

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-275

CHEMISTRY REVIEW(S)

Memorandum

To: NDA 22-275

CC:

From: Amit K. Mitra, Ph.D

Through: Ramesh. Sood, Ph.D

Date: 8/7/2008

Re: Final CMC recommendation- Approval

The recommendation from the Office of Compliance (OC) on facilities inspection was unavailable at the time of last review (Chemistry Review #2, dated 28-JUL-2008). Therefore, the application was deemed "Approvable" pending "Acceptable" recommendation from the OC. The OC has now provided an "Acceptable" recommendation. Therefore, the NDA is recommended to be approved with respect to CMC.

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

/s/

Amit K. Mitra
8/7/2008 05:28:14 PM
CHEMIST

Ramesh Sood
8/8/2008 07:10:26 AM
CHEMIST

**Samsca®
(tolvaptan)
Tablets**

NDA 22-275

**Division Director Review
Chemistry, Manufacturing, and Controls**

Applicant: Otsuka Pharmaceutical Development and Commercialization, Inc.
2400 Research Blvd.
Rockville, MD 20850

Indication: Short-term improvement of signs and symptoms of worsening heart failure beyond that achieved with standard of care and for the treatment of hypervolemic and euvolemic hyponatremia (including patients with heart failure, cirrhosis, SIADH, *etc.*) and for the prevention of worsening hyponatremia.

Presentation: Samsca® (tolvaptan) Tablets are available in three strengths as variously shaped, blue, shallow convex, bevel-edged, immediate release tablets debossed with "OTSUKA" on one side and strength on the other side:
15 mg is triangular debossed with "15,"
30 mg round debossed with "30," and
60 mg [REDACTED]

b(4)

and are packaged in unit dose blisters (10, [REDACTED])
[REDACTED]

b(4)

EER Status: Pending

Consults: EA – Categorical exclusion granted under 21 CFR §25.31(b)
Methods Validation – Revalidation by Agency will not be requested.

Original Submission: 22-OCT-2007

Post-Approval Agreements:

Within 2 months post-approval, "Otsuka agrees to submit the validation report of [REDACTED] and consequent replacement of the dissolution test for the [REDACTED] [REDACTED] as a supplement. Full validation data for the [REDACTED] method will also be included in the supplement."

b(4)

Drug Substance:

The drug substance, tolvaptan, is a small, synthetic, new molecular entity (NME) with an empirical formula of $C_{26}H_{25}ClN_2O_3$ and a molecular weight of 448.94. Known chemically as benzamide, N-[4-[(7-chloro-2,3,4,5-tetrahydro-5-hydroxy-1H-1-benzazepin-1-yl)carbonyl]-3-methylphenyl]2-methyl-, it is a white crystalline powder, non-hygroscopic, that melts at 227.5 °C. It is practically insoluble in water over pH 2.0 to 12.0 (0.00005 w/v% at 25°C), slightly soluble in ethyl acetate, sparingly soluble in ethanol, soluble in methanol, and freely soluble in benzyl alcohol. The octanol:water partition coefficient was reported to be greater than 5000 at 25° C. The molecule has one chiral center, leading to two enantiomers, and was developed as the racemate. b(4)

_____ The applicant reported tolvaptan to be a BCS class IV compound with moderate permeability and low pH-independent solubility.

_____. Strict control of related substances and other attributes of the starting materials were in agreement with the Agency's prior advice. The process is controlled by end-product testing. b(4)

The structure of tolvaptan was elucidated using elemental analysis, 1H and ^{13}C Nuclear Magnetic Resonance spectroscopy (NMR), high resolution Fast Atom Bombardment Mass Spectrometry (FAB-MS), InfraRed absorption spectroscopy (IR), optical resolution by chiral high performance liquid chromatography (HPLC), differential thermal analysis (DTA) and UltraViolet spectroscopy (UV).

The proposed release specification for tolvaptan includes: description, identification by IR, identification by UV, identification by Reverse Phase High Performance Liquid Chromatography (RP-HPLC), melting point, heavy metals, assay by RP-HPLC, impurities by RP-HPLC, residual solvents by Gas Chromatography (GC), loss on drying, and residue on ignition. The reference standard is manufactured using the commercial drug substance manufacturing process, recrystallized, and tested to meet more stringent specification.

Adequate stability data were provided to support the requested _____ retest date for the bulk drug substance, stored at controlled room temperature, _____ b(4)

Conclusion: Drug substance is Acceptable.

