

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-697

CHEMISTRY REVIEW(S)

ONDQA Division Director's Memo
NDA 21-697, Vaprisol (Conivaptan HCl Injection)
Date: December 23, 2005

Introduction

Vaprisol 5mg/mL in 4 mL ampoules is diluted and administered by intravenous injection for the treatment of euvolemic hyponatremia in hospitalized patients. Each 4 mL ampoule of the drug product contains 20 mg of drug (Conivaptan HCl), 1.2 g propylene glycol, 0.4g ethanol, Water for Injection, and lactic acid to adjust the apparent pH to 3.0.

As per the labeling, this drug product is meant to be diluted prior to administration with D5W (5% Dextrose Injection, USP) for single use. It may be diluted for use as a loading dose in 100 mL of D5W in an infusion bag or as a continuous infusion in 250 mL of D5W in an IV bag. D5W is the only diluent specified to be used in the labeling. Other diluents such as Lactated Ringer's Injection and 0.9% Sodium Chloride Injection are not compatible and are specifically cited in the labeling to not be used.

The diluted solution is not adequately stable beyond 24 hours. The labeling states that diluted solutions should be used promptly and administration completed within 24 hours of mixing. The labeling also states that, if particulate matter, cloudiness, or discoloration are observed, the solution should not be used.

The drug product is packaged in 4 mL clear glass one-point cut ampoules; 10 ampoules to a carton. The labeled storage condition is 25C with excursions permitted to 15-30C. The labeling further clarifies that the drug product is not to be stored below 15C (as this may cause precipitation). The shelf life of the drug product is fifteen (15) months.

Administrative

The original submission of this 505(b)(1) NDA was found to be APPROVABLE on 30-NOV-2004. The complete response was received 30-JUN-2005 from Astellas Pharma of Deerfield IL. The following consults have been performed and were found to be acceptable; Biometrics, EES, PharmTox, DMETS, Microbiology, and EA (exclusion justified). Only one DMF was cited in this NDA for the glass ampoules and it satisfactory. There are no CMC Phase-IV commitments or post-approval agreements, and there are no other comments to the applicant. The CMC recommendation is for APPROVAL with a fifteen (15) month shelf life.

Drug Substance (Conivaptan HCl): Summary of issues

Conivaptan is a poorly soluble weak base with a pKa of 6.4. The very weak basicity of conivaptan is because the basic nitrogens are in an imidazole ring which is also part of an extended aromatic system within the molecule. This very weakly basic behavior of conivaptan and its low intrinsic solubility are central to the multiple incompatibility issues associated with this drug product.

The drug substance is conivaptan HCl . Because of the low intrinsic solubility of the free base, the drug product is formulated under _____ the necessary concentration in the drug product.

Drug Product: Summary of issues.

As noted above, the drug product is an acidic solution containing cosolvents. All excipients are USP grade. The lactic acid is used to adjust the pH to 3.0. The pH of the drug product is specified to not exceed _____ on stability. At pH values above this, the drug

However, _____ Storage below 15C _____ The stability database supports a _____ shelf under the labeled storage conditions (above). To _____ the glass, the applicant provided a comparability protocol in the NDA to provide for the _____. This comparability protocol was reviewed and found to be acceptable and should eventually allow the drug product to have a longer shelf-life with more compatible packaging.

_____ from intravenous bags in the presence of the diluted formulation was evaluated by the PharmTox reviewer and found to be acceptable.

The specified diluent D5W, is not buffered. Therefore, the diluted drug product lacks pH control as well as diluting out the solubilizing cosolvents. Therefore, the shelf life of the diluted product is limited to 24 hours.

Rik Lostritto, Director, ONDQA Division I

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/s/

Richard Lostritto
12/23/2005 02:13:21 PM
CHEMIST

Richard Lostritto
12/23/2005 02:16:28 PM
CHEMIST



NDA 21-697

Vaprisol™ (Conivaptan HCl IV Injection)

Astellas Pharma U.S., Inc.

**William M. Adams
Office of New Drug Quality Assessment
(ONDQA)**



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Chemistry Review Data Sheet

1. NDA 21-697
2. REVIEW #2
3. REVIEW DATE: 28-Nov-2005
4. REVIEWER: William M. Adams
5. PREVIOUS DOCUMENTS: None

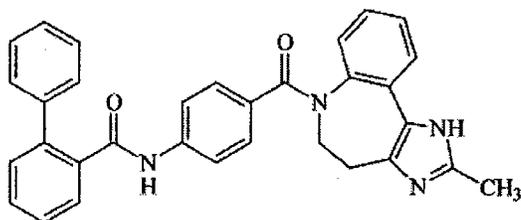
<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	30-Jan-2004
BM Amendment	31-Mar-2004
MR Amendment	28-May-2004
SU Amendment	28-May-2004
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
AZ Amendment	30-Jun-2005
7. NAME & ADDRESS OF APPLICANT:

