

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-697

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use**

NDA NUMBER

21-697

NAME OF APPLICANT / NDA HOLDER

Yamanouchi Pharma America, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

VAPRISOL™ (conivaptan hydrochloride for injection)

ACTIVE INGREDIENT(S)

conivaptan hydrochloride

STRENGTH(S)

5 mg/mL

DOSAGE FORM

4 mL ampule, solution for intravenous administration

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(II) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

5,723,606

b. Issue Date of Patent

3/3/1998

c. Expiration Date of Patent

3/3/2015

d. Name of Patent Owner

Yamanouchi Pharmaceutical Co. Ltd.,

Address (of Patent Owner)

3-11, Nihonbashi-Honcho 2-chome, Chuo-ku

City/State

TOKYO

ZIP Code

JAPAN

FAX Number (if available)

011-81-3-5916-5615

Telephone Number

011-81-3-5916-5111

E-Mail Address (if available)

hara.hiromu@yamanouchi.co.jp

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Jacquelyn Hartley, Director, Regulatory Affairs
Yamanouchi Pharma America, Inc.

Address (of agent or representative named in 1.e.)

S. 61 Paramus Road

City/State

Paramus, New Jersey

ZIP Code

07652

FAX Number (if available)

201-909-5244

Telephone Number

201-291-2556

E-Mail Address (if available)

jacquelyn.hartley@yamanouchi-america.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number (as listed in the patent) 9 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.) Antagonist of arginine vasopressin (AVP) V_{1A} and V₂ receptors; indicated for intravenous treatment of euvolemic or hypervolemic hyponatremia in hospitalized patients.

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

Jacquelyn Hartley

January 30, 2004

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Jacquelyn Hartley, Director, Regulatory Affairs

Address

Mack Centre IV, S. 61 Paramus Road

City/State

Paramus, New Jersey

ZIP Code

07652

Telephone Number

201-708-2714

FAX Number (if available)

201-909-5244

E-Mail Address (if available)

jacquelyn.hartley@yamanouchi-america.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXCLUSIVITY SUMMARY

NDA # 21-697

SUPPL # N/A

HFD # 510

Trade Name Vaprisol Injection

Generic Name conivaptan hydrochloride

Applicant Name Astellas Pharma US, Inc.

Approval Date, If Known December 29, 2005

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

N/A

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Lina AlJuburi, Pharm.D., M.S.
Title: Regulatory Project Manager, Division of Metabolism and Endocrinology Products
Date: February 7, 2006

Name of Office/Division Director signing form: Mary Parks, M.D.
Title: Acting Director, Division of Metabolism and Endocrinology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Mary Parks
2/8/2006 04:48:39 AM

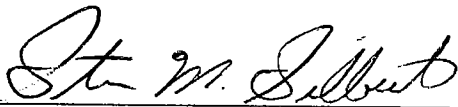
NDA 21- 697
YM087 (conivaptan
hydrochloride) Injection

Yamanouchi

CTD Module 1
Debarment Certification

DEBARMENT CERTIFICATION

Yamanouchi Pharma America, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.



DATE: November 19, 2004

Steven Silbert
Senior Director
Clinical Administration and Quality Assurance

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

DA/BLA #: 21-697 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: July 1, 2005 Action Date: December 29, 2005

HFD-510 Trade and generic names/dosage form: Vaprisol (conivaptan hydrochloride) Injection

Applicant: Astellas Pharma US, Inc. Therapeutic Class: vasopressin receptor antagonist

Indication(s) previously approved: None

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): one

Indication #1: treatment of euvolemic hyponatremia in hospitalized patients

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

X No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 5 Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- X Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. 6 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 18 Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): 10/31/10

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager

cc: NDA 21-697
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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

/s/

Lina Aljuburi
2/8/2006 02:56:37 PM

Aljuburi, Lina

From: Aljuburi, Lina
Sent: Thursday, December 29, 2005 3:46 PM
To: CDER-APPROVALS
Subject: Approval of NDA 21-697 Vaprisol (conivaptan hydrochloride) Injection

Date of approval: December 29, 2005

NDA #: 21-697

Name of drug: Vaprisol (conivaptan hydrochloride) Injection

Name of sponsor: Astellas Pharma US, Inc.

Indication: treatment of euvolemic hyponatremia in hospitalized patients

Dosage form: solution for injection

Route of administration: intravenous injection

Rx

Drug classification: 1, New Molecular Entity

Review priority rating: Standard

***Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
301-796-1168 (phone)
301-796-9712 (fax)***

Aljuburi, Lina

From: Raineri, Donald [Don.Raineri@us.astellas.com]
Sent: Thursday, December 29, 2005 2:33 PM
To: Aljuburi, Lina
Subject: RE: Vaprisol Action Letters

Hi, Lina-

This message serves as confirmation that I have received the action letters for Vaprisol.

Happy New Year to you!

Kind regards,

Don

From: Aljuburi, Lina [mailto:ALJUBURIL@cder.fda.gov]
Sent: Thursday, December 29, 2005 1:09 PM
To: Raineri, Donald
Subject: Vaprisol Action Letters

Good afternoon, Don

— action letters have just issued regarding Vaprisol (conivaptan hydrochloride) Injection:

NDA 21-697 Approval for the indication for treatment of euvolemic hyponatremia in hospitalized patients

<<AP_letter_to_sponsor_12.29.05.pdf>>

L

J

Please reply to this email to confirm receipt.

Feel free to contact me if I may be of further assistance.

Many thanks,
Lina

*Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
301-796-1168 (phone)
301-796-9712 (fax)*

12/29/2005

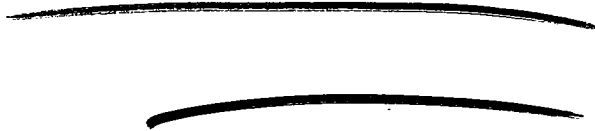
Aljuburi, Lina

From: Raineri, Donald [Don.Raineri@us.astellas.com]
Sent: Thursday, December 29, 2005 1:03 PM
To: Aljuburi, Lina
Subject: FW: PackageInsert_FINAL_AgreedUpon12.29.05.pdf
Importance: High

Dear Lina,

We at Astellas are in full agreement with the text of the attached Vaprisol PI.

There are 2 minor clerical issues that I noticed:



Thanks so much for your diligent efforts to drive this labeling to finalization!

Best wishes for a Happy New Year!

Don

From: Aljuburi, Lina [mailto:ALJUBURIL@cder.fda.gov]
Sent: Thursday, December 29, 2005 10:58 AM
To: Raineri, Donald
Subject: PackageInsert_FINAL_AgreedUpon12.29.05.pdf

12/29/2005

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 29, 2005

TO: The File

FROM: Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

SUBJECT: **Final agreed upon package insert**
NDA 21,697, Vaprisol (conivaptan hydrochloride) Injection

Background

On January 30, 2004, Yamanouchi Pharma America, Inc. submitted NDA 21-697 for Vaprisol (conivaptan HCl) Injection (YM087; 5 mg/mL, 4 mL per ampule). This new molecular entity is dual antagonist of arginine vasopressin (AVP) V_{1A} and V₂ receptors. The application was submitted with two proposed indications:

1. treatment of euvolemic hyponatremia in hospitalized patients and
2. treatment of hypervolemic hyponatremia in hospitalized patients.

On November 30, 2004, an approvable letter was issued. The deficiencies included clinical, clinical pharmacology and biopharmaceutics, and chemistry. The NDA sponsorship was later transferred from Yamanouchi Pharma America, Inc. to Astellas Pharma US. On June 30, 2005, Astellas Pharma US submitted a complete response to the November 30, 2004, approvable letter.

Review of the application, as amended, yielded the decision to take an approval (AP) action for use of conivaptan hydrochloride in euvolemic hyponatremia in hospitalized patients. However, an approvable (AE) action will be taken for the use of conivaptan hydrochloride in hypervolemic hyponatremia in hospitalized patients.

NDA 21-697 holds the approved indication: treatment of euvolemic hyponatremia in hospitalized patients.

A large handwritten signature is written across the bottom of the page, enclosed within a large, hand-drawn bracket.



Final Agreed-Upon Package Insert

After much discussion regarding the package insert (PI), the sponsor submitted a revised version of the label on December 23, 2005. Following that submission, additional revisions were made to the PI, specifically to the “**Indications and Usage**” and “**CLINICAL STUDIES**” sections. The revisions were emailed to the sponsor on December 29, 2005. The sponsor concurred via email (which is attached below followed by the complete package insert that was agreed-upon on, and subsequently approved, on December 29, 2005.) The revisions are as follows:

Indications and Usage

VAPRISOL is indicated for the treatment of euvolemic hyponatremia (e.g. the syndrome of inappropriate secretion of antidiuretic hormone, or in the setting of hypothyroidism, adrenal insufficiency, pulmonary disorders, etc.) in hospitalized patients.

This addition (underlined above) was previously discussed and agreed upon but was later inadvertently taken out by DMEP.

CLINICAL STUDIES

Figures 2 and 3 in the CLINICAL STUDIES section were revised to improve legibility. The figures appeared very busy with many points on the x-axis, small fonts for labeling, etc. The sponsor was asked to try to address this issue.

