

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204485Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

NDA # 204-485 (Division of Cardiovascular and Renal Products)
 Date: 18-Oct-2013, Resubmission
 Product Name: Vasostrict™ (vasopressin injection, USP)
 Company Name: Par Sterile Products, LLC
 Subject: Overall OC Recommendation
 Updated Drug Product Specification (Amendment 28-Mar-2014)
 Updated Labeling (Amendment 28-Mar-2014)

Overall Recommendation

Pursuant the overall **Acceptable OC Recommendation** issued on 04-Apr-2014 (refer to attachment to this Memo), the overall quality recommendation is for “approval”.

Updated Drug Product Specification

The applicant has provided the following updated drug product specification.

Revised Release and Shelf Life Drug Product Specification

Test	Methods	Release Limits	Shelf Life Limits
Description	00215	A 3 mL vial containing a clear, colorless to practically colorless solution, essentially free of visible particulates	A 3 mL vial containing a clear, colorless to practically colorless solution, essentially free of visible particulates
pH	31636	2.5 – 4.5	2.5 – 4.5
Volume in Container	95204	NLT (b) (4)	Not Applicable
Identification (HPLC)	20545	Positive The UV spectrum of the peak in the sample matches the vasopressin peak in standard	Not Applicable
Chlorobutanol	20451	(b) (4)	
Assay (HPLC)	20545	(b) (4)	
Degradation products	20545	NMT (b) (4) %	NMT (b) (4) %
(b) (4)		NMT (b) (4) %	NMT (b) (4) %
		NMT (b) (4) %	NMT (b) (4) %
		NMT (b) (4) %	NMT (b) (4) %
		NMT (b) (4) %	NMT (b) (4) %
		NMT (b) (4) %	NMT (b) (4) %
Total Degradation Products		NMT (b) (4) %	NMT (b) (4) %
Particulate Matter (USP <788> Method 1)	07020	NMT (b) (4) μm NMT (b) (4) μm	NMT (b) (4) μm NMT (b) (4) μm
Bacterial Endotoxin	60570	NMT (b) (4)	NMT (b) (4)
Sterility	80200	Passes Test	Passes Test

Evaluation: Adequate. The firm has revised the limits for several test parameters in the shelf-life and release specifications to make both specifications identical except for the levels of Total Degradation Products that are different. In the release specification, revision of the pH and Assay acceptance criteria was made, and in the shelf-life specifications the revision of the acceptance criteria for Assay and for chlorobutanol was made. The limits for Assay comply with the USP requirements in both sets of the specifications. All revisions in the shelf-life and release specifications are acceptable.

Structured Product Labeling (SPL)

The applicant has provided the updated Product Data Elements (PDE) in the Structured Product Labeling (SPL) text.

Evaluation: Adequate.

Carton/Container Labels

The applicant has removed the word “synthetic” from the drug product container and carton labels, as requested. Acceptable.

Recommendation and Conclusion on Approvability

NDA 204-485 for Vasostriect™ (vasopressin injection, USP), 20 units /ml, is recommended for APPROVAL from a Chemistry, Manufacturing and Controls standpoint. The drug substance DMF (b) (4) remains adequate. Based on the drug product stability data, the 12-month expiration dating period is recommended for drug product stored in the proposed container/closure system at the recommended storage condition, between 15°C and 25°C (59°F and 77°F)”. The overall Acceptable OC recommendation for drug substance and drug product facilities is issued on 04-Apr-2014.

Attachment

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application:	NDA 204485/000	Sponsor:	PAR STERILE PRODUCTS
Org. Code:	110		1 UPPER POND RD BLDG D 3RD FL
Priority:	7		PARSIPPANY, NJ 07054
Stamp Date:	26-SEP-2012	Brand Name:	VASOSTRICT
PDUFA Date:	18-APR-2014	Estab. Name:	
Action Goal:		Generic Name:	VASOPRESSIN INJECTION
District Goal:	27-MAY-2013	Product Number; Dosage Form; Ingredient; Strengths	001; INJECTION; VASOPRESSIN; 20UNT/1ML

FDA Contacts:	L. SOLDATOVA	Prod Qual Reviewer	3017961758
	E. PFEILER	Micro Reviewer (HF-22)	3017960642
	T. BOUIE	Product Quality PM	3017961649
	Q. NGUYEN	Regulatory Project Mgr (HFD-110)	3017960510
	K. SRINIVASACHAR	Team Leader	3017961760

