

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-275

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

**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

22-275

NAME OF APPLICANT / NDA HOLDER

Otsuka Pharmaceutical Co., Ltd.

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)

SAMSKA

ACTIVE INGREDIENT(S)

Tolvaptan

STRENGTH(S)

15mg, 30mg, 60mg

DOSAGE FORM

Tablet

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
5,258,510

b. Issue Date of Patent
11/02/1993

c. Expiration Date of Patent
11/02/2010

d. Name of Patent Owner
Otsuka Pharmaceutical Co., Ltd.

Address (of Patent Owner)
2-9, Kanda-Tsukasamachi, Chiyoda-ku

City/State
Tokyo, Japan

ZIP Code
101-8535

FAX Number (if available)

Telephone Number
81-3-3292-0021

E-Mail Address (if available)

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)

 Otsuka America Pharmaceutical, Inc.

Address (of agent or representative named in 1.e.)
2440 Research Boulevard

City/State
Rockville, MD

ZIP Code
20850

FAX Number (if available)
(301) 212-8643

Telephone Number
(240) 683-3049

E-Mail Address (if available)
sheila.cleary@otsuka.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) 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.)

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
10/11/2007

Sheila A. Cleary

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.

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Sheila A. Cleary	
Address Otsuka America Pharmaceutical, Inc. 2440 Research Boulevard	
City/State Rockville, MD	
ZIP Code 20850	
Telephone Number (240) 683-3049	
FAX Number (if available) (301) 212-8643	
E-Mail Address (if available) sheila.cleary@otsuka.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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/fdahm/fdahm.htm>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

**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

22-275

NAME OF APPLICANT / NDA HOLDER

Otsuka Pharmaceutical Co., Ltd.

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)

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ACTIVE INGREDIENT(S)

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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

5,753,677

b. Issue Date of Patent

05/19/1998

c. Expiration Date of Patent

05/19/2015

d. Name of Patent Owner

Otsuka Pharmaceutical Co., Ltd.

Address (of Patent Owner)

2-9, Kanda-Tsukasamachi, Chiyoda-ku

City/State

Tokyo, Japan

ZIP Code

101-8535

FAX Number (if available)

Telephone Number

81-3-3292-0021

E-Mail Address (if available)

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)

 Otsuka America Pharmaceutical, Inc.

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

2440 Research Boulevard

City/State

Rockville, MD

ZIP Code

20850

FAX Number (if available)

(301) 212-8643

Telephone Number

(240) 683-3049

E-Mail Address (if available)

sheila.cleary@otsuka.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?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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).	<input type="checkbox"/> Yes	<input type="checkbox"/> 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.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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.)	<input type="checkbox"/> Yes	<input type="checkbox"/> 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?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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.)	<input type="checkbox"/> Yes	<input type="checkbox"/> 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?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Patent Claim Number (as listed in the patent) 1, 3, 6, 9, 16, 20, 25, 31, 34, 50, 51, 52, 53, 55, 58 and 75	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?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> 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.) Worsening Heart Failure Hyponatremia	

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
10/11/2007

Sheila A. Cleary

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
Sheila A. Cleary

Address
Otsuka America Pharmaceutical, Inc.
2440 Research Boulevard

City/State
Rockville, MD

ZIP Code
20850

Telephone Number
(240) 683-3049

FAX Number (if available)
(301) 212-8643

E-Mail Address (if available)
sheila.cleary@otsuka.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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

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

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
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- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/fdahtm/fdahum.htm>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXCLUSIVITY SUMMARY

NDA # 22-275

SUPPL #

HFD # 110

Trade Name Samsca

Generic Name tolvaptan

Applicant Name Otsuka

Approval Date, If Known

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.

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:

d) Did the applicant request exclusivity?

YES NO

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

5 years (NME)

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?

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

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: Dan Brum
Title: RPM
Date: 8/1/08

Name of Office/Division Director signing form: Robert Temple, M.D.
Title: Office Director

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

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/s/

Robert Temple
8/1/2008 05:27:01 PM

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-275 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DCRP PDUFA Goal Date: 8/22/08 Stamp Date: 10/23/07

Proprietary Name: SAMSCA

Established/Generic Name: tolvaptan

Dosage Form: tablets

Applicant/Sponsor: Otsuka

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): one
(Attach a completed Pediatric Page for each indication in current application.)

Indication: euvolemic and hypervolemic hyponatremia

Q1: Is this application in response to a PREA PMC/PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMC/PMR #: _____

Does the division agree that this is a complete response to the PMC/PMR?

- Yes. Please proceed to Section D.
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
 No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 No: Please check all that apply:
 Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 Deferred for some or all pediatric subpopulations (Complete Sections C)
 Completed for some or all pediatric subpopulations (Complete Sections D)
 Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 Extrapolation in One or More Pediatric Age Groups (Complete Section F)
(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):
 Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	0 yr. __ mo.	5 yr. __ mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input checked="" type="checkbox"/> Other	<u>6</u> yr. __ mo.	<u>17</u> yr. __ mo.	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): <u>TBD</u>							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cdernmhs@fda.hhs.gov) OR AT 301-796-0700.

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:					
Population		minimum	maximum		
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.		

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

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/s/

Dan Brum
8/13/2008 01:13:08 PM

CERTIFICATION: DEBARRED PERSONS

Otsuka Pharmaceutical Development & Commercialization, Inc. hereby certifies that it did not use and will not use in any capacity the services of any person listed as debarred as of the April 16, 2007 Debarment List under Section 306(a) or (b) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 335(a) and (b)] as published in the FEDERAL REGISTER, in connection with this Application for tolvaptan oral tablets.

Signed:

See appended electronic signature page

George Hemsworth, Ph.D.
Executive Director, Regulatory Affairs
Otsuka Pharmaceutical Development & Commercialization, Inc.
2440 Research Blvd.
Rockville, MD 20850



Otsuka Pharmaceutical Development & Commercialization, Inc.

OPC-41061

SIGNATURE PAGE

Short Title: 22275_debarment statement_revised_07Nov2007

Object ID: 090085488069d22f

Document Version: 2.0,Approved,CURRENT

Approval Name
Hemsworth_George

Approval Capacity
Regulatory

Approval Date Local
07-Nov-2007 13:45:42

1.12.14 Environmental Analysis

CATEGORICAL EXCLUSION STATEMENT

The subject of the proposed action (NDA for tolvaptan, a new active substance) will not significantly affect the quality of the human environment and meets the requirements for a categorical exclusion from submitting an environmental assessment, 21 CFR 25.31(b). In addition, to the best knowledge of Otsuka Pharmaceutical Co., Ltd., no extraordinary circumstances exist [21 CFR 25.15 (d)]. This drug is manufactured using a synthetic process and is not known to be derived from any wild-sourced plant and/or animal material. Additionally, the expected introduction concentration (EIC) of the substance at the point of entry into the aquatic environment will be well below 1 part billion. (See also Confidential Appendix 1.)

1 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Withheld Track Number: Administrative-12



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-275

INFORMATION REQUEST LETTER

Otsuka Pharmaceutical Company, Ltd.
Attention: Kusuma Mallikaarjun, Ph.D.
2440 Research Blvd.
Rockville, MD 20850

Dear Dr. Mallikaarjun:

Please refer to your New Drug Application (NDA) dated October 23, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SAMSCA (tolvaptan) 15, 30, and 60 mg Tablets.

We also refer to our complete response letter dated August 22, 2008, your submission dated October 2, 2008, our response dated November 2, 2008, and your November 20, 2008 resubmission that included your proposed Risk Evaluation and Mitigation Strategy (REMS).

In our August 22, 2008 letter, we notified you that a REMS was required for SAMSCA to ensure that the benefits of the drug outweighed the risk of overly rapid correction of serum sodium leading to osmotic demyelination. As part of the REMS, we indicated that the REMS must include a Medication Guide to help prevent serious adverse events and Elements to Assure Safe Use _____ including an Implementation System. b(4)

We have completed our review of your proposed REMS as described in your submissions of October 2, 2008 and November 20, 2008. Although we believe a REMS is necessary to ensure the safe use of SAMSCA, upon further consideration, we do not believe that a _____ is warranted. We believe that osmotic demyelinating syndrome (ODS) is a risk associated with any therapeutic intervention aimed at correcting serum sodium; none of the available therapies to date have indicated a need for restrictions. There is no evidence that treatment with SAMSCA places the patients at any greater risk for the development of ODS than any other treatment approach. Moreover, the key strategy for risk mitigation is hospitalization and close monitoring of serum sodium; this is the standard of care for severe or symptomatic hyponatremia, the population for which SAMSCA is indicated. In addition, we have determined that the proposed elements to assure safe use _____ b(4)

_____ (that you proposed) could interfere with the availability of SAMSCA and increase the risks of interrupted therapy. Specifically, the proposed elements to assure safe use could hinder patient access to SAMSCA following hospital discharge and thereby increase the risk of clinically significant interruptions in therapy. Therefore, although, we continue to believe that a

REMS is necessary to ensure the benefits of SAMSCA outweigh its risks, we have concluded that it is not necessary to include elements to assure safe use as part of the REMS.

Based on our current understanding of the risk of osmotic demyelination with SAMSCA therapy, we have determined that the SAMSCA REMS must include the following elements:

1. Medication Guide

A Medication Guide is necessary to inform patients of the serious risk, particularly the risk of osmotic demyelinating syndrome. The Medication Guide may help prevent the risk of ODS by informing patients of necessary measures to mitigate the risk of osmotic demyelinating syndrome.

2. Communication Plan

You should revise the proposed Dear Healthcare Provider Letter. In Appendix B, we have outlined the necessary revisions. You should also develop a Prescriber Education Brochure as part of the REMS proposal. The Prescriber Brochure is considered as an element under the Communication Plan in the REMS document. The Prescriber Brochure is intended to explain to healthcare providers of the need for initiation and re-initiation of SAMSCA in the hospital, need for frequent monitoring during initiation and titration, and use in an appropriate patient population. In Appendix C, we have listed key points for you to consider in developing the Prescriber Brochure.

You should submit a revised proposed REMS using the template included in Appendix A. The revised proposed REMS must include the elements described above in addition to a timetable for submission of assessments. You may include additional information in an update to the REMS Supporting Document.