Figure 2: Mean (SE) Change from Baseline in Sodium Concentrations with VAPRISOL 40 mg/day

Figure 2 from December 23, 2005, submission:



Revised Figure 2 from the approved label:

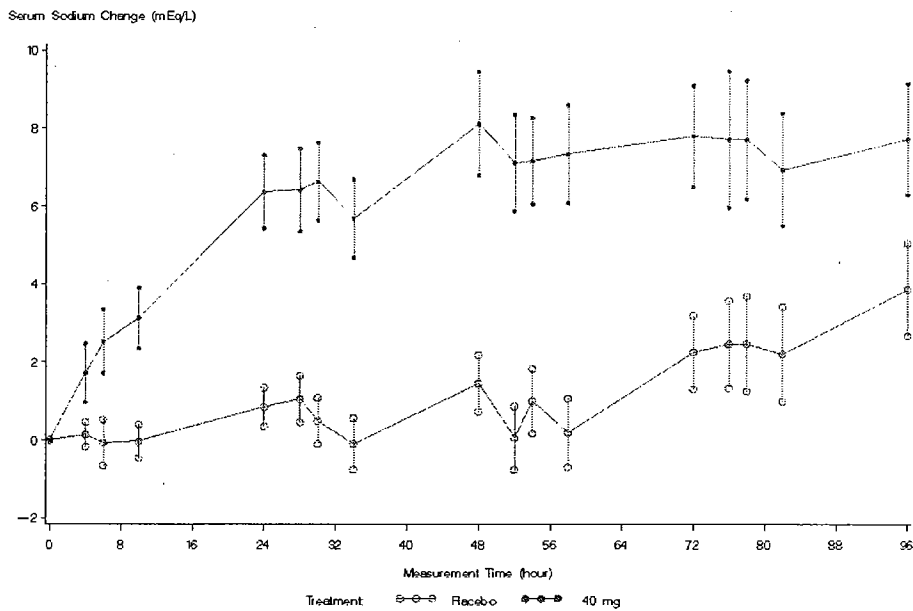
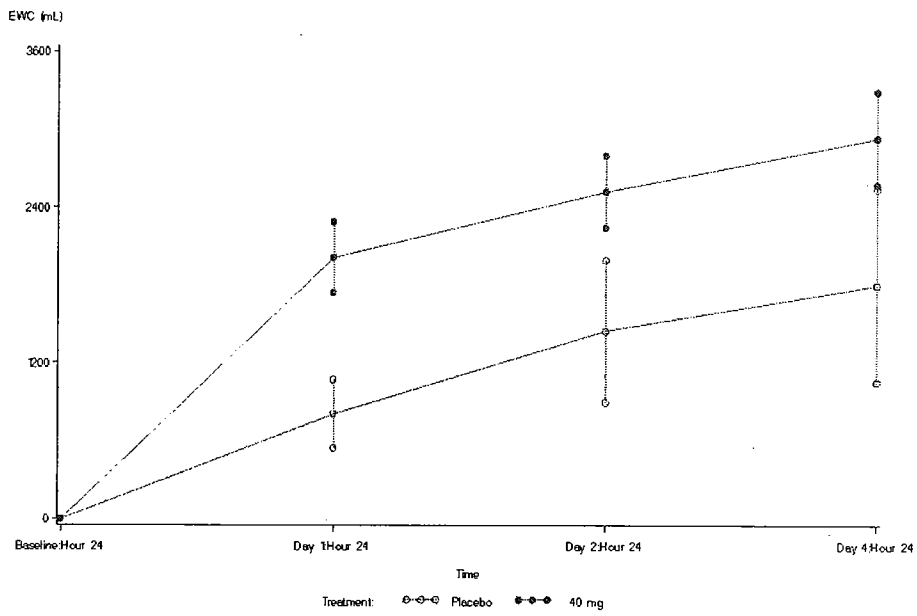


Figure 3. Baseline-Corrected Cumulative Effective Water Clearance

Figure 3 from December 23, 2005, submission:



Revised Figure 3 from the approved label:



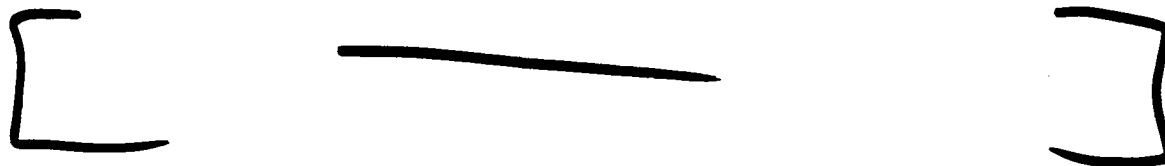
Aljuburi, Lina

From: Raineri, Donald [Don.Raineri@us.astellas.com]
Sent: Thursday, December 29, 2005 1:03 PM
To: Aljuburi, Lina
Subject: FW: PackageInsert_FINAL_AgreedUpon12.29.05.pdf
Importance: High

Dear Lina,

We at Astellas are in full agreement with the text of the attached Vaprisol PI.

There are 2 minor clerical issues that I noticed:



Thanks so much for your diligent efforts to drive this labeling to finalization!

Best wishes for a Happy New Year!

Don

From: Aljuburi, Lina [mailto:ALJUBURIL@cder.fda.gov]
Sent: Thursday, December 29, 2005 10:58 AM
To: Raineri, Donald
Subject: PackageInsert_FINAL_AgreedUpon12.29.05.pdf

27 Page(s) Withheld

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✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Lina Aljuburi
12/29/2005 03:19:23 PM
CSO

ADRA Rev #2 of Action Package for NDA 21-697, Vaprisol (conivaptan HCl) Injection

Reviewer: Lee Ripper, HFD-102

Date received: December 12, 2005

Date of review: December 19, 2005

Date original NDA received: January 30, 2004

UF goal date: December 31, 2005

ACTION DATE: December 23, 2005

Proposed Indications and Action Type:

AP: Tx of euvolemic hyponatremia in hospitalized patients.

AE: Tx of hypervolemic hyponatremia in hospitalized patients.

RPM: Lina AlJuburi

Drug Classification: 1S

505(b)(1) application

Patent Info: Form 3542a submitted, AC

Debarment Certification: 11/22/04 version AC.

Safety Update: Dated 5/28/04, MOR #1, page 155

Clinical Inspection Summary: One clinical site audited; form 483 issued, data deemed AC. In addition, the field inspected the applicant's management procedures for protocol #1025-007 (which apparently was another designation for study #087-CL-027, the major IV efficacy trial); form 483 was issued; the applicant responded in writing that it would make appropriate changes in its procedures.

ODS/DMETS Review of Proprietary Name: 12/1/05: *DMETS does not object to Vaprisol.*

DSRCS Review of PPI: N/A

DDMAC Review: No written review, DMETS review states proprietary name is acceptable from a promotional perspective.

EA: Categorical exclusion, CMC #1, page 103

EER: 11/23/04: EER signed off as AC. 12/19/05: *EES does not show any of the facilities as under an OAI alert or potential OAI alert.*

Financial Disclosure: MOR #1, page 29. Also, see #1 below.

CMC section to Eric Duffy, 12/20/05

P/T section to Ken Hastings, 12/20/05.

1. One financial disclosure form 3454 was received with the original application. The applicant checked _____

Since some of the studies were sponsored by _____ the applicant was asked to separate the lists of investigators by sponsor of the study, and resubmit the lists as attachments to three copies of form 3454,

- a. one copy with box #1 checked and the list of investigators in studies sponsored by Yamanouchi,
- b. the second copy of the form with _____

_____ and the corresponding list of investigators, and

c. the third copy of the form with box

and the corresponding list of investigators.

12/19/05: The FD form 3454 appears to be incorrect. One copy of form 3454 has box _____ Investigators in studies sponsored by Astellas. But many of the attached pages say "Financial Disclosure Form Received from Investigator for Yamanouchi." Is there a relationship between Yamanouchi and Astellas or did the new applicant take literally the comment in the AE letter about checking _____ and attaching a list of studies sponsored by Yamanouchi?

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/s/

Leah Ripper
12/19/2005 08:54:55 PM
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/s/

Lina Aljuburi
12/23/2005 03:34:07 PM
CSO

**MEMORANDUM OF MEETING MINUTES FOR
PREAPPROVAL SAFETY CONFERENCE**

MEETING DATE: December 16, 2005
TIME: 12:00 to 1:00 pm
LOCATION: White Oak Campus, Bldg 22, Room 1309
APPLICATION: NDA 21-697
DRUG NAME: Vaprisol (conivaptan hydrochloride) Injection
TYPE OF MEETING: PreApproval Safety Conference (PASC)

MEETING CHAIR: Robert Meyer, M.D.

MEETING RECORDER: Lina AlJuburi, Pharm.D., M.S.

FDA ATTENDEES: (Title and Office/Division)

Office of Drug Evaluation (ODE) II

Robert Meyer, M.D.	Director
Curtis Rosebraugh, M.D.	Deputy Director
Leah Ripper	Associate Director of Regulatory Affairs

Division of Metabolism & Endocrinology Products (DMEP)

David Orloff, M.D.	Director
Mary Parks, M.D.	Deputy Director and Clinical Team Leader
Karen Mahoney, M.D.	Medical Officer
Karen Davis-Bruno, Ph.D.	Pharmacology/Toxicology Team Leader
Lina AlJuburi, Pharm.D.	Regulatory Project Manager

Office of Pharmacoepidemiology and Statistical Science

Japo Choudhury, Ph.D.	Biometrics Reviewer
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Office of Clinical Pharmacology and Biopharmaceutics

Sang Chung, Ph.D.	Biopharmaceutics Reviewer
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Office of Drug Safety (ODS)

Rosemary Johann-Liang	Medical Officer/Team Leader
Lanh Green, Pharm.D.	Safety Evaluator/Team Leader
Joslyn Swann, Pharm.D.	Safety Evaluator
Sammie Beam	Regulatory Project Manager

BACKGROUND:

On January 30, 2004, Yamanouchi Pharma America, Inc. submitted NDA 21-697 for Vaprisol (conivaptan HCl) Injection (YM087; 5 mg/mL, 4 mL per ampule). This new molecular entity is dual antagonist of arginine vasopressin (AVP) V_{1A} and V₂ receptors. The application was submitted with two proposed indications:

1. treatment of euvolemic hyponatremia in hospitalized patients and
2. treatment of hypervolemic hyponatremia in hospitalized patients.

On November 30, 2004, an approvable letter was issued. The deficiencies included clinical, clinical pharmacology and biopharmaceutics, and chemistry. The NDA sponsorship was later transferred from Yamanouchi Pharma America, Inc. to Astellas Pharma US. On June 30, 2005, Astellas Pharma US submitted a complete response to the November 30, 2004, approvable letter.

MEETING OBJECTIVES:


- To educate ODE II Director, ODS and DDMAC about the NDA safety database of Vaprisol, especially aspects of the safety database that could be important postapproval.
- To plan and agree on postapproval safety surveillance strategy for Vaprisol, including any commitments CDER would want from the sponsor.
- To consider whether particular postmarketing safety studies or other safety evaluation schemes by the sponsor are needed and whether they should be agreed to by the sponsor prior to approval of Vaprisol (i.e., noted as postmarketing, P4, or commitments in the approval letter).
- To ensure that attendees are aware of the planned labeling for Vaprisol and to ensure that any concerns about potential medication errors relative to labeling have been addressed.
- To discuss the qualitative and quantitative consistency of risk communication in proposed labeling.
- To discuss the impact of proposed labeling on expected adverse reaction reporting regulation compliance.