Overall Recommendation:	ACCEPTABLE	on 04-APR-2014	by R. SAFAAI-JAZI	()	3017964463
	PENDING	on 23-JAN-2014	by EES_PROD		
	PENDING	on 16-NOV-2013	by EES_PROD		
	PENDING	on 15-NOV-2013	by EES_PROD		
	ACCEPTABLE	on 08-JAN-2013	by EES_PROD		
	PENDING	on 26-DEC-2012	by EES_PROD		
	PENDING	on 26-DEC-2012	by EES_PROD		
	PENDING	on 23-OCT-2012	by EES_PROD		
	PENDING	on 23-OCT-2012	by EES_PROD		

Establishment:	CFN: (b) (4)	FEI: (b) (4)	
			(b) (4)
			(b) (4)
DMF No:		AADA:	
Responsibilities:	FINISHED DOSAGE RELEASE TESTER		
Profile:	CONTROL TESTING LABORATORY	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	24-OCT-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	CFN: (b) (4)	FEI: (b) (4)	
			(b) (4)
DMF No:		AADA:	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	27-DEC-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Attachment (Cont'd)

Establishment:	CFN: (b) (4)	FEI: (b) (4)
	(b) (4)	
DMF No:		AADA:
Responsibilities:	DRUG SUBSTANCE OTHER TESTER	
Profile:	CONTROL TESTING LABORATORY	OAI Status: NONE
Last Milestone:	OC RECOMMENDATION	
Milestone Date:	29-OCT-2012	
Decision:	ACCEPTABLE	
Reason:	BASED ON PROFILE	

Establishment:	CFN: 1818977	FEI: 1818977
	JHP PHARMACEUTICALS, LLC	
DMF No:	ROCHESTER, , UNITED STATES 483071740	AADA:
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER	
Profile:	FINISHED DOSAGE MANUFACTURER	
Profile:	CONTROL TESTING LABORATORY	OAI Status: NONE
Last Milestone:	OC RECOMMENDATION	
Milestone Date:	24-OCT-2012	
Decision:	ACCEPTABLE	
Reason:	BASED ON PROFILE	
Profile:	(b) (4)	OAI Status: NONE
Last Milestone:	OC RECOMMENDATION	
Milestone Date:	01-DEC-2013	
Decision:	ACCEPTABLE	
Reason:	DISTRICT RECOMMENDATION	

Establishment:	CFN: (b) (4)	FEI: (b) (4)
	(b) (4)	(b) (4)
DMF No:		AADA:
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER	
Profile:	CONTROL TESTING LABORATORY	OAI Status: NONE
Last Milestone:	OC RECOMMENDATION	
Milestone Date:	04-APR-2014	
Decision:	ACCEPTABLE	
Reason:	DISTRICT RECOMMENDATION	

Establishment:	CFN: (b) (4)	FEI: (b) (4)
	(b) (4)	(b) (4)
DMF No:		AADA:
Responsibilities:	DRUG SUBSTANCE OTHER TESTER	
Profile:	CONTROL TESTING LABORATORY	OAI Status: NONE
Last Milestone:	OC RECOMMENDATION	
Milestone Date:	18-NOV-2013	
Decision:	ACCEPTABLE	
Reason:	BASED ON PROFILE	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LYUDMILA SOLDATOVA
04/08/2014

OLEN M STEPHENS
04/08/2014

NDA 204-485

Vasostriect™(vasopressin injection, USP)

Par Sterile Products, LLC

Lyudmila N. Soldatova, Ph. D.
Office of New Drug Quality Assessment
for
Division of Cardiovascular and Renal Products

Review of Chemistry, Manufacturing, and Controls

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S DRUG SUBSTANCE [Name, Manufacturer].....	
P DRUG PRODUCT [Name, Dosage form].....	N/A
A APPENDICES	N/A
R REGIONAL INFORMATION	N/A
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	N/A
A. Labeling & Package Insert	N/A
B. Environmental Assessment Or Claim Of Categorical Exclusion	N/A
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Chemistry Review Data Sheet

1. NDA 204-485
2. REVIEW #: 2
3. REVIEW DATE: 18-March-2014
4. REVIEWER: Lyudmila N. Soldatova

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Chemistry Review Data Sheet

Resubmission	18-OCT-2013
Amendment	05-MAY-2013
Amendment	23-DEC-2013
Amendment	25-FEB-2014
Amendment	25-FEB-2014
Amendment	04-MAR-2014
Amendment	06-MAR-2014

7. NAME & ADDRESS OF APPLICANT:

Name: JHP Pharmaceuticals LLC
Morris Corporate Center 2
Address: One Upper Pond Road
Building D, 3rd Floor
Parsippany, NJ 07054
Representative: Gerald G. Vasquez, Manager Regulatory Affairs
Telephone: 973-658-3551

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Pitressin® Injection
- b) Non-Proprietary Name (USAN): Vasopressin Injection, USP
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 7
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Treatment of vasodilatory shock, including post-cardiotomy shock and septic shock.