You will need to revise the proposed information needed for assessments to include revised surveys (Appendix D). As part of the pharmacovigilance plan, you will submit as expedited reports cases of suspected osmotic demyelination reported with use of SAMSCA. For suspected cases of osmotic demyelinating syndrome, you will collect information on the patient, including radiologic confirmation of diagnosis of osmotic demyelinating syndrome, rate of initial sodium correction, and concomitant risk factors and provide an analysis of these events in the REMS assessment. You will also monitor trends for the events associated with osmotic demyelination. The following events may be associated with this potential outcome, seen in any patient exposed to the product:

- a. Slurred speech
- b. Difficulty swallowing
- c. Quadraparesis
- d. Seizures
- e. Coma
- f. Death

Promotional Materials:

NDA 22-275
REMS IR Letter
SAMSCA (tolvaptan)

We remind you that REMS materials should focus on the risks that the REMS is intended to mitigate, and are not appropriate for use in a promotional manner. We have determined that the following materials make promotional claims and/or presentations and do not represent materials appropriate for REMS communication. Therefore, we do not consider these pieces to be part of the REMS. We recommend that you submit these materials to DDMAC in compliance with advertising and promotion regulations:

- Hospital Pharmacist Letter
- Patient Guide

REMS Materials

You should remove the following items from your proposed REMS as they are no longer considered part of the REMS:

A large rectangular area of the document has been redacted with a thick black line.

b(4)

Prominently identify subsequent submissions related to the Proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 22-275
PROPOSED REMS – AMENDMENT**

Labeling with Boxed Warning (Appendix E)

We recommend a Boxed Warning delineating the most serious risk of too rapid rise of serum sodium leading to osmotic demyelination syndrome, hence the requirement to initiate and re-initiate SAMSCA in a hospital setting which allows for appropriate monitoring of serum sodium. Physicians should monitor patients' serum sodium concentrations during initial hyponatremia treatment and ensure that correction rates are maintained within recommended limits.

If you have any questions, please call Dan Brum, PharmD, RAC, Regulatory Project Manager, at 301-796-0578.

Sincerely,

[See appended electronic signature page]

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosed: Appendices A (REMS Template), B (Dear Healthcare Provider Letter), C (Prescriber Brochure Critical Points), D (Comments on proposed surveys), and E (draft labeling text)

32 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Norman Stockbridge
4/8/2009 12:11:33 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-275

Otsuka Pharmaceutical Company, Ltd.
Attention: Kusuma Mallikaarjun, Ph.D.
2440 Reasearch Blvd.
Rockville, MD 20850

Dear Dr. Mallikaarjun:

We acknowledge receipt of your October 2, 2008 resubmission to your New Drug Application (NDA) for Samsca (tolvaptan) 15, 30, and 60 mg Tablets, which included a Proposed Risk Evaluation and Mitigation Strategy (REMS).

We also refer to our complete response letter dated August 22, 2008 in which we requested a REMS for Samsca and provided a template for guidance on REMS format and content. In addition, we requested that you provide a REMS Supporting Document to include specific sections.

We acknowledge that your October 2, 2008, submission contains a REMS Supporting Document and appendices; however, it does not contain a concise Proposed REMS that is limited to the information outlined in the REMS Template (see Appendix A). Furthermore, your REMS Supporting Document does not include all of the required sections.

We do not consider this a complete response to our action letter; therefore, the review clock will not start at this time. To address the deficiencies in your submission, we recommend that you do the following:

Proposed REMS Template and Relevant Materials

- Submit a Proposed REMS that contains concise information specific to Samsca using the attached REMS Template (see Appendix B).
- Append copies of all relevant REMS materials including _____
_____ Proposed REMS document.

b(4)

2 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Withheld Track Number: Administrative- 14

Other

b(4)

If you have any questions, please call Dan Brum, Pharm.D., MBA, Regulatory Project Manager,
at (301) 796-0578.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Drugs
Office of Drug Evaluation I
Center for Drug Evaluation and Research

4 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Norman Stockbridge
11/6/2008 02:17:09 PM

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: August 1, 2008

TO: Dan Brum
Regulatory Health Project Manager
Aliza Thompson, M.D./Clinical Reviewer
Shari Targum, M.D./Medical Officer
Division of Cardio-Renal Drug Products (DCRDP) HFD-110

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

FROM: Sharon K. Gershon, Pharm.D.
DSI Regulatory Reviewer

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-275

Sponsor: Otsuka Pharmaceutical Development

DRUG: Samska (tolvaptan) 15 and 30 mg tablets

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION:
Protocol 156-03-236: Reduction in mortality and improvement in patient-assessed global clinical status in subjects hospitalized with worsening congestive heart failure.
Protocol 156-03-238: achieve and maintain increased serum sodium for the treatment of nonhypovolemic hyponatremia arising from a variety of etiologies

CONSULTATION REQUEST DATE: December 20, 2007

ACTION GOAL DATE: July 30, 2008

PDUFA DATE: August 23, 2008

I. BACKGROUND:

This audit was conducted as part of a routine PDUFA inspection request. The application was submitted to support the following indications: reduce mortality and improve clinical status in patients with worsening congestive heart failure; and achieve and maintain increased serum sodium for treatment of hyponatremia arising from a variety of etiologies. Three studies and seven study sites were audited as part of the inspection. These sites were selected for audit because they were all a top enrolling study site for the particular study, and they produced results for the primary efficacy outcome that were more favorable for the study drug than that seen for the study population as a whole.

Specific issues addressed during the inspection included whether the electronic capture documents (CRFs) submitted by the investigator accurately represented the data in the source documents. Site 521 (Jandik), showed a large disparity in deaths (many more in placebo arm) and a more favorable drug effect on weight than that seen in the study population as a whole. Data from sites 152 (Krueger) and 787 (Macarie) also showed a more favorable drug effect on weight than that seen in the study population as a whole. Data from sites 35 (Josiasen), 39 (Levine), 200 (Gross) and 123 (Filipovsky) showed a more favorable drug effect on serum sodium than that seen in the hyponatremia study population as a whole.

The indications and their respective studies were as follows:

I. Proposed Indication: Reduction in mortality and improvement in patient-assessed global clinical status in subjects hospitalized with worsening congestive heart failure.

Protocol Used to Support the Indication:

156-03-236 (Heart Failure): “Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Long Term Efficacy and Safety of Oral Tolvaptan Tablets in Subjects Hospitalized with Worsening Congestive Heart Failure.”

II. Proposed Indication: achieve and maintain increased serum sodium for the treatment of nonhypovolemic hyponatremia arising from a variety of etiologies

Protocols Used to Support the Indication:

156-03-238 (Hyponatremia): “International, multicenter, randomized, double-blind, placebo-controlled, efficacy and safety study of the effects of titrated oral tolvaptan tablets in patients with hyponatremia. “SALT 2 TRIAL)” (Sodium Assessment with Increasing Levels of Tolvaptan in Hyponatremia 2)

156-02-235 (Hyponatremia): “Multicenter, randomized, double-blind, placebo-controlled, efficacy and safety study of the effects of titrated oral tolvaptan tablets in patients with hyponatremia. “SALT 2 TRIAL)” (Sodium Assessment with Increasing Levels of Tolvaptan in Hyponatremia)

Tolvaptan is an oral vasopressin antagonist with relative affinity for the V2 receptor which has been shown to induce a diuresis with proportionally more free-water than sodium loss. The current study is being undertaken in order to evaluate whether tolvaptan, an oral AVP inhibitor, will be effective in correcting mild to moderate hyponatremia, and to elucidate the effect of this correction on the subject’s well-being.

II. Clinical Inspection Summary

Clinical Investigator/Site #	No. of Subjects	Inspection Dates	Protocol	Field Classification	EIR Receipt Date
Site # 521 Josef Jandik, MD Interni oddeleni, Oblastni Nemocnice Nachod Bartonova 591 547 01 Nachod Czech Republic	46 screened; 45 randomized; 12 subjects died during study	7/21- 7/25/2008	156-03-236 (CHF)	VAI- data acceptable	pending
Site #787 Cezar Eugen Macarie MD Institutul de Boli Cardiovasculare 258, Fundenia Str. 022328 Bucharest	52 enrolled; 2 discontinued due to AEs; 7 died during study	7/28 – 8/1/2008	156-03-236 (CHF)	VAI – data acceptable	pending
Site #123 Jan Filipovsky, MD, PhD Fakultni Nemocnice Plzen E. Benese 13 Plzen-Boy 305 99 Czech Republic	35 screened; 13 randomized; 7 completed	7/14 –18/2008	156-03-238 (SALT 2)	VAI – data acceptable	pending
Site #200 Peter Gross, MD Universitätsklinikum Carl Gustav Carus Fetscherstr, 74 Dresden 1307 Germany	21 enrolled	5/26 – 30/2008	156-03-238 (SALT 2)	VAI – data acceptable	7/10/2008
Site #152 Steven K Krueger, MD, FACC Bryan LGH Heart Institute 3901 Pine Lake Road, Suite 300 Lincoln, NE 68516	75	3/3 – 7/2008	156-03-236 (CHF)	VAI – data acceptable	5/15/2008
Site #039 Barton Levine, MD Veteran’s Administration Greater Los Angeles Health Care Center 11301 Wilshire Blvd Building 500, Room 6024 Los Angeles, CA 90073	17	2/4 – 28/2008	156-02-235 (SALT 2)	VAI – data acceptable	4/5/2008
Site #035 Richard C Josiassen, PhD The Arthur P Noyes Research Foundation Norristown, PA 19401	12	3/3 – 7/2008	156-02-235 (SALT 2)	NAI – data acceptable	3/25/2008

NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAIr = Deviation(s) from regulations, response requested. Data acceptable
OAI = Significant deviations for regulations. Data unreliable
Pending = Inspection not completed

1. Josef Jandik, MD, Interni oddeleni, Oblastni, Nemocnice Nachod, Bartonova 591
547 01 Nachod Czech(156-03-236 CHF)

- a. **What was inspected?** The inspection followed the routine Compliance Program for Clinical Investigators (CP 7348.811). Forty-six subjects were screened in this study. One subject withdrew consent at Day 1. Forty-five subjects received treatment. Twelve subjects died during the study. Documents pertaining to each fatality were collected. The inspection reviewed source records, and assessed their consistency with the Case Report Forms, and data listings. The inspection reviewed weights and survival for all but six of the enrolled subjects.
- b. **General Observations:** A one-observational item FDA-483 was issued to Dr. Jandik, for not conducting the investigation according to the investigational plan [21 CFR 312.60]. Specifically, the protocol required that all serious adverse events were to be reported to the sponsor immediately (within 24 hours) after the investigator became aware of the event. The investigation found that not all SAEs were reported as required. Two deaths, one cancer event and one hospitalization were not reported within 24 hours to the sponsor, as required by the protocol. Examples were for Subjects 9596 (uterine cancer), 1098 (hospitalized), 5560 and 9020 (deaths). For Subject 9596, the event began on January 14, 2006 and was reported on February 24, 2006. Subject 9020 died on [REDACTED] of ventricular fibrillation after worsening CHF, and the event was reported on February 17, 2005. Subject 5560 died of worsening CHF on [REDACTED] and the event was reported on September 30, 2005. Subject 1098 was hospitalized on [REDACTED] due to global status deterioration with fever, and the event was reported on February 22, 2005.

b(6)

Due to time constrictions, Subjects' weights (at screening, day 1, W4, W8, ET and F/U) and survival data was reviewed for all but six subjects. No discrepancies were noted. During the review of source documents, some discrepancies associated with the cardiovascular assessments were observed. Some discrepancies appeared to be transcription errors from source records to CRFs, while others appeared to be the investigator's failure to report symptoms reported by patients (dyspnea, fatigue), as described on the NYHA category assessments.