Drug Product:

Samsca® (tolvaptan) Tablets are available in three strengths as variously shaped, blue, shallow convex, bevel-edged, immediate release tablets debossed with "OTSUKA" on

one side and strength on the other side: 15 mg is triangular debossed with "15," 30 mg is round debossed with "30," and 60 mg [REDACTED]

b(4)

The drug product is packaged in unit dose blisters (10, [REDACTED])

b(4)

The composition of the 15 mg strength tablet is tolvaptan (15.000 mg), hydroxypropylcellulose NF [REDACTED] lactose monohydrate NF [REDACTED], corn starch NF [REDACTED] microcrystalline cellulose NF [REDACTED], low-substituted hydroxypropyl cellulose NF [REDACTED] FD&C Blue [REDACTED] and magnesium stearate NF [REDACTED] to give a total tablet weight of 87.000 mg. The 30 mg tablet is mass proportional using the same blend to give a total tablet weight of 174.000 mg. [REDACTED]

b(4)

Specification of the drug product includes: description, identification by RP-HPLC concurrent with diode array UV, impurities and degradation products by RP-HPLC, content uniformity by weight and RP-HPLC, dissolution, and assay by RP-HPLC. The drug substance reference standards are the same for the drug product.

Adequate stability data were provided to support requested expiration dating of 36 months for the 15 and 30 mg strengths and 24 months for the 60 mg strength at room temperature, 59°- 86°F (15°- 30°C) for the drug product packaged in the proposed final containers.

Conclusion: Drug product is Acceptable.

Additional Items:

All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.

The applicant agreed to place at least one commercial production batch of tolvaptan drug substance product per year on stability following the approved stability protocol.

The applicant agreed to place the first three [REDACTED] commercial lots for each strength, [REDACTED] on long term and accelerated stability following the approved stability protocol and submit the results to the Annual Report.

b(4)

The applicant agreed to place at least one commercial production lot of the drug product per year on stability for each strength and package configuration following the approved stability protocol.

The applicant submitted a methods validation package containing all relevant documentation (tests, methods, and acceptance criteria) for the control of the drug substance and the drug product. These methods are routine and will not be submitted to FDA laboratories for validation.

Overall Conclusion:

From a CMC perspective, the application is recommended for **Approval**, pending a satisfactory recommendation from the Office of Compliance.

Blair A. Fraser, Ph.D.
Director
DPA I/ONDQA

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

/s/

Blair Fraser
7/31/2008 01:15:23 PM
CHEMIST



NDA 22-275

Samsca (tolvaptan) tablets

**Otsuka Pharmaceutical Co. Ltd
Amit K. Mitra, Ph.D
Office of New Drug Quality Assessment**

**Reviewed for the Division of Cardiovascular and Renal
Products**



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Chemistry Review Data Sheet

1. NDA 22-275
2. REVIEW #:2
3. REVIEW DATE: 28-JUL-2008
4. REVIEWER: Amit K. Mitra, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents

22-OCT-2007

Document Date

22-OCT-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

30-MAY-2008
06-JUN-2008
10-JUN-2008
30-JUN-2008

Document Date

30-MAY-2008
06-JUN-2008
10-JUN-2008
18-JUL-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Otsuka Pharmaceutical Development &
Commercialization, Inc.
Address: 2440 Research Blvd., Rockville, MD 20850
Representative: George Hemsworth, Ph.D



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Telephone:

240-780-4131

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Samsca
- b) Non-Proprietary Name (USAN): Tolvaptan
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Selective vasopressin V₂ receptor antagonist

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 15, 30 and 60 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

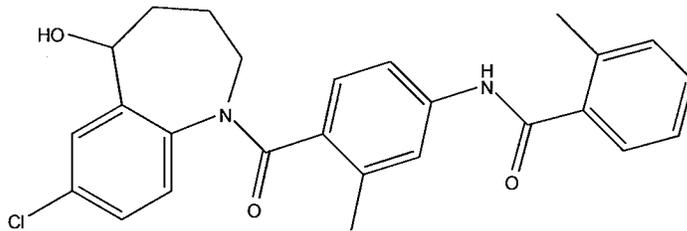
SPOTS product – Form Completed

Not a SPOTS product

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

Chemistry Review Data Sheet

$C_{26}H_{25}ClN_2O_3$



1. Benzamide, *N*-[4-[(7-chloro-2,3,4,5-tetrahydro-5-hydroxy-1*H*-1-benzazepin-1-yl)carbonyl]-3-methylphenyl]-2-methyl-

2. (±)-4'-[[(7-Chloro-2,3,4,5-tetrahydro-5-hydroxy-1*H*-1-benzazepin-1-yl)carbonyl]-*o*-tolu-m-toluidide

