marketed drug product are the same as those for the lots (FG-14-0168, LJP15008, LJP15018, 2451-101, 2451-102) evaluated in the pivotal Phase 3 clinical trial (LJ501-CRH01). Per the Applicant, there were no changes in the formulation of LJPC-501 during clinical development. [Note that some clinical lots of LJPC-501 (5 mg/vial) used in the early stage of the Phase 3 study were manufactured at comparable scale (b) (4) L) by (b) (4) using the same unit operations and in-process controls as (b) (4) (manufactured at a scale of (b) (4) L); (b) (4) proposed commercial scale is (b) (4) L, i.e., (b) (4) times the manufacturing scale for the clinical trial and registration (stability) lots. The Applicant stated that a comparative analysis of the manufacturing unit operations, specifications and batch analysis data demonstrates the comparability of the LJPC-501 clinical trial lots produced at these three manufacturing sites; refer to the Drug Product and the Process/Facilities Reviews for the evaluation of the comparability assessment across manufacturing sites, as provided in in 3.2.P.2.3.].

Note that two of the (b) (4) manufactured Phase 3 clinical lots [2451-101, 2451-102] are also registration (stability) lots. Additionally, one lot manufactured by (b) (4) was split and filled into 5 mg/vial and 2.5 mg/vial sub-lots #2451-25 and 2451-5, respectively, for use in a bridging stability study. Per the Applicant, the Assay and the Degradants data during 6 months

accelerated stability testing of inverted and upright vials demonstrated comparability of the two proposed presentations in terms of stability (in addition to formulation composition and container-closure system). Note that the 2.5 mg/vial presentation was developed to avoid waste during clinical use (since it had been observed during the clinical trial that most patients did not require the full contents of the 5 mg/vial).

The proposed commercial drug substance manufacturer ((b) (4)) is the same as used for the API of the Phase 3 clinical lots.

Bridging between the proposed and listed drug or literature formulations of Angiotensin II

As previously agreed with FDA, bridging to the literature drug products (including those with different amino acid sequence and origin; see Table 1 below) was justified mainly using comparative *in vitro* functional and receptor binding data generated by the Applicant. The Applicant stated that comparable EC_{50} values for the AT1 receptor and comparable IC_{50} values for the AT2 receptor were shown by LJPC-501 (containing human ile-5 angiotensin II acetate as API), (b) (4) bovine val-5- angiotensin II acetate (b) (4) *[research grade] human Ile^5-angiotensin II acetate* (b) (4) . Per the Pharmacology/Toxicology Reviewer LJPC-501 exhibits comparable *in vitro* functional and receptor binding activities to (b) (4) human and bovine Angiotensin-II.

Table 1. Comparison of Proposed and Literature Formulations of Angiotensin II

Product	**LJPC-501**	**Hypertensin**	**Human Angiotensin II acetate** (b) (4)	**Bovine angiotensin II acetate** (b) (4)
Manufacturer	(b) (4)	Ciba	(b) (4)	
API Form (origin)	Ile^5-angiotensin II acetate (human)	Val^5-angiotensin II amide (bovine)	Ile^5-angiotensin II (human)	Val^5-angiotensin II (bovine)
API Amino Acid Sequence	**Asp^1**-Arg-Val-Tyr-**Ile^5**-His-Pro-Phe^8 [a]	**Asn^1**-Arg-Val-Tyr-**Val^5**-His-Pro-Phe^8	**Asp^1**-Arg-Val-Tyr-**Ile^5**-His-Pro-Phe^8	**Asp^1**-Arg-Val-Tyr-**Val^5**-His-Pro-Phe^8
Formulation	2.5 mg/mL angiotensin II, 25 mg/mL mannitol, pH 5.5	(b) (4)		

[a] Ile^5-angiotensin II used to manufacture LJPC-501 is identical to the endogenous human form of angiotensin II.
Source: Adapted from Sections 2.6.1 and 2.7.1

Note that Hypertensin® (NDA 12-791) was the product used in 73% (11/15) of the submitted medical/clinical literature studies and in 39% (9/23) of the submitted nonclinical literature studies (see Table 1 of Section 1.2). However, it was not possible for the Applicant to conduct a direct side-by-side analytical and *in vitro* pharmacodynamic comparability assessment between the proposed drug product (LJPC-501) and the Ciba-Geigy reference product, Hypertensin®

because the once "Listed Drug" is no longer marketed. Nevertheless, the Applicant had provided information that when taken together would facilitate establishing an indirect bridge between the proposed and the reference drug products: (1) (b) (4) (b) (4) (b) (4) (2) Based on the results of compatibility studies conducted by the Applicant (Section 3.2.P.2.6), once diluted with 0.9% NaCl solution, the injectable LJPC-501 solution takes on the pH (~5.5) and osmolality (~ 290 mOsm/kg) of the vehicle. The LJPC-501 solution demonstrated physical and chemical stability up to 18 months of long-term storage (at 5 ± 3°C; Section 3.2.P.8). (3) Based on literature studies, the *in vivo* biological activities and the metabolic clearance rates of Ile^5-angiotensin II (produced by (b) (4)) and Val^5-angiotensin II [amide] (Hypertensin®, by Ciba, Basel) were reported to be similar (Oelkers 1975; Donato 1972); the plasma half-life for both Angiotensin-II products was reported to be < 1 minute consistent with the half-life reported by Magness (1994) following IV administration of Hypertensin® in pregnant and nonpregnant females, and (as confirmed by the Clinical Pharmacology Reviewer) by Admiraal (1993) following administration of (b) (4) Ile^5-Ang II. (4) In the pivotal Phase 3 clinical trial for the proposed drug product [LJPC-501], the observed lack of a difference in plasma Angiotensin II concentrations between baseline and post-3-hour infusion (as confirmed by the Clinical Pharmacology Reviewer) is consistent with the reported short half-life of exogenously administered Ile^5- and Val^5- forms of Ang II. (5) In *in vitro* studies conducted by the Applicant (Section 2.6.2), LJPC-501 solution, (b) (4) human Ile^5-angiotensin II acetate and (b) (4) bovine Val^5-angiotensin II acetate (b) (4) were all shown to possess comparable functional and receptor binding activities (as confirmed by the Pharmacology/Toxicology Reviewer). (b) (4) (6) The amino acid sequence, chemical form, and origin of LJPC-501's proposed commercial API (b) (4) (see Table 1 above). (7) [Of note, Kono (1985) reported that the Ile^5-Ang II purchased from the (b) (4) exhibited stronger and more prolonged pressor activity in humans than Hypertensin®.] Any small differences in pharmacodynamic activites between the proposed product and Hypertensin® is likely not clinically significant because Angiotensin-II is administered under a controlled clinical setting and the dosage is titrated (as frequently as every 5 minutes, per the Phase 3 study protocol and Section 2.2 of the proposed US Package Insert) until the desired hypertensive effect in the patient is achieved. Note that Sections 2.2 and 5.0 of the labeling of (b) (4)® state the requirement for close blood pressure monitoring every 5 minutes to guide dosage titration. For the evaluation of the comparative CMC data submitted, refer to the Drug Product Review.