11. DOSAGE FORM: Sterile solution (injection)

Chemistry Review Data Sheet

12. STRENGTH/POTENCY: 1 ml/vial (20 pressor units)

13. ROUTE OF ADMINISTRATION: Intravenous Infusion

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

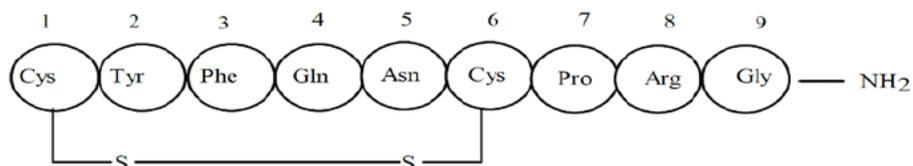
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Cyclo (1-6) L-Cysteinyl-L-Tyrosyl-L-Phenylalanyl-L-Glutaminyl-L-Asparaginyl-L-Cysteinyl-L-Prolyl-L-Arginyl-L-Glycinamide.

Molecular Formula: C₄₆H₆₅N₁₅O₁₂S₂

Molecular Weight:

1084.23



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	Review #2 12-Feb-2014	Drug substance
	III			3	Adequate	N/A	Container/ closure

Chemistry Review Data Sheet

(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	N/A	Container/ closure
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¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no relevant revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		Office of Compliance
Pharm/Tox	Approvable	10-Apr-2013	Rama Dwivedi, Ph.D.
Biopharm	Approval	15-Mar-2013	Elsbeth Chikhale, Ph.D.
DMEPA	Proprietary name, Vasostriect is acceptable	06-Feb-2014	Janine Stewart, Pharm.D.
DMEPA	Container & Carton Labels: Acceptable	27-Feb-2014	Janine Stewart, Pharm.D.
Methods Validation	Acceptable	As per this Review	Lyudmila Soldatova, Ph.D.
EA	Categorical Exclusion is granted	1-May-2013	Lyudmila Soldatova, Ph.D.
Microbiology	Approval	08-Apr-2013 03-Dec-2013	Erika Pfeiler, Ph.D.

The Chemistry Review for NDA 204-485

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 204-485 for Vasostrict™ (vasopressin injection, USP), 20 units /ml, is recommended for APPROVAL from a Chemistry, Manufacturing and Controls standpoint pending the overall OC recommendation. The drug substance DMF (b) (4) remains adequate. Based on the drug product stability data, the 12-month expiration dating period is recommended for drug product stored in the proposed container/closure system at the recommended storage condition, between 15°C and 25°C (59°F and 77°F).

The overall OC recommendation for drug substance and drug product facilities is currently pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None as per this review.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Refer to the Review #1 dated 09-May-2013 for this NDA regarding the description of the Drug Product and Drug Substance.

The NDA received a complete response action in the first cycle of NDA primarily due to CMC deficiencies. In this NDA resubmission, the applicant has provided response to the deficiencies outlined in the CR Letter and an information request issued on 07-Feb-2014 during this review cycle. The response to these information requests addressed all CMC issues, and no more unresolved deficiencies remain.

The major issues in this NDA submission were: the acceptance criterion for Assay in the shelf-life specifications, the lack of the stability data for the proposed product without overages, and the expiration period. The other issues related to several impurities/degradants were resolved based on the adequate responses.

Regarding the limits for Assay in the shelf-life specifications, JHP has updated the drug product specification from (b) (4) to 90.0% - 110.0% of Vasopressin Units, which is consistent with USP monograph for Vasopressin Injection. In the resubmitted NDA, the applicant has provided the 12-month stability data for three primary stability batches produced without the overages that were stored at the long term (25°C/ 65% RH), intermediate (30°C/ 75% RH), and accelerated (40°C/ 75% RH; 3-month data) conditions. The recommended storage condition is: between 15°C and 25°C (59°F and 77°F). The statistical evaluation of the 12-month stability