- c. **Limitations to the inspection:** The observations noted are based on preliminary communications with the FDA field investigator and a facsimile copy of the Form FDA-483. The EIR is currently being finalized and will be submitted to DSI upon completion. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.
- d. **Assessment of Data Integrity:** The data for Dr. Jandik's site, associated with Protocol 156-03-236(CHF) submitted to the Agency in support of NDA 22-275, appear reliable based on available information. The general observations described above are based on preliminary

communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

2. Peter Gross, MD, Universitätsklinikum Carl, Gustav Carus, Fetscherstr, 74 Dresden 1307 Germany (156-03-238 hyponatremia)

a. **What was inspected?** The inspection followed the routine Compliance Program for Clinical Investigators (CP 7348.811). Twenty-six subjects were screened, there were 5 screen failures (reported as failure to meet inclusionary criteria). Twenty-one subjects were randomized and 16 subjects completed the study. A full review of file records for all 21 subjects was done. Informed consent documents were verified as signed prior to initiating research procedures for all subjects. The inspection assessed consistency between data recorded on electronic CRFs (e-CRFs) to the source documents and data listings. The inspection reviewed inclusion/exclusion criteria, primary and secondary endpoints, clinical laboratory results, adverse event reports, concomitant therapies, and test article drug accountability records.

b. **Limitations:** _____ assisted the interpretation of study records and provided translations from German to English and English to German. The study used an electronic CRF system from _____. The data was transmitted online from the site to Otsuka, and had electronic signatures and audit trail capabilities.

b(4)

c. **General Observations:** Subject records were satisfactorily organized. The investigator was found to be adequate in the execution of the Protocol. The study was found to be well controlled and well documented. No significant regulatory deviations were observed. Consistent with the routine clinical investigator compliance program assessments the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. CRFs were assessed for data consistency with the source documents. A one-observational FDA-483 was issued to Dr. Gross for failure to prepare or maintain adequate and accurate case histories [21 CFR 312.62(b)]. Specifically, 1) the inspection found that for Subject 2038, data listings from the electronic CRF (e-CRF) under the Urine Collection heading, listed start and stop times for the 24 hour post-dose urine collection period and urine volumes that were different from the values recorded in source documents. For example, the e-CRF documented that Day 1, 24-hour post dose start time as 0800, whereas the source documents recorded the time as 0900; the e-CRF documented the Day 2, 24-hour post-dose urine volume as 1050 mL, whereas the source documents recorded urine volume as 1150 mL; for Subject 4013, the ICD maintained in source record files is dated April 26, 2004, where as the data listings state IC was obtained on May 10, 2004. There was no written IC dated May 10, 2004 in source documentation.

d. **Assessment of Data Integrity:** The data from Dr. Gross' site, associated with the audited Protocol 156-03-238 (hyponatremia), submitted to the agency in support of NDA 22-275, may be considered acceptable. The discrepancies noted during the inspection relating to inconsistent entries do not affect the validity of the data.

3. Cezar Eugen Macarie MD Institutul de Boli Cardiovasculare 258, Fundenia Str.
022328 Bucharest Romania (156-03-236 CHF)

a. **What was inspected?** The inspection followed the routine Compliance Program for Clinical Investigators (CP 7348.811). Fifty-two subjects were enrolled in the study. Two subjects withdrew consent. One subject was withdrawn by the PI for inability to get transportation to the study site. One subject who withdrew consent, died. Two subjects were discontinued due to adverse events. A total of 7 subjects died during the study period. Documents pertaining to these deaths were collected. The CRFs and corresponding source documents were reviewed for 15 subjects. A review of 100% of Informed Consent Documents was done; all subjects signed and dated ICDs prior to initiating study procedures. One subject (#6552) was mistakenly un-blinded when one sub-investigator tried to remove a medication label that was erroneously pasted on the wrong page of the CRF. The progress notes disclosed that the un-blinded sub-investigator did not perform any subsequent study visits, as instructed by the CRO/sponsor. Review of weight data for the 15 subjects showed no discrepancies. Weight reported for 17 additional subjects at different times during the study (V0, Day 1, Discharge or Day 7, different weeks during the study) disclosed no discrepancies.

b. **Limitations to the inspection:** The observations noted are based on preliminary communications with the FDA field investigator and a facsimile copy of the Form FDA 483. The EIR is currently being finalized and will be submitted to DSI upon completion. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

c. **General Observations:** A 3-part, one item-FDA-483 was issued for failure to conduct the investigation according to the investigational plan [21 CFR 312.60]. Specifically: 1) not all Serious Adverse Events were reported within 24 hours of knowledge, as required by the protocol (Subjects 8224, 2580, 6140 and 8521); 2) failure by the sub-investigators to date and sign some study progress notes dictated to and recorded by the cardiology student residents; 3) failure to provide the revised informed consent document at the next visit to the subjects enrolled prior to Protocol Amendment 1.

d. **Integrity of data:** The data from Dr. Macarie's site, associated with the audited Protocol 156-03-326(CHF) submitted to the agency in support of NDA 22-275, may be considered acceptable. However, DSI recommends that the data from Subject #6552 where blinding was compromised, be eliminated. The observations noted are based on preliminary communications with the FDA field investigator and a facsimile copy of the Form FDA-483. The EIR is currently being finalized and will be submitted to DSI upon completion. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

4. Jan Filipovsky, MD, PhD, Fakultni Nemocnice Plzen, E. Benese 13, Plzen-Boy 305 99
Czech Republic (156-03-238 hypnatremia)

a. **What was inspected?** The inspection followed the routine Compliance Program for Clinical Investigators (CP 7348.811). A total of 35 subjects were screened for this study; 13 subjects

were randomized; 1 subject withdrew consent, and 4 subjects were discontinued after experiencing adverse events. One subject was discontinued by the clinical investigator due to poor health. However, review of the corresponding medical chart disclosed the subject was administered NaCl infusion while on study treatment that would require immediate discontinuation. The inspection reviewed serum sodium levels reported in the subject's hospital charts with the data listings. No discrepancies were noted. The inspection reviewed laboratory records and 100% signed informed consent documents. A signed and dated ICD for each participating subject was on file. Inclusionary criteria were reviewed and the investigation found that one subject had documented angina at rest Grade IV, which was exclusionary. This observation was noted in the source records, but was not documented in the corresponding hospital chart.

b. Limitations to inspection: Due to time constrictions and inability of the interpreter to read the hospital chart progress notes, a complete review to determine adverse event reporting during hospitalization could not be completed. The sponsor provided the interpreter, and he only reviewed a hospital discharge summary, which was part of the source documents. The observations noted are based on preliminary communications with the FDA field investigator and a facsimile copy of the Form FDA 483. The EIR is currently being finalized and will be submitted to DSI upon completion. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

c. General Observations: A 2 observational item, FDA-483 was issued for: 1) for not conducting the investigation according to the investigational plan [21 CFR 312.60]. Specifically, the protocol required that all serious adverse events were to be reported to the sponsor immediately (within 24 hours) after the investigator became aware of the event. The investigation found that not all SAEs were promptly reported as required by the protocol; and 2) failure to maintain all study documents on file [21 CFR 312.62(c)]. Specifically, the investigation found Dr. Filipovsky failed to report SAEs experienced by 4 subjects (2029, 1031, 2088, and 2073) immediately to the sponsor, and failed to report the hospitalization of a participating subject (2041). Subject 2041 was hospitalized due to accidental injury that caused spontaneous drain of ascites – this event was not reported to the sponsor. Subject 2029 experienced allergic reaction (rash) on July 4, 2004, the event was reported on July 8, 2004. Subject 1031 was hospitalized on [REDACTED] due to continuing dyspepsia and bronchopneumonia. The event was reported on July 8, 2004. Subject 2088 was hospitalized due to mineral misbalance on [REDACTED] the event was reported July 8, 2005. Subject 2090 was hospitalized on [REDACTED] for worsening health state and died on [REDACTED]

b(6)

The investigation also found that the PI failed to maintain all study documents on file for 2 years following the data a marketing application is approved for the indication for which it is being investigated. The PI stated that the study monitor asked him to destroy randomization confirmation facsimiles received from the IVRS system and laboratory requisition forms of samples collected from the subjects that were submitted to the central laboratory. The sponsor provided a set of these destroyed documents.

d. Integrity of Data: The data from Dr. Filipovsky's site, associated with the

audited Protocol 156-03-328(hyponatremia) submitted to the agency in support of NDA 22-275, may be considered acceptable, with the exception of the one subject who did not meet the inclusionary criteria (reported Angina at rest Grade IV). The general observations described above are based on preliminary communication from the field investigator, and a facsimile of the FDA-483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

5. Steven K Krueger, MD, FACC, 3901 Pine Lake Road, Suite 300, Lincoln, NE 68516
(156-03-236 CHF)

a. **What was inspected?** The inspection followed the routine Compliance Program for Clinical Investigators (CP 7348.811). The site screened and enrolled 75 subjects; 43 subjects completed treatment, 32 subjects were withdrawn. The inspection audited 40 subject records, including source records, CRFs, eligibility criteria, drug accountability records, and documentation of adverse events. The inspection audited the Serious Adverse Events (SAE) log which cited a total of 8 deaths.

a. **Limitations to the inspection:** There were no limitations to this inspection.

b. **General observations:** The inspection followed the routine Compliance Program for Clinical Investigators (CP 7348.811). The inspection issued a 1-item FDA-483, for failure to report promptly to the IRB all unanticipated problems involving risk to human subjects. Specifically, Subject #5463 was randomized on August 31, 2004, and expired on [REDACTED] due to heart failure. Neither the clinical investigator, nor the study coordinator submitted this death report to the IRB. The SAE log cited 8 deaths. Each death was reported to the IRB in a timely manner, except for Subject #6698 who died on [REDACTED] and whose death was not reported to the IRB or the sponsor until [REDACTED] approximately 6 weeks later. No other deficiencies were noted. All subjects met eligibility criteria.

b(6)

d. **Integrity of Data:** The data from Dr. Krueger's site, associated with the audited Protocol, 156- 03-236, submitted to the agency in support of NDA 22-275, may be considered acceptable.

6. Barton Levine, MD, Veteran's Administration Greater Los Angeles Health Care Center
11301 Wilshire Blvd, Building 500, Room 6024, Los Angeles, CA 90073
(156-02-235 hyponatremia)

a. **What was inspected:** A total of 18 subjects were screened and signed consent forms. Of these 18 subjects, 17 were randomized into the study. Five (5) of 17 subjects dropped from the study for personal reasons and protocol deviations. Twelve subjects completed the study. The inspection reviewed 12 of 17 subject records, for protocol adherence, inclusionary criteria, laboratory assessments, adverse events, and drug accountability.

b. **Limitations to the inspection:** there were no limitations to this inspection

c. **General Observations:** A multi-part, 2 item FDA-483 was issued to Dr. Levine for failure to prepare and maintain adequate and accurate case histories and not conducting the investigation

according to the signed investigational plan. Specifically, the protocol excluded subjects with a hemoglobin < 10 g/dL. Subject #2020 had hemoglobin of 9.2 g/dL and Subject #2022 had hemoglobin of 9.6 g/dL at screening, and both subjects were randomized into the study. The investigation found that for Subject 2022, the Week 2 physical examination and cardiovascular assessment was performed by an individual who was not listed on the FDA Form 1572, and for Subject 4010, the Week 2 neurological exam was performed by an individual whose name was not listed on the FDA Form 1572. Subject #2037 entered the study on March 29, 2004 and signed Version 7 of the ICD, even though Version 8 was approved by the IRB on March 17, 2004. The amended ICD increased the window period for post dose procedures from 2 hours to 2 to 4 hours, increased the amount of blood to be drawn to 20 tablespoons. Source records did not document if Subject #2037 met the eligibility criteria.