QUALITY ASSESSMENT

Biowaiver Request

Reviewer's Assessment: *NOT APPLICABLE*

An *in vivo* biowaiver request is not needed for this 505(b)(2) NDA because LJPC-501 efficacy and safety were evaluated, and serum concentrations of Angiotensin I and Angiotensin II were measured (i.e., at baseline and 3 hours) in the Phase 3 clinical trial. Published literature studies using other sources/forms of Angiotensin II were provided as supportive evidence. Per agreement with FDA, dedicated clinical pharmacology (e.g., BA and food-effect) studies were not conducted (since LJPC-501 is a naturally occurring peptide administered via IV infusion, the administered drug is cleared rapidly, and the dose is titrated to effect).

List of Deficiencies:

None

Primary Biopharmaceutics Reviewer:

Gerlie Gieser, Ph.D. (11/17/2017)

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Jing Li, Ph.D. (11/22/2017)

Gerlie Gieser

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Jing Li

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MICROBIOLOGY

Product Background:

NDA: 209360

Drug Product Name / Strength: (b) (4) (angiotensin II) injection (LJPC-501)/2.5 mg angiotensin II /vial (2.5 mg/mL), 5.0 mg angiotensin II /vial (2.5 mg/mL)

Route of Administration: Intravenous infusion

Applicant Name: La Jolla Pharmaceutical Company
10182 Telesis Court
6th Floor, San Diego, CA 92121
Tel: 858-207-4264
Fax: 858-225-6210

Manufacturing Site: (b) (4)

Method of Sterilization: (b) (4)

Review Summary: Recommended for approval

List Submissions Being Reviewed: 6/29/2017; 10/31/2017

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: An IR dated 10/23/2017 to address minor deficiencies was conveyed to the sponsor following Product Quality Microbiology review. The information provided in the amendment dated 10/31/2017 in response to the IR is incorporated in the review.

Concise Description Outstanding Issues Remaining: N/A

Supporting Documents: Microbiology review D11648M33R01.doc (adequate) dated 2/3/2017 was referenced for (b) (4) process.

S Drug Substance

Reviewer's Assessment:

(b) (4)

(b) (4)

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** Sterile, aqueous solution in 3 mL single-use vials in 2 different strengths, 2.5 mg angiotensin II /vial (2.5 mg/mL) and 5 mg angiotensin II /vial (2.5 mg/mL)
- **Drug product composition –**

Components	Quality Standard	Function	Quantity per mL	Drug Product Strength	
				2.5 mg/vial	5 mg/vial
Angiotensin II	In-house	Active Ingredient	2.5 mg	2.5 mg	5 mg
Mannitol	USP/Ph.Eur.	(b) (4)	25 mg	25 mg	50 mg
WFI	USP/Ph.Eur.				(b) (4)
(b) (4) NaOH	NF/Ph.Eur.	pH Adjustment	q.s.	q.s.	q.s.
(b) (4) HCl	NF/Ph.Eur.	pH Adjustment	q.s.	q.s.	q.s.
			Total:		(b) (4)

q.s.=quantum satis (amount needed)

- **Description of container closure system –**

The same container closure system is used for both of the strengths, 2.5mg/vial (b) (4) 1 mL fill volume) and 5 mg/vial ((b) (4) 2 mL fill volume).

Component	Manufacturer	Description
Vial	(b) (4)	3 mL, 13 mm diameter, clear glass vials, USP/Ph.Eur. Type (b) (4) glass
Stopper		(b) (4) gray 13 mm elastomeric stopper (b) (4) (b) (4)
Seal		13 mm diameter aluminum closure with plastic flip-off cap (non-product contacting)

Exhibit batch (drug product regional information.pdf):
2451-103 (5 mg/vial): (b) (4)
2457-102 (2.5 mg/vial) (b) (4)

Proposed commercial batch (p2/13 in 3.2.P.3.3):
2.5 mg/vial: (b) (4)
5 mg/vial: (b) (4)

Reviewer's Assessment:

The sponsor provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

Acceptable

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The application provided an adequate description of the finished drug product package insert.

Acceptable

Primary Microbiology Reviewer Name and Date:
Jianli Xue, Ph.D.
Microbiologist
CDER/OPQ/OPF/DMA
11/27/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Nandini Bhattacharya, Ph.D.,
Microbiologist
CDER/OPQ/OPF/DMA
12/4/2017

Jianli Xue

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