DISCUSSION:

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NDA 21-697 holds the approved indication: treatment of euvoletic hyponatremia in hospitalized patients.

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Labeling

Labeling discussions ongoing with sponsor.

Tracking off label use

ODS discussed the need to track postmarketing use of Vaprisol in euvolemic versus hypervolemic patients. This may best be done by using the patient diagnosis code. Euvolemic use will most often be in patients diagnosed with the syndrome of inappropriate antidiuretic hormone (SIADH). Hypervolemic use will most often be in patients diagnosed with congestive heart failure (CHF).

Postmarketing adverse events

Postmarketing reviews of adverse events should include:

1. atrial arrhythmia
2. serious consequences of hypovolemia
 - a. pre-renal/renal failure
 - b. falls

ACTION ITEMS:

Pending reviews to be finalized in DFS.

Discussions with the sponsor regarding the indications and the labeling.

NDA 21-697 Vaprisol (conivaptan hydrochloride) Injection was approved on December 29, 2005.

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/s/

Lina Aljuburi
2/6/2006 06:26:33 PM

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Lina Aljuburi
12/27/2005 05:46:19 PM

ADRA Rev #1 of Action Package for NDA 21-697, Vaprisol (conivaptan HCl) Injection

Reviewer: Lee Ripper, HFD-102

Date received: November 15, 2004

Date of review: November 16, 2004

Date original NDA received: January 30, 2004

UF goal date: November 30, 2004

ACTION DATE: November 29, 2004

Proposed Indication: Tx of euvolemic or hypovolemic hyponatremia in hospitalized patients.

Action type: AE

RPM: Lina AlJuburi

Drug Classification: 1S

505(b)(1) application

Patent Info: Form 3542a submitted, AC

Debarment Certification: Wording is acceptable, but the certification is not signed. 11/16: Lina called applicant and requested a signed copy. 11/22: *Signed copy received.*

Safety Update: Dated 5/28/04, MOR #1, page 155

Clinical Inspection Summary: One clinical site audited; form 483 issued, data deemed AC. In addition, the field inspected the applicant's management procedures for protocol #1025-007 (which apparently was another designation for study #087-CL-027, the major IV efficacy trial); form 483 was issued; the applicant responded in writing that it would make appropriate changes in its procedures.

ODS/DMETS Review of Proprietary Name: DMETS does not object to Vaprisol.

DSRCS Review of PPI: N/A

DDMAC Review: No written review, DMETS review states proprietary name is acceptable from a promotional perspective.

EA: Categorical exclusion, CMC #1, page 103

EER: Several inspections are outstanding

Financial Disclosure: MOR #1, page 29. Also, see #1 below.

CMC section to Eric Duffy, 11/16/04

P/T section to Ken Hastings, 11/16/04. *Signed review in DFS 11/23.*

1. One financial disclosure form 3454 was received. The applicant checked _____ were sponsored by _____ the applicant should be asked to separate the lists of investigators by sponsor of the study, and resubmit the lists as attachments to three copies of form 3454,

- a. one copy with [redacted] checked and the list of investigators in studies sponsored by Yamanouchi,
- b. the second copy of the form with box [redacted] ("As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant . . .") and the corresponding list of investigators, and
- c. the third copy of the form with box [redacted] ("As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators . . .") and the corresponding list of investigators.

11/23: Added to letter.

2. Add to the letter "Submit full color mock-ups of the carton and container labels."

11/23: Included in letter.

3. The division director's memo is outstanding. *11/23: Signed review in DFS.*

4. The AE letter is outstanding. *Received 11/23.*

Lee Ripper
ADRA, ODE II

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/s/

Leah Ripper
11/23/04 04:50:23 PM
CSO

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(WO: 22, Mailstop 4447)

DATE RECEIVED: October 13, 2005 DATE OF DOCUMENT: June 30, 2005	DESIRED COMPLETION DATE: December 7, 2005 PDUFA DATE: January 1, 2006	ODS CONSULT #: 05-0281
--	---	----------------------------------

TO: David Orloff, M.D.
Director, Division of Metabolism and Endocrinology Products
HFD-510

THROUGH: Lina Aljuburi
Project Manager
HFD-510

FROM: Linda Wisniewski, RN, Safety Evaluator
Linda Kim-Jung, PharmD, Team Leader

PRODUCT NAME: **Vaprisol**
(Conivaptan Hydrochloride Injection)
20 mg/4 mL

NDA# : **21-697**
NDA SPONSOR: **Astellas**

RECOMMENDATIONS:

- A. DMETS has no objections to the use of the proprietary name, Vaprisol. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
- B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize user error.
- C. DDMAC finds the proprietary name, Vaprisol, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-796-0538.

Denise Toyer, PharmD.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 796-2360 Fax: (301) 796-9865

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 796-2360 Fax: (301) 796-9865

**Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
WO: 22; Mailstop: 4447
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: October 21, 2005

NDA#: NDA# 21-697

NAME OF DRUG: Vaprisol
(Conivaptan Hydrochloride Injection)
20 mg/4 mL (5 mg/mL)

NDA HOLDER: Astellas

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolism and Endocrinology Products (HFD-510), for a re-review of the proprietary name, "Vaprisol", regarding potential name confusion with other proprietary or established drug names. DMETS found the proposed proprietary name, Vaprisol, acceptable in ODS Consult 04-0052, dated June 21, 2004. Container labels, carton and insert labeling were submitted for review and comment.

PRODUCT INFORMATION

Vaprisol is a nonpeptide, dual antagonist of arginine vasopressin (AVP) V_{1A} and V₂ receptors and is indicated for the treatment of euvolemic or hypervolemic hyponatremia in hospitalized patients. It is supplied as a sterile liquid in 4 mL clear glass ampules. Each ampule contains 20 mg of Conivaptan Hydrochloride and should only be diluted with 5% Dextrose. The recommended loading dose of Vaprisol is 20 mg intravenously administered as a 30-minute infusion followed by ██████ administered as a continuous infusion over 24 hours. Following the initial day of treatment, Vaprisol is to be administered for an additional one to three days as a continuous infusion of ██████

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to Vaprisol to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁴. The Saegis⁵ Pharma-In-Use database was

¹ MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], Drugs@FDA, the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁵ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Vaprisol. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name, Vaprisol, acceptable from a promotional perspective.
2. The Expert Panel identified four proprietary names that were thought to have the potential for confusion with Vaprisol. These products are listed in Table 1 (see below and page 4), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel.

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Vaprisol	Conivaptan Hydrochloride Injection 20 mg/4 mL (5 mg/mL)	20 mg intravenously administered as a 30-minute infusion followed by ██████ administered as a continuous infusion over 24 hours. Following the initial day of treatment, Vaprisol is to be administered for an additional 1 to 3 days as a continuous infusion of ██████.	NA
Capitol	Chloroxine 2% Shampoo	For treatment of dandruff: Massage into wet scalp and leave on for 3 minutes. Repeat twice weekly.	LA
Visicol	Sodium Phosphate, Dibasic, Anhydrous; Sodium Phosphate, Monobasic, Monohydrate Tablet 0.398 g/1.102 g	40 tablets taken in the following manner: The evening before the colonoscopy procedure, 3 Visicol® Tablets should be taken with at least 8 ounces of clear liquids every 15 minutes (the last dose will be 2 tablets) for a total of 20 tablets. The day of the colonoscopy procedure, (starting 3-5 hours before the procedure) 3 Visicol® Tablets should be taken with at least 8 ounces of clear liquids every 15 minutes (the last dose will be 2 tablets) for a total of 20 tablets. Patients are not to repeat this purgative agent within seven days of a previous administration.	SA/LA
Lopressor	Metoprolol Tartrate Injection: 1 mg/mL Tablets: 50 mg and 100 mg	Hypertension: 100 mg/day to 450 mg/day in one or divided doses. Angina Pectoris: 100 mg/day to 400 mg/day Myocardial Infarction: 5 mg every two minutes for a total dose of 15 mg. Follow with 50 mg every six hours orally. Begin 15 minutes after last IV dose and continue for 48 hours. Maintenance dose of 100 mg twice daily.	LA
Virazole	Ribavirin Solution for Inhalation 6 g/vial	Recommended treatment regimen is 20 mg/mL as the starting solution in the drug reservoir of the Small Particle Aerosol Generator. Treatment is carried out for 12 to 18 hours/day for 3 to 7 days.	SA

*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)

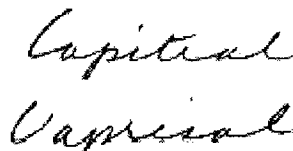
B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Vaprisol were discussed by the Expert Panel.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Vaprisol, the primary concerns related to look-alike and sound-alike confusion with Capitrol, Visicol, Lopressor, and Virazole.

1. Capitrol may look similar to Vaprisol when written. Capitrol is a topical drug product which is indicated for the treatment of dandruff. Both names contain letters that may look similar when scripted (Capi vs. Vapr). The similarities become more noticeable when the 'V' is separated from the rest of the letters (see below) and the capital 'C' is not clearly scripted. Additionally, the last three letters (sol vs. rol) may look similar. The only variance would be the letter 't' in Capitrol. The distinguishing upstroke and cross-bar may help to differentiate these two names when written. Additionally, there are some product characteristics that may help to differentiate these two names when ordered. They include dose (20 mg or 40 mg vs. small amount), frequency (once and continuously vs. twice weekly), strength (20 mg/4 mL vs. 2%), route of administration (intravenously vs. topically), and dosage form (injection vs. topical shampoo). There is a possibility that since both products are supplied in one strength, one dosage form, and are administered via one route of administration, some of this information may be omitted in an order which may further cause confusion between the two names. However, since Vaprisol is an intravenous product, it is more likely that orders for intravenous products will include the route of administration, rate of administration, the final dose, and/or length of treatment. This additional information may help to differentiate these two products when written. Despite the potential for some look-alike similarities involving these two products, the dose, route of administration, and length of treatment will help to differentiate these two products when ordered.