Dr. Levine provided a written response to the FDA-483 in a letter dated March 14, 2008.

d. **Assessment of Data Integrity:** Although regulatory violations were noted, it is unlikely that they would affect data integrity. The data from Dr. Levine's site, associated with the audited Protocol 156-03-328(hyponatremia) submitted to the agency in support of NDA 22-275, may be considered acceptable.

7. Richard C Josiassen, PhD, The Arthur P Noyes Research Foundation, 1001 Sterigere Street Norristown, PA 19401(156-02-235 hyponatremia)

a. **What was inspected:** The inspection audited all 12 subject's records, including source records, CRFs (electronic), and compared the data to the data listings provided from the sponsor. No deficiencies were noted. There were no serious adverse events, and no deaths documented in the records. The inspection audited the drug accountability log, and no deficiencies were noted.

b. **Limitations to the inspection:** There were no limitations to this inspection.

c. **General Observations:** At this site, 18 subjects were screened, 12 subjects were randomized, and all 12 subjects completed the study. The inspection audited all 12 subject's records including source documents, and compared them to the electronic CRFs, and the sponsor's data listings. There were no deficiencies documented during the inspection. There were no deaths or serious adverse events reported. The inspection found the investigator's raw data was well-organized, in good condition, legible and complete. The inspection noted that Dr. Josiassen maintained good control over the study. No discrepancies were observed in review of the drug accountability log. No FDA 483 was issued to Dr. Josiassen.

d. **Assessment of Data Integrity:** The data from Dr. Josiassen's site, associated with the audited Protocol 156-03-325(hyponatremia) submitted to the agency in support of NDA 22-275, may be considered acceptable,

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The study data collected by the Drs. Jandik, Macarie, Filipovsky and Gross (foreign sites), and Drs. Krueger, Levine and Josiassen (U.S. sites) appear reliable in support of their respective

indications. The final reports (EIRs) with supporting exhibits, for Drs. Jandik, Macarie and Filipovsky have not been completed to date. While 6 of the 7 clinical investigators inspected were issued Form FDA 483 inspection observations, it does not appear that the compliance deviations would significantly alter overall study outcome.

Observations noted above are based in part on the preliminary communications and facsimiles of FDA-483's provided from the field investigators. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final remaining EIRs.

{See appended electronic signature page}

Sharon K. Gershon, Pharm.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

Sharon Gershon
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CSO

Tejashri Purohit-Sheth
8/6/2008 04:21:27 PM
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-275

INFORMATION REQUEST LETTER

Otsuka America Pharmaceutical, Inc.
Attention: George Hemsworth, PhD, Executive Director
Regulatory Affairs
2440 Research Boulevard
Rockville, MD 20850

Dear Dr. Hemsworth:

Please refer to your October 22, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SAMSKA (tolvaptan) tablet 15, 30, 60 mg.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA:

Drug Product

1. We have the following comments on your manufacturing process and quality control of the

~~_____~~

b(4)

Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

b(4)

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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Ramesh Sood
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Executive CAC

Date of Meeting: April 15, 2008

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair
Paul Brown, Ph.D., OND IO, Member
C. Joseph Sun, Ph.D., DPAP, Alternate Member
Charles Resnick, Ph.D., DCRP, Team Leader
Xavier Joseph, D.V.M., DCRP, Presenting Reviewer

Author of Draft: Xavier Joseph, D.V.M.

The following summary reflects the Division of Cardiovascular and Renal Products' presentation and the Exec CAC's discussion and recommendations.

NDA # 22-275

Drug Name: Tolvaptan

Sponsor: Otsuka Pharmaceutical Company, Rockville, MD 20850

Background: Tolvaptan, a benzazepine derivative, is being developed for the treatment

_____ with subsequent dilutional hyponatremia. Tolvaptan is a vasopressin antagonist that blocks the binding of arginine vasopressin at the V₂ receptors of the distal portions of the nephron, thereby preventing water reabsorption, and inducing water diuresis (aquaresis) without the depletion of electrolytes.

b(4)

Rat Carcinogenicity Study

In a two-year carcinogenicity study in rats _____ CD (SD); 55/sex/group], tolvaptan was administered by oral gavage to males at 100, 300 and 1000 mg/kg/day and to females at 30, 100, 300 and 1000 mg/kg/day for 104 weeks. (These doses were previously recommended by the Exec CAC.) There was no treatment-related increased mortality in males or females. Numbers of rats surviving to scheduled termination of the study were 23, 36, 30 and 34 males at 0, 100, 300 and 1000 mg/kg/day, and 30, 34, 38, 38 and 37 females at 0, 30, 100, 300 and 1000 mg/kg/day. The body weights for all treatment group rats were lower than control weights throughout the study. At the termination of the study, the mean body weights for males at 100, 300 and 1000 mg/kg/day were 29, 32 and 33% lower than control, respectively. For females, the body weights were 40, 40, 43 and 40% lower than control at 30, 100, 300 and 1000 mg/kg/day. The FDA analyses of the rat tumor data showed no statistically significant treatment-related increased incidence of tumors.

b(4)

Mouse Carcinogenicity Study

In a two-year carcinogenicity in mice [B6C3F1 (SPF); 55/sex/group], tolvaptan was administered by oral gavage to males at 10, 30 and 60 mg/kg/day and to females at 10, 30 and 100 mg/kg/day. (These doses were previously recommended by the Exec CAC.)

There were no statistically significant differences in the mortality rates between control and treated groups of either sex. Numbers of mice surviving to scheduled termination of the study were 48, 49, 49 and 49 males at 0, 10, 30 and 60 mg/kg/day, and 41, 49, 46 and 40 females at 0, 10, 30 and 100 mg/kg/day, respectively. At the termination of the study, the mean body weights at low, mid and high dose levels were 7, 8 and 13% lower than control for males, and 0, 6 and 3% lower than control for females. The FDA analyses of the mouse tumor data showed no statistically significant treatment-related increased incidence of tumors.

Executive CAC Recommendations and Conclusions

Rats

1. The Committee agreed that the study was acceptable, noting prior Exec CAC concurrence with the doses used.
2. The Committee concluded that the study was negative for treatment-related tumors.

Mice

1. The Committee agreed that the study was acceptable, noting prior Exec CAC concurrence with the doses used.
2. The Committee concluded that the study was negative for treatment-related tumors.

Abigail Jacobs, Ph.D.
Acting Chair, Executive CAC

cc:\n
/Division File, DCRP
/Charles Resnick, DCRP
/Xavier Joseph, DCRP
/Dan Brum/DCRP
Adele Seifried, OND IO

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/s/

Abby Jacobs
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INFORMATION REQUEST LETTER

NDA 22-275

Otsuka Pharmaceutical Company, Ltd.
Attention: Kusuma Mallikaarjun, Ph.D.
2440 Reasearch Blvd.
Rockville, MD 20850

Dear Dr. Mallikaarjun:

Please refer to your new drug application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for tolvaptan 15 and 30 mg Tablets.

b(4)

We also refer to the proposed statistical analysis plan (SAP) you submitted on April 7, 2008 via email in preparation for the meeting between FDA, Otsuka, [REDACTED] on April 9, 2008. This meeting was for the purpose of discussing preparation for the June 25, 2008 Cardiovascular and Renal Drugs Advisory Committee Meeting.

We reviewed the proposed SAP and have the following comments and information requests.

The content validity of the EQ-5D and SF-12 has not been demonstrated for the purpose of measuring symptoms of hyponatremia in a clinical study setting to support labeling claims. At face value, the items included in the EQ-5D and SF-12 do not appear to be representative of hyponatremia symptoms that are described in the published literature (e.g., altered mental status). The mental component summary (MCS) and physical component summary (PCS) of the SF-12 are composite scores, which include items that are not direct measurements of the concepts of mental and physical functioning, respectively.

We have concerns about the conclusions that might be drawn from combining data as you have proposed in your April 7, 2008 SAP. It has not been established that the utility index for the SF-12 will effectively match the utility index of the EQ-5D to allow data pooling and efficacy determinations. Overall, it is unclear how combining patient-reported outcome (PRO) data that were collected using different methods, different preferences and health states, and collected at different time points will establish the treatment benefit of either drug. Multiplicity is also not addressed.

Request for Information

- 1) It would be helpful to evaluate whether there were baseline imbalances between treatment groups that may have influenced the findings, and whether any of the PRO findings are driven by a particular subgroup. For example, are findings on

- the MCS of the SF-12 influenced by baseline physical function, age, stage of disease, or some other variable that was measured?
- 2) Please provide the following subgroup analyses (intergroup comparisons of PRO data):
 - a. Cause for hospitalization for inpatients enrolled in the studies
 - b. Breakdown of inpatients and outpatients at enrollment
 - c. Underlying diagnosis (etiology of hyponatremia)
 - d. Demographics (e.g., age, gender)
 - e. U.S. versus non-U.S.
 - f. Baseline PRO data (SF-12, MCS, PCS, EQ-5D index, EQ-5D feeling thermometer)
 - g. Chronicity of hyponatremia (acute versus chronic)
 - h. Inpatient versus outpatient status at the time of PRO assessment (baseline and last observation)
 - 3) To evaluate whether the composite score was driven by a particular component (or item), we need summary data including cumulative distribution function by treatment group and by study for the following:
 - a. EQ-5D "feeling thermometer" question for all studies
 - b. Change from baseline on each individual question of the EQ-5D
 - c. Change from baseline of each item of the SF-12 and the MCS/PCS
 - d. The 12-item Hyponatremia Disease-Specific Survey (Study 156-03-238)
 - 4) For Tolvaptan, please provide the change from baseline for each individual question of the SF-12 (LOCF and OC analyses) for studies 156-02-235 and 156-03-238.
 - 5) Please submit the scoring algorithm for the MCS and PCS of the SF-12.
 - 6) Please provide the actual copy of the SF-12 used in the clinical trials, and explain whether the PRO instruments were self-administered or investigator-administered.
 - 7) We have concerns regarding the impact of missing PRO data. Please provide:
 - a. Missing PRO data by treatment group (include information on missing assessments, as well as incomplete assessments where a subset of items is missing)
 - b. A description of the extent to which missing data were allowed according to the scoring system of each instrument (SF-12 and EQ-5D). If a subset of results was considered uninterpretable, please describe the threshold for making this determination.
 - c. Sensitivity analyses for missing data using a variety of imputation techniques

NDA 22-275

Page 3

- 8) Please submit the Development, Scoring, and Copy of the Hyponatremia Disease-Specific Survey.