Name:	Astellas Pharma U.S., Inc.
Address:	Three Parkway North Deerfield, IL 600152548
Representative:	Donald E. Baker, J.D. Senior Director, Regulatory Affairs
Telephone:	(847) 317-8872
8. DRUG PRODUCT NAME/CODE/TYPE:
 - (a) Proprietary Name: Vaprisol™ (proposed)
 - (b) Non-Proprietary Name (USAN): Conivaptan HCl IV injection
 - (c) Code Name: YM087
 - (d) Chem. Type/Submission Priority: 1S
9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
10. PHARMACOLOGICAL CATEGORY: treatment of euvoletic or hypovoletic in hospitalized patients

Chemistry Review Data Sheet

11. DOSAGE FORM: Solution
12. STRENGTH/POTENCY: 5 mg/mL in 4 mL ampoule
13. ROUTE OF ADMINISTRATION: IV injection
14. Rx/OTC DISPENSED: Rx
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): No
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
 Chemical Name: [1,1'-biphenyl]-2-carboxamide, *N*-[4-[(4,5-dihydro-2-methylimidazo[4,5-*d*][1]benzazepin-6(1*H*)-yl)carbonyl]phenyl]-, monohydrochloride
 Molecular Formula/Weight: C₃₂H₂₆N₄O₂.HCl
 Molecular Weight: 535.05 amu



HCl

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
██████	III	██████	██████	4	N/A	---	---

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 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
IND 56,813	Yamanouchi	Conivaptan HCl, IV (HFD-510)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

IND 55,607	Yamanouchi	Conivaptan HCl, IV (HFD-510))
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18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Acceptable for Carcinogenicity	27-May-2004	C.Liu
EES	Acceptable	23-Nov-2004	DO recommendation
Pharm/Tox	Acceptable	22-Sep-2004	F.Alavi
Biopharm	None		
LNC	None		
Methods Validation	Acceptable	CMC Review #1	M.Adams
DMETS	Trade name Acceptable	22-Mar-2004	C.Holquist
EA	Exclusion Justified	CMC Review #1	M.Adams
Microbiology	Acceptable for Sterility Assurance	21-May-2004	P.Stinavage

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 21-697

The Executive Summary

I. RECOMMENDATIONS

A. RECOMMENDATION & CONCLUSION ON APPROVABILITY

The proposed application can be APPROVED from the CMC perspective..

B. RECOMMENDATION ON PHASE 4 (Post-Marketing) COMMITMENTS, AGREEMENTS &/or RISK MANAGEMENT STEPS, if Approvable

No phase 4 studies are proposed.

II. SUMMARY OF CHEMISTRY ASSESSMENTS

A. DESCRIPTION OF THE DRUG PRODUCT & DRUG SUBSTANCE

DRUG PRODUCT

Vaprisol™ is a clear, colorless solution for IV infusion solution filled [redacted] a 4 mL clear, colorless type I glass ampoule. The solution is 5 mg/mL Conivaptan HCl in a [redacted] propylene glycol [redacted] ethanol co-solvent adjusted to pH 3.0 with [redacted] lactic acid. The ampoule is intended to provide 20 mg of the salt. All excipients are meet USP monograph requirement and all, except Lactic Acid, are tested for [redacted].

The pharmaceutical development section indicates that the proposed co-solvent and titration to pH 3.0 are needed to address the low drug substance solubility in water. At pH [redacted] and above, Conivaptan free base [redacted]. During product development, [redacted] solution pH to approach the upper limit (pH [redacted]). This pH rise results [redacted].

[redacted] months, solution pH stabilizes. The process is enhanced by storage at or below 15°C and the [redacted] re-dissolves at 25°C. The label storage statement indicates "store at 25°C" and "do not store below 15°C".

Drug product is manufactured and tested at various locations in Japan. The formulation is based on drug substance

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 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process



CHEMISTRY REVIEW



Chemistry Assessment Section

The firm justified a request for a categorical exemption from the environmental assessment requirements under 21 CFR 25.31(b) based on a calculation of the estimated introduction concentration being <1 ppb.

B. DESCRIPTION OF HOW THE DRUG PRODUCT IS INTENDED TO BE USED

Vaprisol™ is to be admixed with 5% Dextrose Injection and 180 mg Conivaptan HCl administered by IV injection over 4 days. On day 1, a 20 mg bolus is administered over 30 minutes (0.20 mg/mL at 3.33 mL/minute) followed by a continuous infusion over 23.5-24.0 hours. On days 2-4, a continuous infusion (as above) is administered each day.

C. BASIS FOR APPROVABILITY OR NOT APPROVAL RECOMMENDATION

The submitted CMC is now complete and adequate to support APPROVAL (AP) of the proposed new drug application. The listed facilities have been found to meet cGMP requirements.