2. Visicol may look similar to Vaprisol when scripted. Visicol is used in the preparation of patients prior to colonoscopy. Both names begin and end with letters that may look similar when scripted (Vap vs. Vis and isol vs. icol). However, Vaprisol contains a downstroke for the letter 'p' which may help to differentiate these two names when written. There are some product characteristics that may help to differentiate these two products, as well. They include dose (20 mg or 40 mg or 3 tablets), frequency of administration (once and continuously vs. every 15 minutes), strength (20 mg/4 mL vs. 0.398 g/1.102 g), route of administration (intravenous vs. oral), and dosage form

(injection vs. tablet). Another factor to consider in the similarity assessment is that since the directions for Visicol are lengthy, the order may not include the specific dosing regimen and instead have a general direction of 'use as directed'. However, since Vaprisol is an intravenous product, it is likely that the order will include the route of administration, the final dose, rate of administration, and/or length of treatment. These additional directions of use may help to provide differentiation between these two products when ordered. Despite some orthographic similarities, the route of administration, dose, frequency of administration, directions for use, and length of infusion (with respect to Vaprisol) will help to decrease confusion involving these two drugs.

Visicol
Vaprisol

3. Lopressor may look similar to Vaprisol when written. Lopressor is indicated in the treatment of hypertension, angina pectoris, and myocardial infarction. Both names begin with letters that may look similar (Vap vs. Lop) which contributes to the similar appearance of the names when scripted. If the 'V' is scripted so that it is not contiguous with the rest of the letters (aprisol), it may look similar to the letter 'L' (see below). These beginning letters are followed by the letters 'riso and resso' which also look similar. However, the upstroke for the letter 'l' at the end of the Vaprisol may help to differentiate these two names when scripted. Additionally, there are product differences that may help to minimize confusion as well. They include dose [20 mg or 40 mg vs. 5 mg (IV), or 100 mg to 450 mg (PO)], frequency of administration (once then continuously vs. every two minutes (IV), daily, or divided doses), and strength (20 mg/4 mL vs. 1 mg/ mL, 50 mg, and 100 mg). There is an overlap at the route of administration (intravenous) and dosage form (injection). However, orders for intravenous medications usually include the final dose to be administered, rate of administration, frequency of administration, and duration of therapy. This additional information may help to differentiate these two products when ordered. Despite some orthographic similarities, product characteristics, such as the dose, duration of therapy, and frequency of administration may help to differentiate these two products when ordered.

Lopressor *Lopressor*
Vaprisol *Vaprisol*

4. Virazole may look and sound similar to Vaprisol. Virazole is indicated in the treatment of hospitalized infants with severe respiratory syncytial virus (RSV). Both names contain three syllables which may contribute to phonetic similarities involving these two names. Although the endings of each name sound similar (sol vs. zole), the beginnings (vira vs. vapr) are phonetically different which may help to differentiate each name when spoken. Orthographically, both names begin with similar appearing letters (vap vs. vir). Although both names may have a downstroke for the letters 'p' and 'z', they may be scripted using block or printed letters

that do not utilize a differentiating downstroke, such as in the samples below, which results in both names looking similar. There are some differentiating product characteristics, such as dose (20 mg or 40 mg vs. 6 g/300 mL), dosage form (injection vs. inhalation), frequency of administration (once and continuously vs. 12-18 hours/day), strength (20 mg vs. 6 g), and route of administration (intravenously vs. inhalation). Additionally, the administration directions for Virazole might be standardized and be written with a general direction 'administer per unit protocol', however, an order for Vaprisol, an intravenous drug product, would most likely include the route of administration, final dose, and length of therapy. This additional information may help to differentiate the two products when ordered. Despite the potential for orthographic similarities, the route of administration, final dose, and length of therapy would help to differentiate these two products when ordered.

*VIRAZOLE
VAPRISOL*

*Virazole
Vaprisol*

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Vaprisol, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL

1.

2.

B. CARTON LABELING

1.

C. PACKAGE INSERT LABELING

No comments.

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/s/

Linda Wisniewski
11/30/2005 02:38:26 PM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
12/1/2005 07:58:08 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
12/1/2005 01:08:30 PM
DRUG SAFETY OFFICE REVIEWER
Also signing for Carol Holquist, DMETS Director, in her
absence.

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/s/

Lina Aljuburi
10/7/2005 04:39:00 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-697

Astellas Pharma US, Inc.
Attention: Laura Navarre
Associate Director, Regulatory Affairs
3 Parkway North
Deerfield, IL 60015-2548

Dear Ms. Navarre:

We acknowledge receipt on July 1, 2005, of your June 30, 2005, resubmission to your new drug application for Vaprisol (conivaptan hydrochloride) Injection, 5 mg/mL, 4mL per ampule.

We consider this a complete, class 2 response to our November 30, 2004, action letter. Therefore, the user fee goal date is January 1, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. An assessment of your request will be made during the review of the application.

If you have any questions, please call me at 301-827-6414.

Sincerely,

{See appended electronic signature page}

Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Lina Aljuburi
7/12/05 01:30:29 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-697

Astellas Pharma US, Inc.
Attention: Donald Baker, J.D.
Senior Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015-2548

Dear Mr. Baker:

We acknowledge receipt on April 7, 2005, of your April 6, 2005, correspondence notifying the Food and Drug Administration of the change of ownership, effective April 1, 2005, of the following new drug application (NDA):

Name of Drug Product: Vaprisol® (conivaptan hydrochloride injection)

NDA Number: 21-697

Name of New Applicant: Astellas Pharma US, Inc.

Name of Previous Applicant: Yamanouchi Pharma America, Inc.

Your correspondence provided the information necessary to effect this change, and we have revised our records to indicate Astellas Pharma US, Inc. as the sponsor of record for this application.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

We remind you that you are responsible for any correspondence outstanding as of the effective date of the transfer.

We request that you notify your suppliers and contractors who have DMFs referenced by your application of the change in ownership so that they can submit a new letter of authorization (LOA) to their Drug Master File(s).

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submissions to the Central Document Room at the following address:

NDA 21-697

Page 2

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
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If your submission only contains paper, send it to the following address:

U.S. Postal Service/Courier/Overnight Mail:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please call me at 301-827-6414.

Sincerely,

{See appended electronic signature page}

Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: Yamanouchi Pharma America, Inc.
Attention: Rudolph Lucek
Vice-President, Regulatory Affairs
Mack Center IV, 4th floor
S. 61 Paramus Road
Paramus, NJ 07652

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/s/

Lina Aljuburi
4/12/05 04:36:09 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-697

Yamanouchi Pharma America, Inc.
Attention: Jacquelyn Hartley
Director, Regulatory Affairs
Mack Centre IV, 4th Floor
S. 61 Paramus Road
Paramus, NJ 07652

Dear Ms. Hartley:

Please refer to your New Drug Application (NDA) submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act for Vaprisol (conivaptan hydrochloride) Injection (YM087; 5 mg/mL, 4 mL per ampoule)

We also refer to the meeting between representatives of your firm and the FDA on February 1, 2005. The purpose of the meeting was to discuss the deficiencies and requests for additional information listed in the November 30, 2004, approvable letter.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 827-6414.

Sincerely,

(See appended electronic signature page)

Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of minutes from meeting held on February 1, 2005

MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 1, 2005
TIME: 4:00 to 5:30 pm
LOCATION: Parklawn Building, Conference Room "C"
APPLICATION: NDA 21-697
DRUG NAME: Vaprisol® (conivaptan hydrochloride) Injection
TYPE OF MEETING: Type C; Guidance

MEETING CHAIR: David Orloff, M.D.

MEETING RECORDER: Lina AlJuburi, Pharm.D., M.S.

FDA ATTENDEES: (Title and Office/Division)

Robert Meyer, M.D.	Director, Office of Drug Evaluation II
David Orloff, M.D.	Director, Division of Metabolic and Endocrine Drug Products (DMEDP)
Mary Parks, M.D.	Deputy Division Director and Clinical Team Leader, DMEDP
Karen Mahoney, M.D.	Medical Officer, DMEDP
Sang Chung, Ph.D.	Clinical Pharmacology and Biopharmaceutics Reviewer
Eric Duffy, Ph.D.	Director, Division of New Drug Chemistry II (DNDCII)
Stephen Moore, Ph.D.	Chemistry Team Leader, DNDCII
William Adams	Chemistry Reviewer, DNDCII
Lina AlJuburi, Pharm.D.	Regulatory Project Manager, DMEDP

EXTERNAL CONSTITUENT ATTENDEES:

Yamanouchi Pharma America, Inc.

Robert Desjardins, M.D.	Chief Development Officer, Euro-American Development
Neila Smith, M.D.	Medical Advisor, Research and Development, Drug Safety
Donna Tempel, Ph.D.	Vice President, Project Management
Osamu Inagaki, Ph.D.	Deputy Director, Project Coordination Department, Drug Development Division
Masakazu Andoh	Acting Head, Statistics and Data Management
Rudy Lucek	Vice President, Regulatory Affairs
Jacquelyn Hartley	Director, Regulatory Affairs
Christine Maulhauser	Director, Regulatory Affairs CMC
Kasutoshi Ban	Research Officer, Parenteral Formulation Research

BACKGROUND:

On January 30, 2004, Yamanouchi Pharma America, Inc. submitted NDA 21-697 for Vaprisol (conivaptan hydrochloride) Injection (YM087). This vasopressin antagonist is a new molecular entity. The sponsor is seeking approval for the indication of treatment of euvolemic or hypervolemic hyponatremia in hospitalized patients. An oral formulation, to be used as a chronically administered drug for the outpatient management of hyponatremia and/or congestive heart failure, was abandoned by the sponsor, because of safety concerns related to CYP3A4 inhibition by conivaptan hydrochloride potentially being the cause of two cases of rhabdomyolysis in the clinical trials (drug interaction between conivaptan hydrochloride and a statin.) Prior to submission of this NDA, the sponsor proposed to submit only one adequate and well-controlled study using the intravenous (IV) formulation in hyponatremia, and to use the results of their larger program using the oral formulation in hyponatremia and congestive heart failure (CHF) to support safety. DMEDP had stated that only the IV hyponatremia trial (Study 087-CL-027) would be considered pivotal. Usefulness of the oral formulation data for assessing safety would depend on comparability between the two formulations in areas relevant to safety.

Upon completion of the reviews, several clinical, biopharmaceutics, and chemistry deficiencies were found to be approvability issues. These items were outlined in the approvable letter that was issued to the sponsor on November 30, 2004.

This end of review conference was requested on December 10, 2004, and the meeting information package was submitted on January 10, 2005.

MEETING OBJECTIVES:

To discuss the deficiencies and requests for additional information listed in the November 30, 2004, approvable letter.