If you have any questions, please call Dan Brum, Pharm.D., Regulatory Health Project Manager, at (301) 796-0578.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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Norman Stockbridge
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/s/

Ramesh Sood
3/19/2008 11:29:08 AM

DEPARTMENT OF HEALTH AND HUMAN
SERVICES
FOOD AND DRUG ADMINISTRATION

**PRESCRIPTION DRUG USER FEE
COVERSHEET**

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>

<p>1. APPLICANT'S NAME AND ADDRESS</p> <p>OZSUKA PHARMACEUTICAL DEVELOPMENT & COMMERCIALIZATION INC. BOYDK 2440 RESEARCH BLVD Rockville MD 20850 US</p>	<p>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER</p> <p>22-275</p>
<p>2. TELEPHONE NUMBER</p> <p>240-683-3569</p>	<p>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>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:</p> <p><input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:</p>

<p>3. PRODUCT NAME</p> <p>SAMSKA (TOLVAPTAN)</p>	<p>6. USER FEE I.D. NUMBER</p> <p>PD3007787</p>
--	---

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

<p><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)</p>	<p><input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE</p>
<p><input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act</p>	<p><input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY</p>

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO

OMB Statement:
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:

<p>Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448</p>	<p>Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852</p>	<p>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.</p>
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<p>SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE</p> <p><i>Suzanne B. Ray</i></p>	<p>TITLE</p>	<p>DATE</p> <p>10/18/2007</p>
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9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
\$1,178,000.00

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**DIVISION OF CARDIOVASCULAR & RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION**



US Mail address:
CDER, DCRDP (HFD-110)
10903 New Hampshire Ave.,
Silver Spring, MD 20993-0002

FDA
10903 New Hampshire Ave
Silver Spring, MD 20993-00025600

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Transmitted via email: lily.chan@otsuka.com

Attention: Lily Chan, Pharm.D.

Company Name: Otsuka Pharmaceutical Company, Ltd.

Phone: 240.683.3532

Subject: INDs — 54,200 7 May 07 Pre-NDA Meeting Minutes

b(4)

Date:

Pages including this sheet:

From: CDR John David

Phone: 301-796-1059

Fax: 301-796-9838

*******PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!**

b(4)

Minutes of a meeting between Otsuka Pharmaceutical Company, Ltd. and the FDA Division of Cardiovascular and Renal Products

Sponsor: Otsuka Pharmaceutical Company, Ltd.
Drug: OPC-41061 (tolvaptan)
INDs: █████ /54,200
Date of request: January 4, 2007
Date request received: January 5, 2007
Date of confirmation: January 18, 2007
Date of pre-meeting: April 23 and February 27, 2007
Date of meeting: May 7, 2007 (originally March 14, 2007 but re-scheduled)
Time: 11:00 am – 12:30 pm
Place: 10903 New Hampshire Ave.
Bldg #22, Room 1309
Silver Spring, MD 20993

b(4)

Type/Classification: Type B/Pre-NDA
Meeting Chair: Robert Temple, M.D.
Meeting recorder: John David

FDA Participants:

Division of Cardiovascular and Renal Products

Robert Temple, M.D. Director, Office of Drug Evaluation I, HFD-101
Norman Stockbridge, M.D., Ph.D. Director, Division of Cardiovascular and Renal Products, HFD-110
Maryann Gordon, M.D. Medical Officer, HFD-110
Jialu Zhang, Ph.D. Statistician, HFD-710
Peter Hinderling, M.D. Clinical Pharmacology, HFD-860
Xavier Joseph, Ph.D. Pharmacologist, HFD-110
John David Regulatory Health Project Manager, HFD-110

Division of Metabolism and Endocrinology Products

Karen Mahoney, M.D. Clinical Reviewer, HFD-510
S. W. Johnny Lau, Ph.D. Clinical Pharmacology Reviewer, HFD-870
Sally Choe, Ph.D. Clinical Pharmacology Reviewer, HFD-870

Otsuka Pharmaceutical Company, Ltd. Participants:

Cesare Orlandi, M.D. Vice President, Clinical Development
Taro Iwamoto, Ph.D. Chief Operating Officer
Frank Czerwiec, M.D., Ph.D. Senior Director, Clinical Development
Chris Zimmer, M.D. Senior Director, Clinical Development
Monroe Klein, Ph.D. Vice President, Global Regulatory Affairs
George Hemsworth, Ph.D. Executive Director, Regulatory Affairs
Lily Chan, Pharm.D. Senior Manager, Regulatory Affairs
Hitoshi Imamura, Ph.D. Manager, Regulatory Affairs
George Chao, Ph.D. Vice President, Biometrics

b(4)

Robert McQuade, Ph.D. Vice President, Global Medical Affairs
Yoshitaka Yamamura, M.S. Global Project Leader
Martin Rose, Ph.D. Vice President, U.S. Medical Affairs

b(4)

sodium <135 mEq/L and serum sodium <130 mEq/L), volume status (euvolemia and hypervolemia), underlying disease entity (cirrhosis, heart failure, SIADH, and other), and tolvaptan dose. In addition, you should calculate the number of hyponatremic patients in each of these categories who have been treated with tolvaptan for at least six months and for at least one year.

Questions for the Divisions:

Clinical

[redacted]

b(4)

[redacted]

[redacted]

b(4)

2. Otsuka previously received feedback from the DMEP concerning cut-off values chosen for "Potentially Significant Laboratory Test Abnormalities." Based on the DMEP feedback, Otsuka has revised the cut-off values. Does the DCRP and DMEP concur with Otsuka's revised cut-off values chosen for "Potentially Significant Laboratory Test Abnormalities"?

[redacted]

b(4)

March 7, 2007 Preliminary Response: The proposed criteria are acceptable to DMEP except for the following:

- The upper bound for Toxicity Grade 1 for serum calcium should be 11.0 mg/dL rather than 11.5 mg/dL.
- You should establish potentially significant laboratory criteria for elevations in white blood cell count and hemoglobin

In addition, DMEP requests inclusion of "shift analyses" in the safety section of the NDA. For each of the laboratory parameters, these analyses should show the number and proportion of patients with a normal laboratory value at baseline who develop abnormally high (i.e. above the upper limit of the reference range) and, where appropriate, abnormally low (i.e. below the lower limit of the reference range) laboratory values during treatment with study drug.

Regulatory/Administrative

3. Otsuka previously received concurrence from the DMEP concerning the overall format and content of the NDA, including the size and sources of the safety database. These understandings will be presented in the briefing package for the pre-NDA Meeting. **Does the DCRP agree with the understandings previously reached with the DMEP as stated in their responses to the briefing package?**

March 7, 2007 Preliminary Response: DCaRP agrees with the understandings previously reached with the DMEP in regards to the overall format and content of the NDA, including the size and sources of the safety database.

4. Otsuka will provide the overall organization and structure of the Integrated Summary of Effectiveness (ISE) for the CHF indication and Integrated Summary of Safety (ISS) for CHF and hyponatremia in the briefing package to be submitted 4 weeks prior to the meeting. **Does the Division concur with the overall organization and presentation of the ISE and ISS?**

March 7, 2007 Preliminary Response: DMEP reiterates the importance of presenting the safety data by severity of baseline hyponatremia (Figure 3.4-2 on page 370 of Volume 1 does not list this subgroup analysis in the left-hand column that pools hyponatremia data from 12 studies).

5. Otsuka will provide templates with draft table shells for the pivotal phase 3 final study report which are based on the ICH E3 guideline in the briefing package. **Does the Division concur with the format and content of the final study report are adequate?**

March 7, 2007 Preliminary Response: DCaRP concurs that the format and content of the final study report are adequate.

Chemistry, Manufacturing and Controls

b(4)

March 7, 2007 Preliminary Response: The Division agrees with the proposed approach.

b(4)

7. In the developmental stages and in Long Term Stability Studies we used content uniformity test for the 15-, 30-, and 60-mg tablets. Now according to the harmonization of Uniformity of Dosage Units <905>, official in USP 30 effective May 1, 2007, mass variation test is applicable to the 60-mg tablets. We propose to switch to mass variation test for the 60-mg tablets starting from the first commercial batches. **Does the Agency agree with this proposal?**

March 7, 2007 Preliminary Response: The proposal is acceptable provided your control strategy for the manufacturing process ensures blend uniformity.

Meeting recorder: _____
John David

Meeting concurrence: _____
Robert Temple, M.D.

Draft: jd/5-7-07
Final: jd/5-21-07

RD:
Lau 5/11/07
Choe 5/15/07
Zhang 5/9/07
Joseph 5/10/07
Hinderling 5/9/07
Mahoney 5/9/07
Gordon 5/15/07
Stockbridge 5/16/07
Temple 5/17/07

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/s/

Robert Temple
5/22/2007 01:06:52 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 54,200

Otsuka Maryland Research Institute, Inc.
Attention: Anutosh Saha, Ph.D.
Senior Director, Regulatory Affairs
2400 Research Boulevard
Rockville, MD 20850

Dear Dr. Saha:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tolvaptan tablets (OPC-410610).

We also refer to the draft PreNDA pre-meeting minutes we sent to you by email on April 21, 2006, and your response email dated April 21, 2006, in which you requested to cancel the meeting.

The official minutes of the pre-meeting are enclosed.

If you have any questions, please call Jennifer Johnson, Regulatory Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

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

Enclosure: PreNDA pre-meeting minutes for tolvaptan tablets

MEMORANDUM OF PRE-MEETING MINUTES

APPLICATION: IND 54,200
DRUG NAME: Tolvaptan tablets (OPC-410610)
TYPE OF MEETING: Type B; PreNDA

MEETING CHAIR: Mary Parks, M.D.