III. ADMINISTRATIVE

A. REVIEWER'S SIGNATURE

William M. Adams, ONDQA

B. ENDORSEMENT BLOCK

M.Adams/ONDQA/CMC Reviewer
S.Moore/ONDQA/PAL

C. CC BLOCK

R.Lostritto/ONDQA/Dir DPMA
B.Fraser/ONDQA/DPMA I/Chief Branch II
L.Aljuburi/DMEP/PM

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✓ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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/s/

Mike Adams
12/5/2005 11:27:32 AM
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Stephen Moore
12/5/2005 02:22:33 PM
CHEMIST

NDA 21-697
Vaprisol (conivaptan HCl) Injection

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: Yamanouchi Pharma America, Inc.
Paramus, NJ

Indication: Treatment of euvolemic or hypervolemic hyponatremia

Presentations: 20 mg/4.0 mL (5 mg/mL) in glass ampoules

EER Status: Acceptable 10/16/2003

Consults: DMETS – tradename acceptable 22-MAR-2004
EA – none - categorical exclusion
Micro – acceptable – 2-JUN-2004

Original Submission: 12-DEC-2002
NOTE: this is an NME

Drug Substance Conivaptan HCl is a white to pale powder with pH dependent solubility in water. [REDACTED]

[REDACTED] The manufacturing process and controls are considered adequate. Impurities are well controlled. Specifications are considered acceptable. The total [REDACTED] acceptance criterion has been requested to be tightened based upon observed data. It is manufactured by Yamanouchi Pharmaceutical Co., Ltd. at its Takahagi Plant in Akahama, Takahagi-shi, Japan (EER pending). The drug substance is relatively stable and based on the data submitted, a retest period of [REDACTED] is granted.

Information requests for drug substance manufacture will be sent in the action letter.
Conclusion Drug substance is acceptable.

Drug Product Vaprisol 5 mg/mL is an injectable product formulated in [REDACTED] propylene glycol/[REDACTED] ethanol aq solution with added lactic acid to adjust the pH. Diluent compatibility studies simulating proposed administration (IV bolus followed by 2-4 day infusion) were conducted. Lactated Ringers and saline admixtures [REDACTED], however D5W solutions were seen to be satisfactory. Admixture in D5W only is therefore recommended. [REDACTED]

The drug product is manufactured at the Yamanouchi, Yaizu-shi, Shizuoka-ken Japan manufacturing facility, (EER pending). Manufacturing controls are considered adequate. The ampoules _____ Specifications are adequate with the exception of _____ criteria.

Stability data included in the application supports an expiry of 15 months – additional data are requested. The storage statement indicates that the product should not be stored below 15°C to avoid _____ of the drug substance. Note that _____ is _____ To address this issue the firm has proposed a comparability protocol to provide for _____

All associated DMFs are acceptable.

Labeling will be addressed in subsequent cycle(s).

Information requests for drug substance manufacture will be sent in the action letter.

Conclusion Drug Product is acceptable

Overall Conclusion:

From a chemistry perspective, the application is recommended for an approvable action.

Additional Deficiency Comment:

Eric P. Duffy, PhD

Director, DNDC II/ONDC

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/s/

Eric Duffy
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CHEMIST



NDA 21-697

Vaprisol™ (Conivaptan HCl IV Injection)

Yamanouchi Pharma America, Inc.

William M. Adams
Division of Endocrine and Metabolism Drug Products



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Chemistry Review Data Sheet

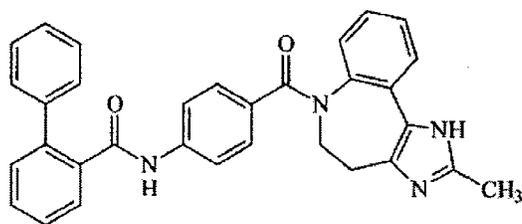
1. NDA 21-697
2. REVIEW #1
3. REVIEW DATE: 29-Sep-2004
4. REVIEWER: William M. Adams
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	30-Jan-2004
MR Amendment	28-May-2004
SU Amendment	28-May-2004
7. NAME & ADDRESS OF APPLICANT:

Name:	Yamanouchi Pharma America, Inc.
Address:	Mack Centre IV, 4 th Floor South 62 Paramus Road Paramus, NJ 07652
Representative:	Jacquelyn Hartley Director, Regulatory Affairs
Telephone:	(201) 291-2556 (201) 909-5244 FAX
8. DRUG PRODUCT NAME/CODE/TYPE:
 - (a) Proprietary Name: VaprisolTM (proposed)
 - (b) Non-Proprietary Name (USAN): Conivaptan HCl IV injection
 - (c) Code Name: YM087
 - (d) Chem. Type/Submission Priority: 1S
9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
10. PHARMACOLOGICAL CATEGORY: treatment of euvolemic or hypovolemic neutremia in hospitalized patients
11. DOSAGE FORM: Solution