Executive Summary Section

data for primary stability batches without overages concluded that 13 months of expiration period could be granted. This expiry period is limited primarily due to the failure of Assay to comply with the acceptance criteria of (b)(4). Due to significant changes at the accelerated conditions after 3 month and out-of-spec stability data for assay at 12 months of storage at the intermediate conditions, the expiry cannot be extrapolated as per ICH Q1E. As a result, a 12 months expiration dating period can be granted for drug product. It should be noted that the applicant was advised to explore the possibility of storage the product at 5°C. JHP has provided the 9-month stability data for three batches stored at 5°C that demonstrates that the drug product without overages is more stable at the refrigerated condition, as was expected for this peptide product. However, in response to advice, the applicant clarified that “given that the drug product is kept in rapid-use settings such as the ICU or ambulances, a room temperature shelf life is needed”, and rejected the option of storage of the product at the refrigerated condition. The applicant, JHP Pharmaceuticals, LLC has changed their name to Par Sterile Products, LLC. Regarding the drug substance, DMF (b)(4) remains Adequate; the DMF holder has provided the adequate response to the Information Request in the Review #1 for this DMF. An overall acceptable OC recommendation for drug substance and drug product facilities is currently pending.

B. Description of How the Drug Product is Intended to be Used

Vasostriect® (vasopressin injection, USP), was developed by JHP Pharmaceuticals, LLC. for the Treatment of vasodilatory shock, including post-cardiotomy shock and septic shock. Dilute Vasostriect® in normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W) prior to use. Discard unused diluted solution after 18 hours at room temperature or 24 hours under refrigeration.

For post-cardiotomy shock, start with a dose of 0.03 units/minute. For septic shock, start with a dose of 0.01 units/minute. If the target blood pressure response is not achieved, titrate up by 0.005 units/minute at 10-15 minute intervals. The maximum dose for post-cardiotomy shock is 0.1 units/minute and for septic shock 0.07 units/min. After target blood pressure has been maintained for 8 hours without the use of catecholamines, taper Vasostriect® by 0.005 units/minute every hour as tolerated to maintain target blood pressure.

C. Basis for Approvability or Not-Approval Recommendation

NDA 204-485 is recommended for APPROVAL from CMC standpoint pending the overall OC recommendation. The NDA received a complete response action in the first cycle of NDA; the deficiencies listed in the CR Letter have been resolved in the resubmitted NDA. The drug substance DMF (b)(4) remains Adequate. An overall acceptable OC recommendation for drug substance and drug product facilities is currently pending.

III. Administrative**A. Reviewer's Signature**

Lyudmila N. Soldatova

Executive Summary Section

B. Endorsement Block

Chemist: Lyudmila Soldatova, Ph.D./XX-FEB-2014
CMC Branch Chief: Olen Stephens, Ph.D.
CMC Lead: Kasturi Srinivasachar, Ph.D.

C. CC Block

Quality Project Manager: Yvonne Knight
Clinical Project Manager: Nguyen Quynh

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/s/

LYUDMILA SOLDATOVA
03/18/2014

OLEN M STEPHENS
03/18/2014

NDA 204-485

Pitressin® Vasopressin Injection, USP

JHP Pharmaceuticals, LLC

Lyudmila N. Soldatova, Ph. D.
Office of New Drug Quality Assessment
for
Division of Cardiovascular and Renal Products

Review of Chemistry, Manufacturing, and Controls

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Chemistry Review Data Sheet

1. NDA 204-485
2. REVIEW #: 1
3. REVIEW DATE: 01-MAY-2013
4. REVIEWER: Lyudmila N. Soldatova

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

26-SEP-2012

Amendment

01-FEB-2013

Amendment

19-FEB-2013

7. NAME & ADDRESS OF APPLICANT:

Name: JHP Pharmaceuticals LLC

Address: Morris Corporate Center 2
One Upper Pond Road
Building D, 3rd Floor
Parsippany, NJ 07054

Representative: Gerald G. Vasquez, Manager Regulatory Affairs

Chemistry Review Data Sheet

Telephone: 973-658-3551

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Pitressin® Injection
- b) Non-Proprietary Name (USAN): Vasopressin Injection, USP
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 7
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Treatment of vasodilatory shock, including post-cardiotomy shock and septic shock.

11. DOSAGE FORM: Sterile solution (injection)

12. STRENGTH/POTENCY: 1 ml/vial (20 pressor units)

13. ROUTE OF ADMINISTRATION: Intravenous Infusion

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

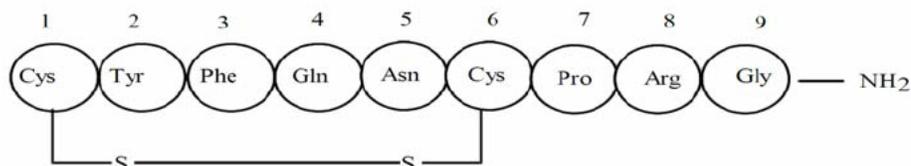
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemistry Review Data Sheet