DISCUSSION POINTS:

The sponsor requested responses to the following questions. The questions are repeated below and the responses are bolded.

CLINICAL

1. Does the Division agree that the number of patients/subjects who received a dose of 40 mg/day or greater are adequate for the evaluation of the safety of VaprisolTM?

The number of subjects who received 40 mg/day or greater is acceptable. However, the Sponsor's proposal does not adequately address whether a lower intravenous dose will also be effective and safe. This was and will be an "approvability" issue. The sponsor will need to provide adequate data regarding the efficacy of a lower

dose or doses, or an adequate justification for why data are not needed, before conivaptan HCl can be approved.

2. Does the Division agree to the format and content of the proposed safety amendment (re: proposal submitted September 15, 2004)?

The format and content as proposed in the September 15, 2004, submission is not acceptable. The proposal indicates that only new information will be submitted. The safety amendment should include new safety data combined with the data that has already been submitted during the first review cycle. This information should be presented in tables, including a comparison of frequencies of adverse events in the original NDA with the re-tabulated frequencies that include the new data. Please refer to the November 30, 2004, action letter.

3. Does the Division concur that 40 mg/day is a safe and efficacious dose and a regimen of 2 to 4 days provides a suitable balance of efficacy and drug exposure?

The sponsor needs to better justify why a lower dose has not been studied. Given that the 40 mg oral dose is effective and has a lower bioavailability than an equivalent intravenous dose, it is very likely that an intravenous dose lower than 40 mg/day will be safe and efficacious. Since it appears some of the reported adverse events are dose-related, a lower dose, if still efficacious, would provide a better safety profile and therefore a better benefit-risk balance.

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS

4. Does the Division agree with our proposed method of analysis for evaluating the relationship between pharmacodynamic response and creatinine clearance?

This proposed method is acceptable. It is strongly recommended that a wide range of values for creatinine clearance be included.

5. Does the Division agree with our rationale regarding the need for a loading dose?

Based on the information provided in the meeting information package, the Division does not agree with the rationale for the need of a loading dose. Results of the simulation are not consistent with the results from Study 087-CL-083 and several other studies. According to the results of Study 087-CL-083, plasma conivaptan HCl concentrations after the loading dose were significantly higher (e.g. several fold) than steady-state concentrations after infusion. Safety issues (e.g., injection site reaction) may be correlated with high plasma concentrations after the loading dose. In addition, there was no reasonable justification with pharmacodynamic data for the benefits of a loading dose. Therefore, the sponsor has not provided reasonable justification of a loading dose.

During the meeting, the sponsor acknowledged that the simulation was flawed, and injection site reactions were believed to be related to conivaptan HCl. However, the sponsor stated that the 20 mg loading dose showed acceptable safety profiles.

Most reactions were observed after Day 1, and there were no cases of dose (40 mg and 80 mg) related hypotension. Injection site reactions can be a delayed adverse event. The Division believes that the high concentration after the loading dose cannot be excluded as a factor for the injection site reactions after Day 1. If clinical trials are conducted in the future, the Division recommends that the sponsor optimizes the loading dose of conivaptan HCl.

CHEMISTRY

6. If we perform the testing as outlined in the draft protocol (see Attachment 2), will this fulfill the Agency's request from Chemistry comment number 8. If not, what specific _____ should be investigated?

POST-MEETING COMMENTS:

After discussions with the sponsor during the meeting and internal discussions at the Office level, the Division believes that the sponsor's proposal as presented in the meeting information package and meeting held on February 1, 2005, may well constitute a complete response to the approvable letter issued for NDA 21-697 on November 30, 2004, though the Division and Office remain concerned that the dose and dosing regimens are not optimal. Whether less than optimal doses that are otherwise well supported by data and rationales can lead to approval is a review issue, however, not a filing issue. .

The decision regarding whether or not the Division will request that this NDA go before an Advisory Committee will be made when the complete response is submitted. In either case, the Advisory Committee will not be scheduled for a meeting date on or before May 2005.

REQUEST FOR INFORMATION:

This request for information was emailed to Jackie Hartley on February 16, 2005.

When the sponsor submits the complete response to the approvable letter, the Division requests that the sponsor identify all patients from the entire development program (not just the resubmission population) who had any of the following:

- Doubling of serum creatinine over baseline
- Tripling of serum creatinine over baseline

- Serum creatinine >4 mg/dL at any time during study
- Event designated as a serious renal adverse event by an investigator, regardless of opinion regarding drug-relatedness
- Hospital admission because of worsening renal function
- Oliguria for >24 hours
- Dialysis at any time during treatment or followup

For each of these patients, please include the following information:

- Unique patient identification number
- Treatment group
- Initial dose of conivaptan
- Dose of conivaptan at time creatinine first doubled over baseline
- Dose of conivaptan at time creatinine first went over 4 mg/dL
- Any dose reductions prior to time serum creatinine doubled or went over 4 mg/dL
- Treatment start date
- Treatment stop date
- Baseline serum creatinine and date
- Value and date of first serum creatinine that was double baseline or higher
- Value and date of first serum creatinine that was >4 mg/dL
- Maximum serum creatinine and date
- Presence or absence of congestive heart failure
- Presence or absence of conivaptan concentration >1000 ng/mL at any time during study
- Time from first serum creatinine that was 2x baseline (or >4 mg/dL) to first normal serum creatinine
- Last serum creatinine and date
- Dates of hospitalization during study
- Date of death
- Date(s) of discontinuation or interruption of study drug and dates of resumption
- All urine output measurements
- All urinalysis results
- All serum potassium results
- All dates of dialysis
- Any other data that might help to distinguish between prerenal (volume-depletion-related) renal dysfunction and primary nephrotoxicity

Minutes preparer: Lina AlJuburi

Chair concurrence: David Orloff

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/s/

Lina Aljuburi
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-697

Yamanouchi Pharma America, Inc.
Attention: Jacquelyn Hartley
Director, Regulatory Affairs
Mack Centre IV, 4th Floor
S. 61 Paramus Road
Paramus, NJ 07652

Dear Ms. Hartley:

Please refer to your New Drug Application (NDA) submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act for Vaprisol (conivaptan hydrochloride) Injection (YM087; 5 mg/mL, 4 mL per ampoule)

We also refer to your December 10, 2004, correspondence, received December 13, 2004, requesting a meeting to discuss the deficiencies and requests for additional information listed in the November 30, 2004, approvable letter.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: Tuesday, February 1, 2005
Time: 4:00 to 5:00 pm
Location: Parklawn Building
3rd Floor Conference Center, Room "C"
5600 Fishers Lane
Rockville, MD 20857

CDER participants (tentative):

David Orloff, M.D.	Director, Division of Metabolic and Endocrine Drug Products (DMEDP)
Mary Parks, M.D.	Deputy Division Director and Clinical Team Leader
Karen Mahoney, M.D.	Medical Officer
Hae-Young Ahn, Ph.D.	Clinical Pharmacology and Biopharmaceutics Team Leader
Sang Chung, Ph.D.	Clinical Pharmacology and Biopharmaceutics Reviewer
Stephen Moore, Ph.D.	Chemistry Team Leader
William Adams	Chemistry Reviewer
Lina AlJuburi, Pharm.D.	Regulatory Project Manager

NDA 21-697

Page 2

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at aljuburil@cder.fda.gov so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Lina AlJuburi, (301) 827-6414 or the division secretary, (301) 827-6430.

Provide the background information for this meeting (three copies to the PIND and 11 desk copies to me) at least four weeks prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by January 4, 2005, we may cancel or reschedule the meeting.

If you have any questions, please call me at (301) 827-6414.

Sincerely,

{See appended electronic signature page}

Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Lina Aljuburi
12/27/04 01:25:01 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-697

Yamanouchi Pharma America, Inc.
Attention: Jacquelyn Hartley
Director, Regulatory Affairs
Mack Centre IV, 4th Floor
S. 61 Paramus Road
Paramus, NJ 07652

Dear Ms. Hartley:

Please refer to your New Drug Application (NDA) submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act for Vaprisol (conivaptan hydrochloride) Injection (YM087; 5 mg/mL, 4 mL per ampoule)

We also refer to the meeting between representatives of your firm and the FDA on July 19, 2004. The purpose of the meeting was to discuss the adequacy of the subject exposure data included in the NDA to support the safety of conivaptan hydrochloride.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-6414.

Sincerely,

{See appended electronic signature page}

Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA minutes from meeting held on July 19, 2004

10 Page(s) Withheld

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/s/

Enid Galliers
9/5/03 06:25:17 PM

MEMO TO FILE

Re: NDA 21697 Plans for Content of Eventual Safety Amendment

Date and Time of Telephone Conversation: 26 Aug 04/ 1456

Participants: Dr. Karen Murry Mahoney, Medical Officer, DMEDP; and Ms. Jacqueline Hartley, Yamanouchi Pharma.

On 26 Aug 04, Ms. Jacqueline Hartley of Yamanouchi returned a phone call to me after I had left a message for her in response to her previous fax. On 20 Aug 04, Ms. Hartley had sent a fax to me regarding the studies Yamanouchi intends to include in its planned safety amendment. The company plans to submit an integrated database from the intravenous conivaptan studies -027, -080, -071, -079, -083 and -074. They do not plan to submit an overall database that will include oral program information that was previously submitted. The approach of submitting only information from IV studies is acceptable to me and Dr. Parks. I cannot comment on the adequacy of the numbers of study subjects to be included in this eventual submission, as this information was not included in the fax.

Karen Murry Mahoney, MD

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/s/

Karen Mahoney
8/26/04 03:16:41 PM
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

Mr. Akihiko Matsubara
President and COO
Yamanouchi Pharma America, Inc.
c/o Ms. Sonia R. Brenner, Director, Quality Assurance
Mack Centre IV
S. 61 Paramus Road
Paramus, New Jersey 07652

Dear Mr. Matsubara:

Between June 15 and 22, 2004, Ms. Deborah B. Nixon, representing the Food and Drug Administration (FDA), conducted an inspection of Yamanouchi Pharma America's management procedures for the following clinical study (protocol #1025-007 entitled: "A 4-Day, Double-Blind, Placebo-Controlled, Multicenter Study of IV YM087 (CI-1025) to Assess Efficacy and Safety in Patients with Euvolemic or Hypervolemic Hyponatremia") of the investigational drug Vaprisol™ (conivaptan HCl) injection.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report, the documents submitted with that report, and a June 29, 2004 written response, submitted by Dr. Lawrence E. Posner, we conclude that Yamanouchi Pharma America did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Ms. Nixon presented and discussed with Dr. Posner, Form FDA 483, Inspectional Observations. We wish to emphasize the following:

Yamanouchi Pharma America did not adequately describe in writing the transfer of sponsor obligations to a contract research organization [21 CFR 312.52(a)] in that the contract between Yamanouchi Pharma America and [REDACTED] for the conduct of the study in [REDACTED] did not describe the transfer of responsibility for the clinical trial material (the test article).