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

FDA ATTENDEES: (Title and Office/Division)

Robert Meyer, M.D.	Director, Office of New Drugs II
Mary Parks, M.D.	Acting Director, Division of Metabolism and Endocrinology Products (DMEP)
Theresa Kehoe, M.D.	Acting Clinical Team Leader
Karen Mahoney, M.D.	Clinical Reviewer
Hylton Joffe, M.D.	Clinical Reviewer
Karen Davis-Bruno, Ph.D.	Pharmacology/Toxicology Team Leader
Fred Alavi, Ph.D.	Pharmacology/Toxicology Reviewer
J. Todd Sahlroot, Ph.D.	Biometrics Team Leader
Hae-Young Ahn, Ph.D.	Clinical Pharmacology and Biopharmaceutics Team Leader
Sang Chung, Ph.D.	Clinical Pharmacology and Biopharmaceutics Reviewer
Joslyn Swann, Pharm.D	Safety Evaluator, Office of Drug Safety
Cherye Milburn	Project Manager, Office of Drug Safety
Lina AlJuburi, Pharm.D.	Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Representatives of Otsuka Pharmaceutical Company, Ltd. scheduled to attend the April 24, 2006, meeting

Frank Czerwicz, MD, PhD	Sr. Director, Clinical Development
Cesare Orlandi, MD	Vice President, Clinical Development
Susan Shoaf, PhD	Sr. Pharmacokineticist, Clinical Pharmacology
Mirza Ali, PhD	Senior Director, Biostatistics
John Ouyang, PhD	Senior Manager, Biostatistics
George Hemsworth, PhD	Executive Director, Regulatory Affairs
Anutosh Saha, PhD	Senior Director, Regulatory Affairs
Suva Roy, PhD	Senior Director, CMC Regulatory Affairs
Stephen Trucocchio, MS	Associate Director, Regulatory Submissions
David Martinko	Senior Project Manager
Joy Parris, MD	Senior Director, Clinical Safety and Pharmacovigilance
Khaled Bannout, MD	Assistant Director, Clinical Safety and Pharmacovigilance
Yoshitaka Yamamura, MS	Global Project Leader
Hitoshi Imamura, PhD	Associate Manager, Regulatory Affairs, OPC-J
Norma Browder, PhD	Group Leader, Nonclinical Safety
Lynda Lanning, DVM, DABT	Associate Director, Nonclinical Safety, Toxicology
Maxwell Pan, PhD	Associate Director, Nonclinical Safety, ADME

BACKGROUND:

Otsuka Pharmaceutical Company, Ltd. is developing OPC-410610 (tolvaptan) as an oral formulation (tablets) for the proposed treatment of hyponatremia. Tolvaptan is a vasopressin antagonist that blocks the binding of arginine vasopressin to the V₂ receptors of the distal portions of the nephron. The proposed dose regimen is 15 to 60 mg titrated from 15 mg over several days.

Pivotal Phase 3 Trials

- 1) Protocol 156-02-235: *Multicenter, Randomized, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of the Effects of Oral Tolvaptan in Patients with Hyponatremia*
- 2) Protocol 156-03-238: *International, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of the Effects of Titrated Oral Tolvaptan Tablets in Patients with Hyponatremia*

The initial IND was submitted September 23, 1997.

An End-of-Phase 2 meeting was held with the Sponsor on November 3, 2002.

An End-of-Phase 2 meeting to discuss items with the Office of New Drug Quality Assessment only was cancelled on December 6, 2005, at the Sponsor's request. Written response sent by email on December 2, 2005 followed by a letter issued on December 8, 2005.

The Sponsor requested this PreNDA meeting on February 7, 2006.

The meeting briefing document was submitted on March 23, 2006.

The planned NDA submission date is September 2006.

This drug is also being studied for the treatment of congestive heart failure being reviewed by the Division of Cardiovascular-Renal Drug Products. b(4)

MEETING OBJECTIVES:

To discuss items related to the planned tolvaptan NDA submission for the hyponatremia indication including: overall format, content, size and sources of the safety database, the Pediatric Research Equity Act (PREA), and plans for a Priority review request.

DISCUSSION POINTS:

The Sponsor requested response to the following questions listed in the meeting briefing document. The questions are repeated below, and the responses are in bold.

Clinical

- 1) The Background and Clinical Overview, Section 3.2.2, Exposure, describes in detail the patient exposure data that will be used to support the NDA filing. These data demonstrate that extensive safety data is (sic) available in hyponatremia patients and CHF patients that have been treated with tolvaptan. We believe that the data which are to be submitted in the NDA are sufficient to provide compelling clinical evidence that tolvaptan is safe when given to patients with euvoletic and hypervolemic hyponatremia (including patients with congestive heart failure, cirrhosis, syndrome of inappropriate anti-diuretic hormone, etc.).

Does the Division agree that the planned safety exposure database is adequate to support filing of the NDA?

The proposed lowest starting dose for tolvaptan will likely be 15 mg daily. The number of subjects that have received this minimum daily dose is:

- ~1,100 subjects (165 hyponatremic subjects) for <30 days
- ~180 subjects (82 hyponatremic subjects) for ≥ 6 months
- ~120 subjects (41 hyponatremic subjects) for >1 year

Therefore, only a small number of hyponatremic subjects have been exposed to tolvaptan for at least 6 months (n=82) and for longer than one year (n=41). International Conference on Harmonisation (ICH) guidelines recommend that clinical trials expose ~300-600 subjects to study drug for six months and ~100 subjects for at least one year when the drug is intended for chronic use. Recent FDA guidance on premarket risk assessment also states these ICH target numbers might need to be increased in certain circumstances, such as when the benefit "is of uncertain magnitude (e.g., efficacy determination on a surrogate endpoint). Serum sodium is arguably such a surrogate.

These recommendations from ICH and FDA guidance are appropriate for tolvaptan, which will likely be used chronically in several patient populations. Furthermore, the long-term exposure data are even more limited when the hyponatremic patients are subdivided according to the underlying disease state (e.g. cirrhosis, SIADH) or degree of baseline hyponatremia (e.g. mild vs. severe). Data from the mortality trial in heart failure (>4,000 participants) will bolster the number of heart failure subjects exposed to long-term tolvaptan. However, only preliminary results from this trial will be available at the time of the NDA review (see Question 2 below), few may have hyponatremia, and there may be unique safety signals identified in the other patient populations (e.g. SIADH, cirrhosis) that are not seen in heart failure subjects.

Given the limited number of hyponatremic subjects exposed to tolvaptan at six months and one year that fall significantly below ICH guidelines, it is unlikely that tolvaptan will be approved for indefinite treatment based on the current safety database. The approved duration of treatment will depend on the duration of adequate exposure in clinical trials and may be limited based on results of the safety review.

- 2) At the time of the anticipated NDA submission, there will be two ongoing double-blind U.S. studies (Study 156-03-236 and Study 156-04-247). We will provide a protocol synopsis and enrollment status in the NDA submission for these studies. We expect that un-blinded data may become available only from Study 156-03-236 between the NDA submission date and the Division's action date. Considering the importance of Study 156-03-236, we plan to submit top-line mortality data from this study as proposed in the Background and Clinical Overview, Section 3.2.3., NDA Safety Updates and Data Cut-offs. Does the Division concur with our plan regarding the data submission for the ongoing double-blind studies?

At the time of the NDA submission, the Sponsor should include narratives and tabulations for serious adverse events and deaths for Study 156-03-247 in addition to the study's protocol synopsis and enrollment status.

The Division previously noted a potential cardiac signal in some of the Phase 2 studies in heart failure, including higher rates of ventricular tachycardia, sudden death, and aggravated heart failure. The Division remains concerned about the cardiac signal and the potential for off-label use of tolvaptan in the treatment of heart failure, if tolvaptan were approved for hyponatremia. We remind you that we have consistently requested cardiovascular safety outcome data prior to approval of tolvaptan for the treatment of hyponatremia (please refer Division's letter issued on May 17, 2004, and the End-of-Phase 2 meeting minutes dated November 4, 2003). Submission of your NDA for the treatment of hyponatremia prior to completion of trial 156-03-236 appears unlikely to provide sufficient safety exposure for approval, particularly for chronic use and in the hypervolemic hyponatremic patient population.

At a minimum, the Division will require that the initial hyponatremia NDA submission contain the unblinded safety data for the mortality trial 156-03-236. These data should report overall mortality, cardiac mortality, cardiac adverse event rates (e.g. including serious cardiac adverse event rates and discontinuations due to cardiac adverse event rates), and any other potential safety signals identified in the trials that are included in the hyponatremia NDA. Where possible, the adverse event data from the heart failure mortality trial should be presented according to tolvaptan dose and also pooled across tolvaptan doses. Potential factors contributing to these outcomes (e.g. advanced age, severity of underlying heart failure, etc.) should also be presented. Lack of mortality trial data at the time of the current NDA may affect approvability of tolvaptan for hyponatremia.

Non-clinical

- 3) Module 2 and Module 4 of the ICH Harmonised Tripartite Guideline M4S (The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Safety) include sections describing the inclusion of the Methods of Analysis and Validation (Sections 2.6.4.2 and Section 4.2.2.1). We intend to include preliminary studies as well as studies validating methods for measurements in the dosing suspension/solutions and/or biomaterial from pharmacokinetic and toxicology studies. What is the Division's position with respect to the necessity for inclusion of reports from preliminary studies as well as studies validating methods for measurements in the dosing suspension/solutions and/or biomaterial from pharmacokinetic and toxicology studies in the nonclinical ADME section of the NDA?
The sponsor's proposal to submit preliminary as well as validating methods for measurements in the dosing suspensions/solutions and/or biomaterial from pharmacokinetic and toxicology studies in the nonclinical ADME section of the NDA is acceptable.

- 4) Based on the results of in vitro testing, OPC-41061 was classified as "probably phototoxic" and its metabolite, DM-4103 as "phototoxic". Appendix 1a-d details the protocol and the results of the additional in vivo testing in both guinea pigs and rabbits which were conducted. The results of these studies indicate that both OPC-41061 and its metabolite DM-4103 are negative for phototoxicity. Therefore, we plan no additional nonclinical testing. Does the Division agree with this strategy?

The results of the *in vivo* studies in guinea pig and rabbit need to be reviewed to make this assessment. Pertinent questions include: Are there any data indicating accumulation of parent (OPC-41061) or metabolites (DM-4107, DM-4103) in skin or eye? Has the metabolite, DM-4103, been evaluated for phototoxicity?

- 5) Regarding inclusion of nonclinical study report references in the NDA:
- Does the Division wish to see, in the NDA, copies of the literature referenced in the individual study reports regardless of whether or not they are discussed specifically in Module 2?
 - In addition, would the Division wish to see, in the NDA, copies of any published literature related to tolvaptan which is neither cited in Module 2 nor in the individual study reports?

The sponsor may include any relevant literature references which support their NDA application at their discretion.

Question to Sponsor:

Does racemization occur in humans? Have the study reports of the optical isomers performed in rats been submitted for review?

CMC

- 6) Otsuka is proposing to include the following executed batch records in the application. Does the Agency agree that these are suitable batch records for inclusion in the NDA?
- Current clinical trial batches used for BE studies; Open-label, Randomized, Crossover Study to Assess Dose Strength Equivalence Among 15, 30, and 60 mg Strength Oral Tablets of Tolvaptan Protocol No. 156-01-233
 - Long Term Stability Study batches (15-mg, 30-mg, and 60-mg tablets),
commercial scale tableting run. The compositions of commercial 30-mg and 60-mg tablets are the same as those of current clinical trial batches with the exception of colors. The commercial 15-mg tablet is half the weight of commercial 30-mg tablets

b(4)

- The compositions are shown in Table 5.2.1-1 in Section 5.2.1 of the briefing document. The batch records are in Japanese. To facilitate review of the executed batch records, Otsuka will provide an English translation of the corresponding master batch records in the NDA submission.

Reference is made to Sponsor's submission dated March 9, 2006. This submission is currently under review and response deferred to a later date.

Regulatory/Administrative

- 7) Otsuka plans to request a waiver of the requirements of the Pediatric Research Equity Act. The Background and Clinical Overview, Section 3.11, Request for Pediatric Waiver, provides justification for Otsuka's plan to request a waiver of the requirement as it relates to the tolvaptan hyponatremia indication. Does the Division agree that the justification provided supports Otsuka's plan to request for a waiver of the requirements of the Pediatric Research Equity Act?