Chemical Name: Cyclo (1-6) L-Cysteinyl-L, Tyrosil-L, Phenylalanyl-L-Glutaminyl-L-Asparaginyl-LCysteinyl-L-Propyl-L-Arginyl-L-Glycineamide

Molecular Formula: C₄₆H₆₅N₁₅O₁₂S₂

Molecular Weight: 1084.23



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Inadequate	Pending upon response to Deficiency Letter	Drug substance
	III			3	Adequate	N/A	Container/closure
	III			3	Adequate	N/A	Container/closure

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no relevant revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
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Chemistry Review Data Sheet

N/A		
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18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Overall Acceptable	08-JAN-2013	Office of Compliance
Pharm/Tox	Approvable	10-APR-2013	Rama Dwivedi, Ph.D.
Biopharm	Approval	15-MAR-2013	Elsbeth Chikhale, Ph.D.
LNC	Pending		DMEPA
Methods Validation	Pending	As per this Review	Lyudmila Soldatova, Ph.D.
OCP	Pending		Peter Hinderling, Ph.D.
EA	Categorical Exclusion is granted	1-MAY-2013	Lyudmila Soldatova, Ph.D.
Microbiology	Approval	08-APR-2013	Erika Pfeiler, Ph.D.

The Chemistry Review for NDA 204-485

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 204-485 for Vasopressin Injection, USP cannot be approved in its current form from the CMC standpoint. The approval is contingent upon satisfactory resolution of the drug substance DMF (b) (4) deficiencies, and drug substance and drug product deficiencies summarized in the IR Letter dated 07-Mar-2013.

The Overall Acceptable OC recommendation for drug substance and drug product manufacturing facilities was made on 08-Jan-2013.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None as per this review.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The JHP Pharmaceutical's currently marketed product Pitressin® (vasopressin injection) is the same product initially manufactured and marketed by Parke-Davis for over 100 years, as per applicant's statement. The therapeutic indication is a treatment of vasodilatory shock, including postcardiotomy shock and septic shock. The original formulation contained (b) (4)

(b) (4) the drug product Pitressin® (vasopressin injection) proposed in this NDA submission is a drug product without overages. The dosage form is a sterile solution for injection/intravenous administration. The strength of the Pitressin is 20 pressor units/ml that corresponds to 0.0377 mg vasopressin/ml. The 1 ml of drug product Pitressin contains a 0.5% of preservative chlorobutanol in water for injection and acetic acid for pH adjustment. The excipients used in the formulation are USP/NF grade including acetic acid. The pH is a critical parameter in the Pitressin formulation; in the pH range of 3.4 – 3.6, the vasopressin acid salt is relatively stable in water, and degradation accelerates at the pH that is above and below this range. Antimicrobial effectiveness of chlorobutanol has been established in accordance with USP <51>, and it was found acceptable according to evaluation by Microbiology reviewer. The container closure system consists of a 3 ml (b) (4) Type I USP glass vial with a (b) (4) stopper and (b) (4) cap. The confirmatory photostability study confirmed that the current market packaging provide adequate photo-protection. The microbiological evaluation of the container/closure integrity was performed by Microbiology Reviewer, and it was found adequate. Compatibility study demonstrated that Pitressin appears to

Executive Summary Section

be incompatible with 5% dextrose as diluent/intravenous solution; it is reflected in the Package Insert. Pitressin is manufactured by (b) (4)

(b) (4) (u) (4). The sterility assurance of the drug product after manufacturing and maintenance of sterility over the shelf-life is evaluated in the Microbiology Review. (b) (4)

However, the release and shelf-life specification are different from each other, and different from those provided in the USP Monograph for Vasopressin Injection (except for pH limit at shelf-life); these include pH, assay, impurities and chlorobutanol content; also, the shelf-life limits for some impurities are very high. The applicant was requested in the IR letter to resolve this issue. The batch analysis for three commercial size registration batches demonstrate compliance of all test results with the proposed specifications; the drug product produced both with and without overages utilizes the same manufacturing process. The three-month primary stability data (long-term, intermediate and accelerated) have been submitted for 2 batches in the upright and inverted configurations, and the two-month data are for the third batch. Supportive stability data (9-24 months long-term, 12-month intermediate, and 6-month accelerated stability data) for representative historical commercial drug product manufactured with overages are provided. The additional 9-month stability data should have been submitted by mid-cycle review time. The accelerated studies will only be carried out for 3 months since the product is known to be unstable with assay and impurities going out of specification limits under these conditions. The applicant claims the (b) (4) months expiration dating period based on all available stability data. The provided 2-3 months stability data for primary stability batches are not sufficient to grant the expiration date for drug product Pitressin.