We acknowledge Yamanouchi Pharma America's commitment, as stated in Dr. Posner's June 29, 2004, written response, to make appropriate changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies. Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigator Nixon during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

Joseph P. Salewski
Acting Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

cc:

HFA-224

HFD-510 / Document Room: NDA 21-697, Vaprisol™ (conivaptan HCl)

HFD-510 / Review Division Director: David Orloff, M.D.

HFD-510 / Review Division Medical Officer: Karen Mahoney, M.D.

HFD-510 / PM: Lina Aljuburi

HFD-45 / Division File/ Reading File

HFD-47 / Chron File

HFD-46 / U / Slavin

HFD-47 / GCPB I File #10933

HFR-CE350 DIB (Amador)

HFR-CE3565 BIMO MONITOR (Isbill)

HFR-CE350 FIELD INVESTIGATOR (Nixon)

GCF-1 Seth Ray

FEI#: 3003005576

CIB (GCP I): 10933

FACTS#: 533234

Field Classification: VAI

Headquarters Classification:

_____ 1)NAI

_____ 2)VAI no response required

_____ 3)VAI-R response requested

 X 4)VAI-RR adequate response received prior to issuance of VAI-R letter

_____ 5)OAI-WL warning letter

O: \\(slavin\untitled letters\YPA letter

drafted: AS (8/4/04)

reviewed: JS (8/12/04)

finalized:AS: (8/12/04)

Reviewer's Note to file #10399: Inspection of Yamanouchi Pharma America (YPA), Inc. (Ref: NDA 21-697)

This was a routine pre-approval sponsor inspection. The inspection focused on the sponsor's management of protocol #1025-007. Yamanouchi transferred many responsibilities for the management of the clinical trial to a CRO, \

_____ was inspected on June 21 and 22, 2004 for this NDA, and the inspection was classified as NAI.

In general, the sponsor adhered to FDA regulations in its management of the clinical trial. At the completion of the inspection, a one-item Form FDA 483 was issued pertaining to the contract between YPA and _____

_____ sites. This issue has been cited in the letter. YPA submitted a written response to the Form FDA 483.

Attached to the written response was a template for a new document that YPA has instituted. YPA created a "Trial Specifications Worksheet", which specifies what obligations have been transferred to a CRO. This document is filled out by YPA, and attached to the contract.

The inspection is classified as VAI-RR, response received and accepted.

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/s/

Joseph Salewski
8/13/04 10:57:03 AM

MEMORANDUM OF TELECON

DATE: August 5, 2004

APPLICATION NUMBER: NDA 21-697, Vaprisol (conivaptan HCl) Injection

BETWEEN:

Name: Jacquelyn Hartley, Director, Regulatory Affairs
Phone: 201-708-2714
Representing: Yamanouchi Pharma America, Inc.

AND

Name: Karen Mahoney, M.D., Medical Officer
Lina AlJuburi, Pharm.D., M.S., Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Efficacy analysis excluding site 72

BACKGROUND:

On January 30, 2004, Yamanouchi Pharma America, Inc. submitted NDA 21-697 for Vaprisol (conivaptan hydrochloride) Injection (YM087). This vasopressin antagonist is a new molecular entity. The sponsor is seeking approval for the indication of treatment of euvolemic or hypervolemic hyponatremia in hospitalized patients. An oral formulation to be used as a chronically administered drug for the outpatient management of hyponatremia and/or congestive heart failure was abandoned by the sponsor, because of safety concerns related to CYP3A4 inhibition by conivaptan hydrochloride potentially being the cause of two cases of rhabdomyolysis in the clinical trials (drug interaction between conivaptan hydrochloride and a statin.) Prior to submission of this NDA, the sponsor proposed to submit only one adequate and well-controlled study using the intravenous formulation in hyponatremia, and to use the results of their larger program using the oral formulation in hyponatremia and congestive heart failure (CHF) to support safety. DMEDP had stated that only the intravenous hyponatremia trial (Study 027) would be considered pivotal. Usefulness of the oral formulation data for assessing safety would depend on comparability between the two formulations in areas relevant to safety.

In June 2004, the Division of Scientific Investigations (DSI) conducted an investigation of site 72 (Steven Rosansky, M.D. at WJB Dorn Veterans Hospital 6439 Garners Ferry Road, Suite 111F Columbia, South Carolina) for Protocol #087-CL-027 (#1025-007), "A 4-Day, Double-Blind, Placebo-Controlled, Multicenter Study of IV YM087 (CI-1025) to Assess Efficacy and Safety in Patients with Euvolemic or Hypervolemic Hyponatremia." The investigator came to the conclusion that Dr. Rosansky did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects, specifically 21 CFR 312.60 and 21 CFR 312.62(b). This site screened 25 subjects for the study, randomized 10 subjects and 6 subjects completed the study. In conclusion, the investigator deemed the data acceptable in support of NDA 21-697.

Related INDs in
Related INDs in

TELECONFERENCE:

Because of the irregularities seen on the visit to Dr. Rosansky's site (#072), the sponsor was asked to perform the efficacy analyses for Study 027 after excluding site 072. The sponsor agreed to do so.

The phone call was then concluded.

Minutes Preparer: Lina AlJuburi, Regulatory Project Manager

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/s/

Lina Aljuburi
8/10/04 05:31:29 PM
CSO

Executive CAC

Date of Meeting: August 3, 2004

Committee: David Jacobson-Kram, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-901, Member
Abby Jacobs, Ph.D., HFD-024, Member
Chuck Resnick, Ph.D., HFD-110, Alternate Member
Karen Davis-Bruno, Ph.D., Team Leader
Fred Alavi, Ph.D., Presenting Reviewer

Author of Draft: Fred Alavi

NDA #21-697

Drug Name: conivaptan

Sponsor: Yamanouchi Inc

Background:

Conivaptan is an AVP₂ and AVP_{1A} antagonist indicated for treatment of hyponatremia in patients with Syndrome of Inappropriate Antidiuretic Hormone (SIADH) release. Conivaptan is a new molecular entity and first in class to be marketed. Conivaptan PG/EtOH formulation (— propylene glycol, — ethanol) will be administered via intravenous route to SIADH patients for a maximum of 4 days in the hospital (20 mg bolus followed by 40 mg IV infusion for 4 days). Conivaptan is metabolized by and is a potent inhibitor of CYP3A4.

Mouse Carcinogenicity Study:

The sponsor performed a 2-year mouse carcinogenicity study using 0, 3, 10 and 30 mg/kg/d in male and 0, 1, 3 and 10 mg/kg/d in female mice by oral gavage. The dose selection was based on the MTD determined from a 13-WK mouse study. Conivaptan administration to mice by oral gavage for 104 weeks did not lead to a significant drug-related increase in mortality. Sufficient numbers of mice survived to the end of the study at all doses to allow appropriate statistical analysis of tumor incidence. Conivaptan did not significantly increase the incidence of any type of neoplasm in the 2-year mouse carcinogenicity study. The study design and doses used were adequate to qualify as an acceptable mouse carcinogenicity study.

Rat Carcinogenicity Study:

The 2-year rat carcinogenicity study doses were 0, 0.3, 1, 3 and 10 mg/kg/d in males and 0, 1, 3, 10 and 30 mg/kg/d in females by oral gavage. The dose selection was based on the MTD in the 26-WK and 13-WK rat toxicology studies. After 104 weeks of conivaptan administration to rats by oral gavage, there were significant dose-related increases in mortality relative to controls. The survival rate was significantly reduced by the high dose in both male (10 mg/kg/d) and female (30 mg/kg/d) rats. However, sufficient numbers of rats survived at the end of the study to perform appropriate statistical analysis for incidence of tumors. Conivaptan did not significantly increase the incidence of any type of neoplasm in rats. The study design and doses used in rats were adequate to qualify as an acceptable rat carcinogenicity study.

Executive CAC Recommendations and Conclusions:

Mice:

- The Committee finds that the study was adequate based on deaths at 30 mg/kg/day.
- The Committee concludes that the study is negative for tumorigenicity.

Rats:

- The Committee finds the study to be adequate based on decreased survival at ≥ 3 mg/kg/day
- The Committee concludes that the study is negative for tumorigenicity.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\

/Division File, HFD 510

/KDavisBruno, Team leader, HFD-510

/FAlavi, Reviewer, HFD-510

/LAljuburi, CSO/PM, HFD-510

/ASeifried, HFD-024

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/s/

David Jacobson-Kram
8/5/04 09:57:14 AM

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§ 552(b)(5) Deliberative Process

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/s/

Khin U
7/22/04 02:37:50 PM

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§ 552(b)(5) Deliberative Process

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/s/

Khin U
7/16/04 09:39:10 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-697

Yamanouchi Pharma America, Inc.
Attention: Jacquelyn Hartley
Director, Regulatory Affairs
Mack Centre IV, 4th Floor
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Dear Ms. Hartley:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vaprisol (conivaptan HCl) Injection; 5 mg/mL, 4 mL per ampule.

We also refer to your May 28, 2004, correspondence, received June 1, 2004, requesting a meeting to discuss the results of the oral/IV comparative PK study, replacing the flawed PK analysis and proposals for proceeding.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: Monday, July 19, 2004

Time: 4:00 to 5:00 pm

Location: Parklawn Building, 3rd Floor Conference Center, Chesapeake Room

CDER participants (tentative):

David Orloff, M.D.	Director, Division of Metabolic and Endocrine Drug Products (DMEDP)
Mary Parks, M.D.	Deputy Director
Karen Mahoney, M.D.	Medical Officer
Hae-Young Ahn, Ph.D.	Clinical Pharmacology and Biopharmaceutics Team Leader
Sang Chung, Ph.D.	Clinical Pharmacology and Biopharmaceutics Reviewer
Lina AlJuburi, Pharm.D.	Regulatory Project Manager

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at aljuburil@cder.fda.gov so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Lina AlJuburi, (301) 827-6414 or the division secretary, (301) 827-6430.