The Division will base its decision regarding whether a waiver or a deferral of pediatric study requirements will be granted on the review of efficacy and safety in adult patients.

- 8) Based on the justification provided in the Background and Clinical Overview, Section 3.1.1 Clinical Hyponatremia (last paragraph), Otsuka believes that the NDA we plan to file for the proposed indication of hyponatremia meets the FDA criteria for assignment of a priority review. Does the Division concur?

A decision regarding priority review status will be made at the time of the NDA submission. However, there is now an approved therapy for the treatment of euvoletic hyponatremia and other interventions to treat hyponatremia have been well-characterized in the medical literature. Furthermore, your current plans for NDA submission will be based primarily on improvement of serum sodium. While we have accepted hyponatremia as an acceptable efficacy measure, it remains a surrogate. Your proposal to submit this NDA in advance of completing trial 156-03-236 which would have included clinical outcomes data may preclude a determination that tolvaptan would provide a significant improvement over currently approved therapies or available therapies in the treatment of hyponatremia. The convenience of an oral dosage form over the currently approved intravenous vasopressin receptor antagonist will likely not be a sufficient reason to justify priority review.

- 9) Several studies with tolvaptan have been conducted in Japan. These studies were not conducted under a U.S. IND and the results of these studies will not be used to support the efficacy claims for the hyponatremia indication. These studies will be used to provide supportive safety information. Otsuka plans to submit translated synopses of the clinical study reports (CSR) for the completed Japanese studies. Translated narratives for deaths, SAEs, and discontinuations due to AEs from these studies will be included in the ISS. For the ongoing Japanese studies, Otsuka plans to submit protocol synopses and study enrollment status. Translated CSR synopses for the ongoing Japanese studies will be provided with the 120-Day Safety Update if they become available. Is this proposal acceptable to the Division?

No. Please clarify the number and types of patients that were enrolled in these Japanese studies. While it may be acceptable that these studies will not be needed to support efficacy, all safety information from the Japanese trials will be relevant for the NDA and must be integrated with the U.S. safety database. This should include, at a minimum, comprehensive adverse event and death summary tables, as well as translated narratives for deaths, serious adverse events and adverse events leading to discontinuation. These data must be provided at the time of the original NDA submission.

- 10) Currently, the Japanese safety data are coded to different versions of MedDRA than the version used to code the U.S. safety data. As Otsuka does not plan to integrate the Japanese safety data with the U.S. safety data, we believe that it is not necessary to recode the Japanese safety data to the same version of MedDRA used to code the U.S. safety data. Does the Division concur?

No. To permit full assessment of tolvaptan's safety, the Sponsor should recode the safety data to a single version of MedDRA and provide an integration of the Japanese safety with the U.S. safety database.

- 11) Otsuka intends to submit a paper NDA in the CTD format. Appendix 2 consists of the draft table of contents (TOC) showing the proposed organization of the NDA. Is this organization of the NDA acceptable to the Division?

Please explain why the NDA is not being submitted electronically. While not required from a regulatory standpoint, the Division strongly favors electronic submission of all clinical study reports, clinical pharmacology study reports, comprehensive safety datasets, pivotal efficacy study datasets, and summaries for all disciplines.

Please note that Study 156-97-252 is not currently included in the Table of Contents but should be (supportive efficacy data for the hyponatremia indication per Figure 3.1 – page 185).

- 12) Otsuka has provided a draft TOC, statistical analysis plan, and templates for key tables and figures for the Integrated Summary of Efficacy (ISE) in Appendix 3, and the structure of the efficacy analysis dataset in Appendix 5 (Page 1). Is this plan for the ISE acceptable to the Division?

For the Subject Disposition tables (e.g. Table 5.1-1 on page 198), the Sponsor should avoid vague discontinuation terms such as “withdrew consent” or “withdrawn by investigator” – these general terms are often related to adverse events, which should instead be reported. Any such terms reported must contain documentation that the patient or physician did not discontinue therapy for reasons of safety or efficacy. A listing of any adverse events experienced by the patient by Study Day should accompany any subject identified as discontinuing under these non-specific categories.

The Division agrees with the Sponsor's plans to present separate and pooled efficacy data from the pivotal trials as well as results according to baseline hyponatremia (mild vs. severe), underlying disease (cirrhosis vs. heart failure vs. SIADH/other), and demographic subgroups (age, sex, race). The Sponsor intends to present results separately for the Phase 3 open-label extension trial, each of the controlled Phase 2 hyponatremia studies, and each of the controlled Phase 2 heart failure trials. This approach is reasonable because of differences in study design between trials.

Comments regarding the proposed statistical plan from the Office of Pharmacoeconomics and Statistical Science (Biometrics):

The efficacy analysis dataset should include, at a minimum, all covariates addressed in Figure 3.4.2.2-1 on page 42 of the briefing package.

For subjects at sites 004, 006 and 237 excluded from analyses in the ISE, the Agency requests that you include these subjects in additional statistical analyses, by individual study and for the ISE. Also include efficacy data for these subjects in electronic datasets. Please flag these patients so that they may be easily identified.

- 13) Otsuka has provided a draft TOC, statistical analysis plan, and templates for key tables and figures for the Integrated Summary of Safety (ISS) in Appendix 4, and the structure of the safety analysis dataset in Appendix 5 (Page 7). Is this plan for the ISS acceptable to the Division?

This proposal is acceptable; however, the following additional analyses should also be included:

- a. **The Tables for the pooled phase 2 heart failure trials described above should include an additional column titled "TLV 15-60 mg", which is analogous to the columns included in the other tables (especially since this is the likely dose range for which the Sponsor will seek approval)**
- b. **All safety data should also be presented by degree of baseline hyponatremia (mild vs. severe) – at the End-of-Phase 2 meeting, and in the Special Protocol Assessment provided for the pivotal efficacy trials, the Division stressed the need for sufficient numbers of severely hyponatremic patients to adequately demonstrate safety in the severe group**
- c. **Pooled safety data should also be presented by patient population (e.g. cirrhosis, heart failure, SIADH/other) from Phase 2/3 trials since there may be unique safety signals in each of these different patient populations**
- d. **Pooled safety data should also be presented by volume status (i.e. euvoolemia, hypovolemia) from Phase 2/3 trials since there may be unique safety signals in each of these different patient populations**

The Sponsor's proposal for presenting supportive safety data is acceptable (studies from Japan, those using other formulations, and pooled data from Phase 1 clinical pharmacology studies).

The Division agrees with the Sponsor's proposal to present data regarding the number of subjects exposed to each tolvaptan dose and the duration of exposure (where possible) to each tolvaptan dose. This will permit evaluation as to whether there are sufficient efficacy and safety data for all doses for which the Sponsor is seeking approval in the NDA.

Other modifications are recommended with regard to the adverse event tables:

- a. "Listing of All Deaths" tables (e.g. 9.6.1-2) - please add columns that list the assigned treatment group, dose of study medication at the time of the death, time on treatment prior to death, and time off treatment (if the event occurred after discontinuation of treatment)
- b. Please include a "Listing of All Serious Adverse Events" table that lists each subject's identification number and center number, age, sex, dose at the time of event onset, duration of exposure at time of event onset, adverse event as reported by investigator and/or patient, an indication as to whether the event led to withdrawal, body system and MedDRA preferred term, and the type of serious adverse event (e.g. fatal, life-threatening, etc.)
- c. Please include a "Listing of All Adverse Events Leading to Dropout" table that lists each subject's identification number and center number, age, gender, dose at the time of event onset, duration of exposure at time of event onset, adverse event as reported by investigator and/or patient, body system and MedDRA preferred term, an indication of whether or not the event met the definition for serious, and the outcome
- d. Please include a "Listing of All Treatment Emergent Adverse Events" table that lists each subject's identification number and center number, age, sex, dose at the time of event onset, duration of exposure at time of event onset, adverse event as reported by investigator and/or patient, an indication as to whether the event led to withdrawal, body system and MedDRA preferred term, and whether or not the event met the definition for serious
- e. Please include a "Mean Change from Baseline for Laboratory Parameters" table that lists for each laboratory parameter (1) the number of subjects who had the laboratory parameter assessed at baseline and at least one follow-up time, (2) the baseline means for the parameter, and (3) the means of the change from baseline to each subject's worst on-drug value for the parameter. These data should be generated separately for the tolvaptan arm and for the placebo arm, and should be pooled across studies, where appropriate.

For the Tables showing Deaths (e.g. 9.6-1), the Sponsor should include the following rows:

- a. Deaths in the "Phase 3 Hyponatremia + Phase 2/3 Hyponatremia" studies
- b. Deaths in "All Heart Failure" studies

Some of the cut-off values chosen for “Potentially Significant Laboratory Test Abnormalities” (pages 298-300) appear too high. For example, the Sponsor has chosen a cut-off of >150 U/L for liver transaminases. The upper limit of normal for serum alanine aminotransferase is 30 U/L in some laboratories; therefore, a level of 150 U/L is 5x the upper limit of normal. Other examples of cut-points that appear too high include serum creatinine >2.2 mg/dL, glucose >350 mg/dL, and hematocrit >58%. More reasonable cut-points should be used or justification for the apparently high values should be provided.

The Sponsor should choose a consistent cut-off percentage for reporting “common” adverse events or should otherwise provide justification for varying this cut-point across tables (e.g. 5% in Table 11.3-1 on page 446 vs. 3% in Table 11.4-1 on page 447). Some of the tables (e.g. 11.8.3-1 on page 452) use a 5% cut-off for presenting “Commonly Reported Treatment-Emergent Adverse Events”. A lower, more conventional cut-off value should be used (e.g. 2%) so that important, common adverse events occurring at <5% incidence are not overlooked.

The structure of the safety analysis dataset appears to be acceptable.

- 14) Templates with draft table shells are provided for the pivotal final study reports (Appendix 6) and a synopsis report for an ongoing study (Appendix 7), which are both based on ICH E3 guideline. Does the Division concur that the format and content of these components are adequate?

Yes. A few requested modifications are provided below:

For Table 4.1 on page 407 (Principal Investigators, Study Centers, and Number of Subjects Screened per Center), the Sponsor should also include columns titled “Number of Subjects Discontinued” and “Number of Subjects Discontinued Due to Protocol Violation”

All serious treatment-emergent adverse events should be presented in Tables, not only SAEs that are reported by two or more subjects (e.g. Table 11.6-1 on page 449).

Where possible, the Sponsor should present data regarding the number of subjects exposed to each tolvaptan dose and the duration of exposure to each tolvaptan dose.

- 15) Module 2 and Module 4 of the ICH Harmonised Tripartite Guideline M4S (The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Safety) included sections describing the inclusion, in the nonclinical section, of *in vitro* studies in which human biomaterial was used (Section 2.6.4.5, Section 4.2.2.3, and Section 4.2.2.4). In addition, Module 5 included sections describing the inclusion, in the clinical section, of *in vitro* studies in which human biomaterial was used (Sections 2.7 and Section 5.3.2). Because this NDA is going to be a paper NDA, we intend to include the study reports for these studies in both the appropriate nonclinical (4.2.2.3 and 4.2.2.4) and clinical (5.3.2) section for easy reference for the reviewer. Does the Division agree with this proposal?