The sponsor is referencing (b) (4) DMF (b) (4) for information on the drug substance vasopressin. The original DMF (u) (4) was reviewed by this reviewer, and it was found to be currently Inadequate: IR was sent to DMF holder. Vasopressin is a polypeptide hormone having the properties of causing the contraction of vascular and other smooth muscles, and of antidiuresis (neurohypophyseal antidiuretic hormone). At (b) (4) vasopressin is obtained by synthesis. The partial information on drug substance is provided in the submitted NDA. The proposed specification for vasopressin are based on the USP monograph but this set of tests and limits is not sufficient for release of vasopressin API. Additional tests and limits should be included in the specification; this request was included in the IR letter. In addition, deficiencies were identified for analytical methods used by drug product manufacturer, JHP Pharmaceuticals, to test the drug substance. The batch analysis of the Batches VP1001 and VP1002-1 complies with the limited drug substance specifications by JHP. However, comparison of the CoAs of these batches issued by (b) (4) and by JHP demonstrates discrepancy in the test results for assay and for total impurities; the IR letter includes this issue as well.

B. Description of How the Drug Product is Intended to be Used

The subject of the NDA is Pitressin® (vasopressin injection), being developed by JHP Pharmaceuticals, LLC. for the Treatment of vasodilatory shock, including post-cardiotomy shock and septic shock.

Executive Summary Section

Proposed Pitressin Administration

Pitressin® should be diluted to a concentration of .1 unit/mL to 1.0 unit/mL with normal saline (0.9% sodium chloride) for intravenous administration. Pitressin® is incompatible with 5% dextrose (D5W) and this diluent should NOT be used to dilute Pitressin®. Discard unused diluted solution after 18 hours at room temperature or 24 hours under refrigeration.

C. Basis for Approvability or Not-Approval Recommendation

NDA 204-485 cannot be approved as submitted from the CMC standpoint. The outstanding issues that need to be resolved include deficiencies in the DMF (b) (4), the drug substance and drug product deficiencies in the submitted NDA summarized in the IR Letter, and insufficient amount of stability data for primary stability batches for granting the expiration dating period.

III. Administrative**A. Reviewer's Signature**

Lyudmila N. Soldatova

B. Endorsement Block

Chemist:	Lyudmila Soldatova, Ph.D./01-MAY-2013
CMC Branch Chief:	Ramesh K. Sood, Ph.D.
CMC Lead:	Kasturi Srinivasachar, Ph.D.

C. CC Block

Quality Project Manager: Teshara Bouie
Clinical Project Manager: Nguyen Quynh

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

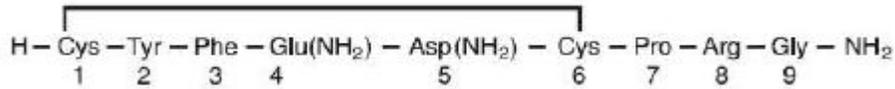
LYUDMILA SOLDATOVA
05/08/2013

RAMESH K SOOD
05/09/2013

Initial Quality Assessment
Branch I

OND Division: Division of Cardiovascular and Renal Products
NDA: 204485
Applicant: JHP Pharmaceuticals, LLC
Letter Date: Sep 25, 2012
Stamp Date: Sep 26, 2012
PDUFA Date: July 26, 2013
Tradename: Pitressin
Established Name: Vasopressin Injection
Dosage Form: Sterile solution (injection), 1 mL/ vial (20 pressor units)
Route of Administration: IV infusion
Indication: Treatment of vasodilatory shock, including post-cardiotomy shock and septic shock

Assessed by: Kasturi Srinivasachar
ONDQA Fileability: Yes



Summary

This is an e-CTD 505(b)(2) NDA application for Vasopressin injection. Vasopressin is a marketed unapproved drug and as agreed to at the pre-NDA meeting, a literature based review to support the proposed indication was considered sufficient in lieu of clinical studies. Only one meeting, a pre-NDA teleconference, was held with the Applicant on Oct. 17, 2011 but no CMC issues were discussed. However, on the same date another pre-NDA meeting for the same drug and same sponsor but for a different indication was held with the Div. of Metabolism and Endocrine Products which involved discussion of CMC and Microbiology issues. Since the sponsor had indicated that NDAs would be submitted simultaneously to both DCRP and DMEP, it was decided that the CMC section would be reviewed by DMEP. CMC issues discussed related to the adequacy of drug substance and drug product specifications and the amount of stability data that would be available at the time the NDA is submitted. The applicant was informed that an overage ^{(b) (4)} was not acceptable solely to allow for stability losses regardless of whether one was used historically in the marketed unapproved product. They were also told that the proposed degradation levels of up to ^{(b) (4)}% over the shelf-life were very high and measures to either stabilize the formulation or storage at lower temperature should be considered. Microbiology issues discussed mainly concerned the proposed drug product endotoxin limits and the need for justification of ^{(b) (4)}. The applicant reversed their original position and submitted only this NDA for the treatment of vasodilatory shock to DCRP. Since they have no plans at this time to submit an NDA to DMEP, the CMC section will be reviewed by Branch 1 in ONDQA.