NDA 21-697

Page 2

Provide the background information for this meeting (three copies to the PIND and 7 desk copies to me) at least two weeks prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by July 2, 2004, we may cancel or reschedule the meeting.

If you have any questions, please call me at (301) 827-6414.

Sincerely,

{See appended electronic signature page}

Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Lina Aljuburi
6/15/04 12:50:39 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-697

Astellas Pharma US, Inc.
Attention: Laura Navarre
Associate Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015

Dear Ms. Navarre:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vaprisol (conivaptan hydrochloride) Injection.

We also refer to your email addressed to Lina AlJuburi, dated May 24, 2005, requesting a waiver of the requirement to submit case report forms in your response to the approvable action letter issued for this NDA on November 30, 2004.

We have reviewed your request and agree that a waiver of the requirement to submit case report forms is justified.

If you have any questions, call Lina AlJuburi, Regulatory Project Manager, at 301-827-6414.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

David Orloff
6/1/05 02:59:07 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-697

Yamanouchi Pharma America, Inc.
Attention: Jacquelyn Hartley
Director, Regulatory Affairs
Mack Centre IV, 4th Floor
S. 61 Paramus Road
Paramus, NJ 07652

Dear Ms. Hartley:

Please refer to your January 30, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vaprisol (conivaptan HCl) Injection; 5 mg/mL, 4 mL per ampule.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on March 30, 2004 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues and your written response is requested:

1. Initial review of the financial disclosure section of the NDA reveals that you did not receive financial disclosure forms from many investigators. We do not note documentation of due diligence on your part to obtain these forms. You must obtain financial disclosure information from all investigators. If you are unable to do so, you must explain how you attempted to obtain the information and why the information is not obtainable. Please refer to the FDA's "Guidance for Industry: Financial Disclosure by Clinical Investigators" which can be found at:
<http://www.fda.gov/oc/guidance/financialdis.html>.
2. In order to minimize the risk of CYP-3A4 drug interactions, during development of conivaptan you agreed to limit the use of conivaptan HCl injection to short-term in-hospital therapy. Do you have a proposal for a program for further risk management?

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

NDA 21-697

Page 2

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, please call Lina AlJuburi, Regulatory Project Manager, at (301) 827-6414.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Lina Aljuburi
4/6/04 03:29:13 PM
for Enid Galliers

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA #: 21-697 Original NDA Submission
Trade Name: Vaprisol Injection
Generic Name: conivaptan hydrochloride
Strengths: 5 mg/mL, 4 mL ampule

Applicant: Yamanouchi Pharma America, Inc.

Date of Application: January 30, 2004
Date of Receipt: January 30, 2004
Date clock started after UN: N/A
Date of Filing Meeting: March 15, 2004
Filing Date: March 30, 2004
Action Goal Date (optional): November 24, 2004
User Fee Goal Date: November 30, 2004

Indication(s) requested: Treatment of euvolemic or hypervolemic hyponatremia in hospitalized patients.

Type of Original NDA: (b)(1) X (b)(2) _____
OR

Type of Supplement: (b)(1) _____ (b)(2) _____
NOTE: A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S X P _____
Resubmission after withdrawal? NO Resubmission after refuse to file? NO
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.) NO

User Fee Status: Paid X Exempt (orphan, government) _____
Waived (e.g., small business, public health) _____

Form 3397 (User Fee Cover Sheet) submitted: YES

User Fee ID # 4604
Clinical data? YES X NO, Referenced to NDA # _____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

NO

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

N/A

Is the application affected by the Application Integrity Policy (AIP)? NO
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? N/A

• Does the submission contain an accurate comprehensive index? YES

• Was form 356h included with an authorized signature? YES

If foreign applicant, both the applicant and the U.S. agent must sign.

• Submission complete as required under 21 CFR 314.50? YES

If no, explain:

• If an electronic NDA, does it follow the Guidance? YES
If an electronic NDA, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

Additional comments:

• If in Common Technical Document format, does it follow the guidance? YES

• Is it an electronic CTD? NO
If an electronic CTD, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

Additional comments:

• Patent information submitted on form FDA 3542a? YES

• Exclusivity requested? NO

Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES

If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as “To the best of my knowledge”

- Financial Disclosure forms included with authorized signature? YES

(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

- List referenced IND numbers: 56,813; _____; 55,607; _____

- End-of-Phase 2 Meeting(s)? Date(s) _____

If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) August 6, 2003

If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? **YES**
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?

N/A

If Rx-to-OTC Switch application: N/A

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?
- Has DOTCDP been notified of the OTC switch application?

Clinical:

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? **N/A**

Chemistry

- Did applicant request categorical exclusion for environmental assessment? **YES**
If no, did applicant submit a complete environmental assessment?
If EA submitted, consulted to Nancy Sager (HFD-357)?
- Establishment Evaluation Request (EER) submitted to DMPQ? **YES**
- If a parenteral product, consulted to Microbiology Team (HFD-805)? **YES**

If 505(b)(2) application, complete the following section: N/A

- Name of listed drug(s) and NDA/ANDA #:
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”).
- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

YES NO
- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the

application should be refused for filing under 314.101(d)(9).

YES NO

- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

YES NO

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

___ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

___ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

___ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

___ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

___ 21 CFR 314.50(i)(1)(ii): No relevant patents.

___ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

___ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)

___ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A YES NO

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?)

N/A YES NO

- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

 - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO

 - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

 - EITHER
 The number of the applicant's IND under which the studies essential to approval were conducted.

IND # _____ NO

OR

A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

N/A YES NO

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 15, 2004

BACKGROUND:

On January 30, 2004, Yamanouchi Pharma America, Inc. submitted NDA 21-697 for Vaprisol (conivaptan HCl) Injection (YM087; 5 mg/mL, 4 mL per ampule). This new molecular entity is dual antagonist of arginine vasopressin (AVP) V_{1A} and V₂ receptors. The sponsor is seeking approval for the indication of treatment of euvolemic or hypervolemic hyponatremia in hospitalized patients. An oral formulation to be

_____ was abandoned by the sponsor, because of safety concerns related to CYP3A4 inhibition by YM087 potentially being the cause of two cases of rhabdomyolysis in the clinical trials (drug interaction between YM087 and a statin.)

ATTENDEES:

Mary Parks, Mike Adams, Stephen Moore, Karen Mahoney, Todd Sahlroot, Fred Alavi, Sang Chung, Dornette Spell-Lesane, Jamie Cross, Laurie Burke, Lina AlJuburi

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Karen Mahoney
Statistical (preclinical):	Cynthia Liu
Statistical (clinical):	Japo Choudhury
Pharmacology:	Fred Alavi
Chemistry:	W. Mike Adams
Environmental Assessment (if needed):	TBD
Biopharmaceutical:	Sang Chung
Microbiology, sterility:	Paul Stinavage
DSI:	Andrea Slavin
Regulatory Project Management:	Lina AlJuburi
Other Consults:	None

Per reviewers, are all parts in English or English translation? **YES**

If no, explain:

CLINICAL FILE X REFUSE TO FILE

• Clinical site inspection needed: **TBD**

• Advisory Committee Meeting needed? **YES, September 9, 2004**

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A

CLINICAL MICROBIOLOGY NA FILE REFUSE TO FILE

STATISTICS FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

• Biopharm. inspection needed: **NO**

PHARMACOLOGY NA FILE REFUSE TO FILE

• GLP inspection needed: **NO**

CHEMISTRY FILE REFUSE TO FILE

• Establishment(s) ready for inspection? **YES**

• Microbiology **YES**

ELECTRONIC SUBMISSION:

Any comments: electronic submission in ctd format available in edr

REGULATORY CONCLUSIONS/DEFICIENCIES:

The application is unsuitable for filing. Explain why:

The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

No filing issues have been identified.

Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

Document no filing issues conveyed to applicant by Day 74.

Meeting Recorder: Lina AlJuburi, Pharm.D., M.S.; Regulatory Project Manager, HFD-510

Meeting Chair: Mary Parks, M.D.; Deputy Director, HFD-510

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/s/

Lina Aljuburi
6/25/04 12:29:15 PM
CSO

USER FEE PAYMENT & PDUFA/FDAMA VALIDATION SHEET

To be completed for ALL original NDAs, efficacy supplements and initial rolling review submissions

Nr. 21697 SUPP TYPE & # NEW NDA Division 510 UFID # 4604

Applicant Name: YAMANOUCHI PHARMA Drug Name: CONIVAPTAN HCL IV INJ

For assistance in filling out this form see the Document Processing Manual for complete instructions and examples.

1. Was a Cover Sheet submitted?
 Yes No

2. Firm in Arrears?
 Yes No

3. Bundling Policy Applied Appropriately? Refer to Draft "Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees"
<http://www.fda.gov/cder/guidance> NA
 Yes No (explain in comments)

4. Administrative Split? (list all NDA#s and Divisions)
 NDA #/Doc Type Div. Fee? (Y/N) NA

5. Type 6?
 Yes No
 Type 6 to which other application?

6. Clinical Data Required for Approval? (Check one)
 Yes*
 Yes, by reference to another application
 NDA # _____ Supp Type & # _____
 No

* Yes if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., adding an adverse reaction, contraindication or warning to the labeling).

7. 505(b)(2) application? (NDA original applications only) Refer to Draft "Guidance for Industry Applications Covered by Section 505(b)(2)"
<http://www.fda.gov/cder/guidance>
 Yes No To be determined

8. Subpart H (Accelerated Approval/Restricted Distribution)?
 Yes No To be determined

9. Exclusion from fees? (Circle the appropriate exclusion. For questions, contact User Fee staff) NA
List of exclusions:

- 2- No fee - administrative split
- 4- No fee - 505b2
- 7- Supplement fee - administrative split
- 9- No fee Subpart H supplement- confirmatory study
- 11- No fee Orphan Exception
- 13- No fee State/Federal exemption from fees

10. Waiver Granted?
 Yes (letter enclosed) No

Select Waiver Type below: Letter Date: _____

- Small Business Barrier-to-Innovation
- Public Health Other (explain)

11. If required, was the appropriate fee paid? NA
 Yes No

12. Application Review Priority
 Priority Standard To be determined

13. Fast Track/Rolling Review Presubmission?
 Yes No

Comments

[Signature]
 PM Signature/Date

02/05/04

This form is the initial data extraction of information for both User Fee payment and PDUFA/FDAMA data elements. The information entered may be subject to change due to communication with the User Fee staff. This form will not reflect those changes. Please return this form to your processing room for processing.