This is acceptable.

16) Otsuka proposes to provide CRFs for subject deaths and discontinuations due to AE for all completed IND clinical studies. Otsuka proposes not to provide CRFs for clinical studies that are ongoing at the time of the initial NDA. Otsuka also proposes not to include translated CRFs from the Japanese clinical studies. Is this proposal acceptable to the Agency?

Full, translated case report forms are not necessary, but translated narratives will be needed.

17) Is it an option for Otsuka to provide CRFs electronically in PDF format and only include a list of subject CRFs provided for each study in the paper copy of the NDA?

Yes, but please see response to Question 11. The clinical reviewer strongly requests electronic submission of the types of information noted in that response.

18) Otsuka plans to submit 2 copies of the paper NDA to the Division and 1 field copy of the paper NDA. Is it an option for Otsuka to submit in addition some portions of the NDA in electronic format as a review aid?

Six copies are required: 1 archival and 5 reviewer copies.

The clinical reviewer strongly requests electronic submission of the types of information noted in the response to Question 11.

Additional Questions and Comments:

- A) **The Sponsor did not conduct a renal impairment study because of low renal clearance for tolvaptan and metabolites. However, renal impairment sometimes affects significantly oral bioavailability of drugs. Therefore, the Division recommends that the Sponsor evaluate the impact of renal impairment on tolvaptan exposure. For example, a relationship between creatinine clearance and tolvaptan exposure can be explored to measure the impact of renal function on tolvaptan exposure using a population pharmacokinetic approach. In addition, it is recommended to explore the relationship between exposure (e.g., AUC) and one of major PD endpoints to assist dosing regimen recommendation in case there is significant impact of renal impairment on exposure.**
- B) **Tolvaptan has one chiral center and is a racemate. Therefore, the Sponsor will need to evaluate the pharmacokinetics of each isomer using a stereospecific assay. Stereospecific pharmacokinetics can be estimated using plasma samples retained from one of previous studies.**
- C) **Please submit dissolution study results including justification of the dissolution method as recommended in Guidance for Industry-Bioavailability and Bioequivalence Studies for Orally Administered Drug Products, General Considerations.**
- D) **The Sponsor plans to conduct a population pharmacokinetic analysis for data obtained in the pivotal Phase 3 studies. Please submit an electronic format for data, control files, and summary of output.**

Comments from the Office of Drug Safety (ODS):

- If the Sponsor and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert [PI] or patient package insert [PPI]) and postmarketing surveillance to manage risks, then the Sponsor is encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).
- For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the following Guidance documents:

Premarketing Risk Assessment: <http://www.fda.gov/cder/guidance/6357fml.htm>

Development and Use of Risk Minimization Action Plans:
<http://www.fda.gov/cder/guidance/6358fml.htm>

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment:
<http://www.fda.gov/cder/guidance/6359OCC.htm>

- If there is any information on product medication errors from the premarketing clinical experience, ODS requests that this information be submitted with the NDA/BLA application.
- The Sponsor is encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.

Additional Comments from the Office of Pharmacoepidemiology and Statistical Science (Biometrics):

Please see attachment.

Minutes prepared by: Lina AlJuburi
Chair concurrence: Mary Parks

Subject: Considerations During Pre-NDA
(Not all may be relevant for each NDA)

From: Japobrata Choudhury, Ph.D.
Mathematical Statistician, Biometrics II (HFD-715)

Based on review experiences, this reviewer would like to remind the drug sponsor about the following, which would expedite the review process, if taken care of before submitting the NDA. This package is generic and is meant just to give an idea. Neither the text nor the tables and figures attached as samples may be appropriate for any particular drug:

- I. i) It should be very clearly stated where each numerical result and/or conclusion is coming from, which set or subset of data or method of analysis you are referring to. Whenever 'p-value' is written, it should be preceded by '2-sided' (we ask for 2-sided p-values). Please make adequate references and cross references with links to appendices or texts. Analysis programs or codes or hand calculation exhibits should be included.
 - ii) All the differences among different studies should be charted: (a) in the overview of studies, with respect to design and conduct of the trial, and (b) in the efficacy overview, with respect to outcomes of the studies, efficacy assessments, and conclusions.
- Or, an altogether separate section may be dedicated to the comparison of the important studies with respect to all aspects.
2. Any deviation from the pre-specified statistical analysis plan should be clearly stated in the NDA at all relevant sections, including the "Statistical Analysis" and "Results" Sections of the study report, and the Summary Section. Analyses following the originally established statistical analysis plan also should be appended.

Kindly provide the following, with **thorough discussion and final comments** where appropriate:

3. (i) A curve for "percent of patients continuing over time" for each treatment group (on the same page or graph).

If there are more than just a few dropouts, graphs for "percent of dropouts" over time for each treatment group (1) for largest centers separately and (2) for one or two major reasons of dropout, if there are any.

Side-by-side comparison (for each important or real covariate and primary efficacy measure separately) of the means (or percents as relevant) of observed cases and those of unobserved

cases using the last available observation (for all treatment groups side by side); all analyses and graphs for both OC (observed cases) and LOCF (last observation carried forward)

Effects of dropouts on OC and LOCF results should be investigated critically and be provided. [Some graphs facilitating these investigations are attached as samples.]

4. i) a. Graphical presentation of efficacy over time

b. Cumulative Distribution Functions (cdf) curves for primary efficacy variables at the primary time-point.

ii) Protocol mentioned Primary Analysis remains the primary analysis. However, thorough exploration of confounding and interaction should be provided (also include subgroup analyses, covariation and interaction p-values, and for each subgroup, descriptive statistics and treatment comparison p-values).

Ninety-five percent confidence intervals for the difference between test drug and placebo in change from baseline at different levels or subgroups (2 or 3 except for centers) of a confounder or prognostic factor/variable (baseline characteristics, center, time, concomitant diseases, concomitant medications, and other prognostic factors/variables) and also the p-values for the corresponding tests should be in the NDA. Each of these is desirable for each important time-point (unless the covariate under consideration is time), e.g., end of study. Some ordering of these confidence intervals is desirable. For example, in the case of "center", first overall, then the largest center, then the next largest center, etc. The sample sizes should be mentioned below the X-axis. (Studies also should be compared this way, if more than two confidence intervals are involved because of the number of studies or efficacy variables.)

In addition to these intervals and p-values, efficient exploratory techniques may be applied, if thought to be helpful.

In case of a paired design, scatter plots of the differences between the test drug and placebo responses (in change from baseline), with prognostic factor/variable values (one page for each) on the x-axis, may be more informative.

iii) To avoid the controversy on interaction and analysis of covariance (see, for example, Fabian, Y. (1991), "On the Problem of Interactions in the Analysis of Variance," JASA 86, pp. 362-375), this reviewer prefers to look at, at least, 2 analyses: (1) usual analysis of covariance with a consideration given to all possibly influencing or interacting factors/variables, and (2) analyses as in (1) separately for subgroups based on each factor/variable suspected to have even modest interaction with the treatment (this interacting factor/variable will no longer be in the model).

All the assumptions needed for model fitting should be checked by (1) formal tests and by (2) residual plots.

iv) Through efficient charts and plots, consistency or inconsistency of outcomes across various statistical methods, methods of handling missing data, studies, investigators, efficacy measures, time, etc. should be precisely presented, and appropriateness or relevance of each (method, study, etc.) discussed. The reasons that could lead to the inconsistency should be investigated, as far as possible.

v) When even the intention-to-treat patient set does not include all randomized patients, characteristics of the excluded patients vis a vis those of the intention-to-treat patients should be investigated and any differences should be adjusted for in the efficacy analyses. Additionally, sensitivity analyses by various types of accounting (e.g. imputing) for those missing patients should be provided. For example, one of the sensitivity analyses could be a worst case analysis, say, by imputing each missing test drug observation by the average of the placebo observations and each of the missing placebo observation by the average of the test drug observations but using the original standard errors (i.e. before imputing).

5. For each safety variable/Adverse Event of importance or concern, kindly provide survival analyses and 95% confidence intervals for the rate of occurrence over different time-points (duration) of exposure.

In addition, the following should be provided:

- I. Flow-description of each study, i.e., description of the study over time: number of patients entering; screening failures; randomization, compliance, dropouts, and various other events with their treatment groups and time-points
- II. If “investigators” are combined for 95% confidence intervals mentioned above, systematic presentation of those individual investigator results which were opposite to these combined results
- III. 2-sided p-values for all (pairwise) comparisons (between treatment groups) on demographics and other prognostics, efficacy, and safety (including laboratory abnormalities) variables (the purpose is different from usual testing of hypotheses)

Inclusion of covariates in the model based on baseline imbalance is not a good statistical practice. However, for screening and exploratory purposes (not confirmatory), as a reviewer, I would like to see analyses by including one at a time, two at a time, etc. of those covariates or prognostic factors for which the baseline pairwise p-values were somewhat small (say, smaller than .08).

IV. Dose-response estimation and testing where relevant, excluding the placebo group (additional one, including the placebo group, may be performed to throw more light, if the usual efficacy (or safety) results are somewhat inconclusive.)

V. Details of randomization, treatment allocation, and drug supply.

VI. Any changes in the diaries or other forms (e.g. Case Report Form), or in the database for whatever reason should be individually reported under "changes in data".

VII. A simple and all-containing "Statistical Analysis Data Set" for statistical reviewers, in SAS transport format to our Electronic Document Room (EDR). Whatever other files are submitted following guidelines, there should be this reviewer-friendly file without the necessity to merge files: on demographics, baseline status, and other prognostic variables, and efficacy (original as well as "derived" or "transformed" like "percent change from baseline", "log of percent change from baseline") on which finally the statistical methods were applied, along with site or investigator and patient identifications. A separate SAS variable corresponding to each efficacy variable (derived or original), **instead** of the need to identify it through one SAS variable EFPARM, is preferable. If providing more than one observation or row of data per patient is more convenient, then state in many places, especially at the top of the define.pdf file, the SAS variables (e.g., time, efficacy variables) through which the multiple observations or rows were created. The define.pdf file should contain the descriptions (how coded, which value stands for what) of variable names on SAS data sets. LOCF data also for each visit should be provided without the necessity for the reviewer to create them from OC data sets. Please provide a flag (or four separate data sets, if that is more convenient) to identify the four patient-sets: (ITT, LOCF), (ITT, OC), (PP, LOCF), and (PP, OC).

VIII. In flexible dose studies, histograms for doses (in each treatment group separately but on the same graph for comparison), for each week or whatever time interval is appropriate.

IX. Statistical Analysis Plan or related decisions, along with the date of finalization, which were not in the protocol; the dates of unblinding of data.

X. Alternative non-parametric analyses (these are helpful in many ways).

In summary, thorough analyses, including graphical tools, for each concern (that may be thought possible) should be provided. A picture is often worth a thousand words. Pictorial representations should be provided wherever possible, in addition to standard formal analyses. However, everything should be provided with discussion and conclusion.