Drug Substance

Vasopressin is a nonapeptide hormone having the properties of causing smooth muscle contraction and antidiuresis. In this application it is manufactured by ^{(b) (4)}

Vasopressin is a white powder with molecular formula $C_{46}H_{65}N_{15}O_{12}S_2$ and molecular weight of 1084.23. It contains a disulfide bridge between cysteines 1 and 6. There is an USP monograph for vasopressin. All CMC information i.e. characterization, manufacture, control strategy and stability is cross-referenced to DMF ^{(b) (4)}. This is a new DMF, submitted in Feb 2012, which has never been reviewed. The manufacturer and DMF holder is ^{(b) (4)}. Specifications for vasopressin are provided in the NDA which are essentially the same as the USP. Batch analysis data for several lots of drug substance have been provided. Based on the stability data in the DMF, a retest date of ^{(b) (4)} is proposed.

Drug Product

The Applicant states that Pitressin (vasopressin injection) currently marketed by JHP Pharmaceuticals is the same product initially manufactured and marketed by Parke-Davis for over 100 years. The marketed formulation contains ^{(b) (4)}. However, in response to Agency recommendations at the pre-NDA meeting, the product has been reformulated to contain no overages. The strength of the product is expressed in pressor units (20 units/mL) which corresponds to 0.0377 mg/mL vasopressin. 1 mL of the product containing acetic acid for pH adjustment and chlorobutanol preservative in water for injection is filled into 3 mL Type 1 glass vials. pH of the formulation is

a critical parameter since vasopressin acid salt is relatively stable in the range 3.4-3.6 but degradation accelerates if the pH is both above and below these values. Antimicrobial effectiveness of chlorobutanol has been established in accordance with USP <51>.

Pitressin is manufactured by (b) (4)

The container closure system proposed is identical to that used for the currently marketed product. It is stated that the glass vials meet USP <660> and the (b) (4) (b) (4) stopper formulation meets USP <381>. (b) (4)

The preservative chlorobutanol is tested with different assay limits for release and shelf-life. Batch data for 3 registration batches have been provided as well as executed batch records. Primary stability data have also been submitted for these 3 batches in the upright and inverted configurations at long term, intermediate and accelerated storage conditions. However, only 3 months' data for 2 lots and 2 months' data for the third lot were submitted in the NDA. The accelerated studies will only be carried out for 3 months since the product is known to be unstable with assay and impurities going out of specification limits under these conditions. Supportive stability data from 7 marketed batches (containing an overage) have been provided and the Applicant claims that stability trends are similar between the registration and marketed batches. Long term data from these supporting batches range from 9-24 months. The Applicant states that a (b) (4) month expiration dating period can be given taking into consideration all the available data.

Critical Review Issues

Drug Substance

- DMF (b) (4) is new and should be reviewed paying particular attention to impurity characterization, drug substance specifications etc. The requirements of the USP monograph for vasopressin are not sufficient since it lacks basic tests for peptides like amino acid composition and sequence. The requirements for impurity reporting are also minimal with only a total specified. It should be noted that peptides are not covered under ICH Q3A, however, vasopressin is a small peptide and therefore amenable to more thorough analysis. In the pre-NDA meeting with DMEP the Applicant was told to identify all impurities >0.5% and specify individual impurities with appropriate acceptance criteria.
- There is a significant difference between JHP and (b) (4) in assay and total impurities results for the same lot of drug substance. The JHP result for total impurities is (b) (4) % whereas the (b) (4) result is (b) (4) even though the JHP analysis was performed (b) (4) years later. The same trend is observed for assay. The DMF analytical methods should be compared with the NDA methods which basically follow USP.

Drug Product

- Since this is a parenteral dosage form, the major critical issue is sterility assurance of the product after manufacture and maintenance of sterility over the shelf-life. These aspects are expected to be covered by the microbiology reviewer.
- Should pH be monitored as a (b) (4) in the manufacture of Pitressin since it is identified as a critical parameter?
- Has the Applicant done any in-use studies to define the length of time the vial may be used after the first withdrawal? They clarified that this was a multiple dose presentation in the pre-NDA meeting with DMEP.