IND 56,81

CC: original archival file
 HFD-007

Processor Name & Date

QC Name & Date

neef
2/3/04

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS Jacquelyn Hartley Yamanouchi Pharma America, Inc. South 61 Paramus Road Mack Centre IV, 4 th Floor Paramus, NJ 07652	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER NDA 21-697
2. TELEPHONE NUMBER (Include Area Code) (201) 708-2714	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: _____ (APPLICATION NO. CONTAINING THE DATA).
3. PRODUCT NAME VAPRISOL™ (conivaptan HCl) - Proposed Name	6. USER FEE I.D. NUMBER 4604


7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CDER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	and Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
--	---	--

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Director, Drug Regulatory Affairs	DATE January 30, 2004
---	--	--------------------------

NDA Filing Meeting Checklist

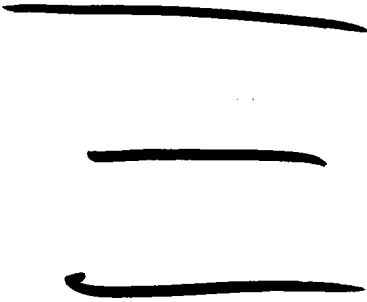
NDA #: 21-697

DRUG: Conivaptan (Vaprisol®)

Sponsor: Yamanouchi Pharmaceuticals

NONCLINICAL PHARMACOLOGY/TOXICOLOGY

ITEM	YES	NO	COMMENT
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	X		
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	X		
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?	X		
4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA? (Please itemize the critical studies included and indicate any significant studies that were omitted from the NDA - e.g., safety pharm, genotox, reprotox, chronic tox, carcinogenicity)	X		Have electronic files of the carcinogenicity studies been submitted for statistical review? Yes Genotoxicity PO, chronic tox studies IV, 4-WK tox in rats & dogs IV and PO reprotox PO, mouse and rat carcinogenicity <i>In vitro</i> Qt studies (hERG & Purkinje) Special safety pharmacology

ITEM	YES	NO	COMMENT
5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?	X		Appear to be adequate
6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (ie., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?	X		
7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	X		(See above)
8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m2 or comparative serum/plasma AUC levels?	X		

ITEM	YES	NO	COMMENT
9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item # 10 below why it is not.	X		The pre-clinical studies submitted were more than generally required to support a 4-day IV conivaptan treatment.
10) Reasons for refusal to file: none			

Fred Alavi, Ph.D.
 Reviewing Pharmacologist

Karen Davis-Bruno, Ph.D.
 Supervisory Pharmacologist

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this page is the manifestation of the electronic signature.**

/s/

Fred Alavi

3/19/04 09:21:38 AM

PHARMACOLOGIST

The NDA 21-697, conivaptan IV application, Pharmtox section was
fileable.

45-Day fileability meeting

Karen Davis-Bruno

3/19/04 09:23:17 AM

PHARMACOLOGIST

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Peter Cooney OPS, Microbiology; HFD-805; PKLN 18B-08		FROM: Division of Metabolic and Endocrine Drug Products Lina AlJuburi, Regulatory Project Manager; HFD-510; PKLN 14B-45 for Mike Adams, CMC Reviewer		
DATE March 15, 2004	IND NO. N/A	NDA NO. 21-697	TYPE OF DOCUMENT Initial NDA submission	DATE OF DOCUMENT January 30, 2004
NAME OF DRUG Vaprisol (conivaptan hcl) Injection		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Vasopressin	DESIRED COMPLETION DATE TBD
NAME OF FIRM: Yamanouchi Pharma America, Inc.				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Filing date March 30, 2004. User fee goal date November 30, 2004. Please review sterility issues in this NDA. Of note, formulation in _____ Mike Adams is the CMC reviewer. This NDA was submitted electronically in ctd format (go to edr.com). This NDA will go to Advisory Committee in September. Feel free to contact me if you have any questions or comments. Many thanks, Lina AlJuburi, Regulatory Project Manager, 301-827-6414				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY Hand delivered to PKLN RM 18B-08		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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

/s/

Lina Aljuburi
3/15/04 01:42:03 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-697

Yamanouchi Pharma America, Inc.
Attention: Jacquelyn Hartley
Director, Regulatory Affairs
Mack Centre IV, 4th Floor
S. 61 Paramus Road
Paramus, NJ 07652

Dear Ms. Hartley:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Conivaptan hydrochloride Injection (YM087; 5 mg/mL, 4 mL per ampule)
Review Priority Classification:	Standard(S)
Date of Application:	January 30, 2004
Date of Receipt:	January 30, 2004
Our Reference Number:	NDA 21-697

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 30, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be November 30, 2004.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request

NDA 21-697

Page 2

for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application. Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/Courier/Overnight Mail:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please call me at (301) 827-6414.

Sincerely,

(See appended electronic signature page)

Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Lina Aljuburi
2/6/04 07:08:55 PM

REQUEST FOR CONSULTATION

TO (Division/Office):
**Director, Division of Medication Errors and
Technical Support (DMETS), HFD-420
PKLN Rm. 6-34**

FROM: Lina AlJuburi, RPM
DMEDP, HFD-510
PKLN Rm. 14B-45

DATE February 18, 2004	IND NO. N/A	NDA NO. 21-697	TYPE OF DOCUMENT NDA	DATE OF DOCUMENT January 30, 2004
NAME OF DRUG Vaprisol (conivaptan hcl) Injection		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Vasopressin	DESIRED COMPLETION DATE September 15, 2004

NAME OF FIRM: Yamanouchi Pharma America, Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

Please review the acceptability of Vaprisol as a trade name.
The NDA was submitted electronically, please go to edr.
Draft Package Insert, Container and Carton Labels can be found in the folder entitled labeling.
Feel free to contact me with any questions or comments.

Many thanks,
Lina AlJuburi, RPM, 827-6414

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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this page is the manifestation of the electronic signature.**

/s/

Lina Aljuburi
2/18/04 04:23:46 PM

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

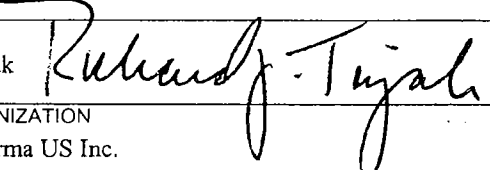
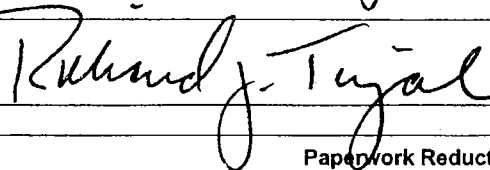
Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See Attached List	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Richard Tajak		TITLE Senior Vice President, Finance
FIRM / ORGANIZATION Astellas Pharma US Inc.		
SIGNATURE 	DATE 6/29/05	

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

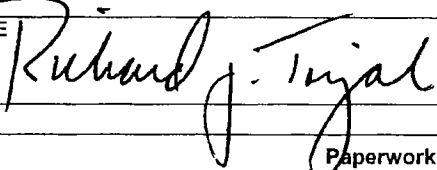
Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Richard Tajak	TITLE Senior Vice President, Finance
FIRM / ORGANIZATION Astellas Pharma US Inc.	
SIGNATURE 	DATE 6/29/05

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

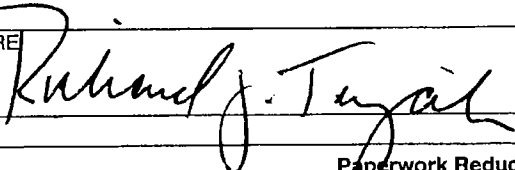
Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Richard Tajak	TITLE Senior Vice President, Finance
FIRM / ORGANIZATION Astellas Pharma US Inc.	
SIGNATURE 	DATE 6/29/05

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning _____, who par-
Name of clinical investigator
ticipated as a clinical investigator in the submitted study Protocol 087-CL-026
Name of

_____, is submitted in accordance with 21 CFR part
clinical study
54. The named individual has participated in financial arrangements or holds financial interests that
are required to be disclosed as follows:

Please mark the applicable checkboxes.

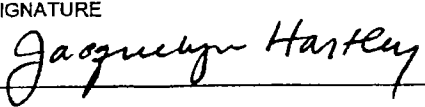
any financial arrangement entered into between the sponsor of the covered study and the
clinical investigator involved in the conduct of the covered study, whereby the value of the
compensation to the clinical investigator for conducting the study could be influenced by the
outcome of the study;

any significant payments of other sorts made on or after February 2, 1999 from the sponsor of
the covered study such as a grant to fund ongoing research, compensation in the form of
equipment, retainer for ongoing consultation, or honoraria;

any proprietary interest in the product tested in the covered study held by the clinical
investigator;

any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in
the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with
a description of steps taken to minimize the potential bias of clinical study results by any of the
disclosed arrangements or interests.

NAME Jacquelyn Hartley	TITLE Director, Drug Regulatory Affairs
FIRM/ORGANIZATION Yamanouchi Pharma America, Inc., Mack Centre IV, 4th Floor, S. 61 Paramus Road, Paramus, NJ	
SIGNATURE 	DATE January 30, 2004

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857



Yamanouchi Pharma America, Inc.

Mack Centre IV
S. 61 Paramus Road, Paramus, NJ 07652
Telephone: (201) 291-2556 Fax: (201) 291-7929

January 9, 2004

U. S. Food and Drug Administration (360909)
Mellon Client Service Center
Room 670
500 Ross Street
Pittsburgh, PA 15262-0001

Ladies and Gentlemen:

**Re: Human New Drug Application Fee
NDA 21-697
YM087 (conivaptan hydrochloride) Injection
User Fee# 4604**

Enclosed please find a check in the amount of \$573,500 made payable to the U.S. Food and Drug Administration. This payment represents the user fee required for the filing of our Original New Drug Application (NDA 21-697) for YM087 (conivaptan hydrochloride) Injection dated January 30, 2004.

If you have any questions, please do not hesitate to contact the undersigned.

Sincerely,

YAMANOUCHI PHARMA AMERICA, INC.

Rudolph W. Lucek
Vice President
Drug Regulatory Affairs
Phone: (201) 909-3041
Fax: (201) 909-5244

Enclosure: Check #53458