Chemistry Review Data Sheet

- 12. STRENGTH/POTENCY: 5 mg/mL in 4 mL ampoule
- 13. ROUTE OF ADMINISTRATION: IV injection
- 14. Rx/OTC DISPENSED: Rx
- 15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): No
- 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



· HCl

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	TY	HOLDE	ITEM REFEREN	COD	STATUS	DATE REVIE COMPLETE	COMMENT
	III			4	N/A	---	---

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 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
IND 56,813	Yamanouchi	Conivaptan HCl, IV (HFD-510))
IND 55,607	Yamanouchi	Conivaptan HCl, IV (HFD-510))

18. STATUS:

CONSULTS/CMC RELAT REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Acceptable for Carcinogenicity	27-May-2004	C.Liu
EES	Pending as of 09/27/04		



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Pharm/Tox	Acceptable	22-Sep-2004	F.Alavi
Biopharm	None		
LNC	None		
Methods Validation	Submitted	30-Jan-2004	M.Adams
DMETS	Trade name Acceptable	22-Mar-2004	C.Holquist
EA	Exclusion Justified	CMC #1	M.Adams
Microbiology	Acceptable for Sterility Assurance	21-May-2004	P.Stinavage

19. ORDER OF REVIEW: N/A



The Chemistry Review for NDA 21-679

The Executive Summary

I. RECOMMENDATIONS

A. RECOMMENDATION & CONCLUSION ON APPROVABILITY

The proposed application is APPROVABLE from a CMC perspective pending submission of the additional CMC information requested in section III of this review. Also, GMP inspections are still pending for multiple manufacturing sites in Japan.

B. RECOMMENDATION ON PHASE 4 (Post-Marketing) COMMITMENTS, AGREEMENTS &/or RISK MANAGEMENT STEPS, if Approvable

No phase 4 studies are proposed.

II. SUMMARY OF CHEMISTRY ASSESSMENTS

A. DESCRIPTION OF THE DRUG PRODUCT & DRUG SUBSTANCE

DRUG PRODUCT

Vaprisol™ is a clear, colorless solution for IV infusion solution filled in a 4 mL clear, colorless type I glass ampoule. The solution is 5 mg/mL Conivaptan HCl in a propylene glycol: ethanol co-solvent adjusted to pH 3.0 with lactic acid. The ampoule is intended to contain 20 mg of the salt. All excipients meet USP monograph requirement and all except Lactic Acid are tested for.

The pharmaceutical development section indicates that the proposed co-solvent was intended to address the low drug substance solubility in water. Adjustment to pH 3.0 with aqueous lactic acid in solution preparation was established to counter the decrease in drug substance solubility with increased pH. At pH active ingredient solubility is less than the formulated strength. During product development, it was found that

This process was enhanced with storage at or below 15°C and the re-dissolves at 25°C. The label storage statement therefore indicates "store at 25°C" and "do not store below 15°C".

The applicant performs drug product manufacture, control, release testing and stability testing. The formulation is based on drug substance potency corrected for water and residual solvents. The commercial manufacturing process consists

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 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process



CHEMISTRY REVIEW



Chemistry Assessment Section

The firm requested a categorical exemption from the environmental assessment requirements under 21 CFR 25.31(b) based on a calculation of the estimated introduction concentration (EIC) being <1 ppb.

B. DESCRIPTION OF HOW THE DRUG PRODUCT IS INTENDED TO BE USED

Vaprisol™ is to be admixed with 5% Dextrose Injection and 180 mg Conivaptan HCl administered by IV injection over 4 days. On day 1, a 20 mg bolus is administered over 30 minutes, continuous infusion over 23.5-24 hours. On days 2-4, a continuous infusion (as above) is administered each day.

C. BASIS FOR APPROVABILITY OR NOT APPROVAL RECOMMENDATION

The proposed application is APPROVABLE (AE) from a CMC perspective based on the need for additional information regarding drug substance manufacture, specifications and stability protocols, and drug product manufacture and specifications. Descriptions of the proposed manufacturing processes require clarification. Specifications for the proposed drug substance and product are not justified by the submitted release and stability data. The drug substance stability protocols require revision to be complete. Updated drug product stability data is being requested.

III. ADMINISTRATIVE

A. REVIEWER'S SIGNATURE

William M. Adams, CMC Reviewer for HFD-510.

B. ENDORSEMENT BLOCK

M.Adams/CMC Reviewer for HFD-510
S.Moore/CMC TL for HFD-510
L.Aljuburi/PM for HFD-510

C. CC BLOCK

E.Duffy/ONDC/Dir DNDC II
B.Fraser/ONDC/Dep Dir DNDC II

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Mike Adams
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Stephen Moore
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