- The Applicant was told in the pre-NDA meeting to perform a one-time bioassay as part of characterization of the product and to correlate it to the HPLC method for assay. Have they done this? Is it necessary to perform a bioassay for this short peptide? Note that in the older USP monograph there was a requirement for a bioidentity test in the drug substance which has now been replaced by mass spectral analysis.
- Has the antimicrobial preservative effectiveness of chlorobutanol been satisfactorily demonstrated over the intended shelf-life of the product?
- Regarding the specification:
 - The Identification test is by HPLC retention time only which is generally not considered specific
 - The release and shelf-life criteria for a number of attributes like pH, assay, impurities and chlorobutanol content are different. Is this acceptable?
 - The shelf-life limits for impurities are very high –two individual impurities are NMT (b)(4) and the total is NMT (b)(4)%. Is this justified? They were informed in the pre-NDA meeting that this was problematic and were advised to consider measures such as storage under refrigeration, short shelf-life etc. Additionally, has the safety of these degradation products been established at these levels by historical use?
 - Is it clear what is meant by Individual Specified NMT (b)(4)%?
 - Is the assay shelf-life criterion of 80%-105% acceptable?
 - Is the assay method based on the USP monograph?
 - Is the bacterial endotoxin limit proposed acceptable based on the proposed dose for vasodilatory shock?
- Has the suitability/compatibility of the container closure system for this product been adequately established?
- Regarding Stability
 - All batch sizes for the registration and supportive studies have been reported as “variable”. Can it be assumed that the primary batches are at least pilot scale i.e. manufactured by a procedure fully representative of and simulating that to be applied to a full production scale?
 - The data available for the primary batches are minimal – 3 months for 2 batches and 2 months for the third batch under long term, accelerated and intermediate conditions. Is the Applicant proposing to provide additional data during the review period? What expiration dating period can be granted for this product given the paucity of data and the high levels of degradation upon storage? How useful are the supportive data from marketed batches manufactured with an overage?
 - The post approval commitment to monitor stability under only long term conditions for the first 3 commercial batches is inadequate.

Labeling

- Neither the container labels nor the package insert state that the vials are multidose even though that seems to be the Applicant's intention as mentioned in the pre-NDA meeting minutes.
- For a multidose injection, the maximum length of time the vial can be used after the first withdrawal should be stated in the labeling.

Comments and Recommendations

The application is fileable -- see attached Filing Check List. Facilities have been entered into EES; the reviewer should confirm the completeness and accuracy of the entries. A microbiology reviewer has been assigned. Methods Validation by DPA is not deemed necessary based on a preliminary review since the 7 criteria in IQP 5105 are not met; however, the reviewer may choose to initiate MV if the in-depth review reveals concerns with any of the analytical methods. A categorical exclusion from environmental assessment has been requested. A single CMC reviewer is recommended since the submission has no QbD elements and much of the drug product information pertains to sterility assurance which will be reviewed by the microbiologist.

Kasturi Srinivasachar
CMC Lead

Nov. 5, 2012
Date

Ramesh Sood
Branch Chief

Nov. 5, 2012
Date

PRODUCT QUALITY -- CMC and BIOPHARMACEUTICS
FILING REVIEW FOR NDA

NDA Number: 204485 **NDA Type:** 7 **Established/Proper Name:** Vasopressin Injection/Pitressin
Applicant: JHP Pharmaceuticals **Letter Date:** Sep 25, 2012 **PDUFA Goal:** July 26, 2013
Stamp Date: Sep 26, 2012
CMC Reviewer: Lyudmila Soldatova

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On initial overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		Some information requested at the pre-NDA meeting not provided

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		
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* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Categorical exclusion requested

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		Information in DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Information in DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Information in DMF (b) (4)
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		Information in DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?		X	N/A The formulation is based on a marketed unapproved product
23.	Have any Comparability Protocols been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		Insufficient primary data to support the requested expiration date
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?		X	No separate package in the Regional Section of Mod 3. However, MV information provided in 3.2.P.5.3.

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		X	Included in Drug Product Manufacturing Section

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		DMF (b) (4) DMF DMF

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		Fileable for Product Quality. A separate filing review will be submitted for Biopharmaceutics
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			NA
36.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			See Biopharmaceutics Filing Review

37.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	X		Request additional drug product stability data and in-use study to assign a maximum time period for the multidose vials after initial withdrawal of drug.
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KASTURI SRINIVASACHAR
11/05/2012

RAMESH K SOOD
11/05/2012