Molecular weight: 448.94

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	T Y P E	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
[REDACTED]	3	[REDACTED]	[REDACTED]	4			
[REDACTED]	3	[REDACTED]	[REDACTED]	4			
[REDACTED]	3	[REDACTED]	[REDACTED]	4			
[REDACTED]	3	[REDACTED]	[REDACTED]	4			

b(4)

1 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

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b(4)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	_____	
IND	_____	

b(4)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	None		
EES	Pending		None
Pharm/Tox	None		
Biopharm	Bio-waiver may be granted based on the response from consult review (see review notes).	29-MAY-2008	Dr. Patrick Marroum
LNC	N/A		
Methods Validation	N/A		
OPDRA	N/A		
EA	Categorical exclusion is	06-JUN-2008	Dr. Amit K. Mitra



CHEMISTRY REVIEW



Chemistry Review Data Sheet

	granted		
Microbiology	N/A		

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ___ No If no, explain reason(s) below:



The Chemistry Review #2 for NDA 22-275

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

“Approvable”, pending “Acceptable” recommendation from the OC.

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

Otsuka agreed to submit the validation report of [redacted] and consequent replacement of the dissolution test for the [redacted] as a supplement. Full validation data for the [redacted] method will also be included in the supplement. Otsuka committed to the task above within 2 months post approval. b(4)

II. Summary of Chemistry Assessments

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

Drug Substance (tolvaptan)

Tolvaptan drug substance is a new molecular entity and it is synthesized as a [redacted] [redacted] a racemic form. The sponsor has reported [redacted] form of the drug substance. Tolvaptan has an asymmetric center and can exist in two enantiomers. Since drug substance is a racemate it exhibits no optical rotation. Each optical isomer was characterized separately. The drug substance is listed in the USAN but the structure is presented with stereochemistry. Therefore, the USAN was requested, through Dr. David Lewis, to correct the chemical structure of the molecule to reflect racemic nature of tolvaptan. The CAS number for tolvaptan is CAS-150683-30-0. The drug substance is insoluble in water and its solubility is not pH dependent between pHs 2-12. It is non hygroscopic and has a melting point of approximately 224°C. The drug substance is reported to have poor solubility in water and moderate in [redacted] b(4)

The starting materials for tolvaptan are not common chemical compounds. However, those molecules were agreed as starting materials by the agency since the sponsor agreed on strict control of related substances and other attributes of the starting materials. [redacted] b(4)

[redacted] The final step of the synthetic process involves recrystallization [redacted] Therefore, under experimental conditions it is possible to form methyl ester of toluene sulfonic acid. Toluene sulfonic acid methyl ester (a potential genotoxic carcinogen) is not listed as the drug related impurities in section 3.2.S.3.2.1. Therefore, the applicant was requested to determine



Executive Summary Section

residual amount of methyl ester of sulfonic acid and adopt a specification for this impurity. The sponsor has demonstrated that the levels of the residual methyl ester of toluene sulfonic acid is at a level _____ in all batches which is well below the currently accepted threshold for toxicological concern at the maximum daily dose of the drug.

b(4)

The sponsor has conducted risk analysis of process parameters and came to the conclusion that there is no critical process parameters for the manufacturing process of tolvaptan drug substance. All isolated intermediates are controlled for purity prior to proceeding to the next step. If the intermediate does not meet the acceptance criterion, it is purified until it meets the acceptance criterion. Therefore, the risk of producing impure product at each process step is low.

Once manufactured, the drug substance is tested for Description (visual), Identification (IR, UV, HPLC), Melting point (capillary melting point), Heavy metals (USP <231>), related substances (HPLC), Residual solvents (GC), Residue on ignition (USP), and Assay (HPLC).

The sponsor has conducted accelerated and stressed stability studies with high temperature, relative humidity, and fluorescent light. Those stability studies indicated that the drug substance is stable under the extreme conditions.

Based on 2 years satisfactory long term and separately 6 months of accelerated stability data on three production batches, the sponsor is requesting a retest period of _____ and it can be granted.

b(4)

.....

b(4)



CHEMISTRY REVIEW



Executive Summary Section

[Redacted]

[Redacted]

b(4)

Drug Product

[Redacted]

The drug product specifications include Identification (Diode array detection, HPLC), Impurities/degradation products (HPLC), Uniformity for dosage units (HPLC for 15 and 30 mg strengths, and weight variation for the 60 mg strength), Dissolution (USP apparatus 2, 50 rpm followed by HPLC), Assay (HPLC).

There are differences in composition between the tablets used in the clinical trials and that of proposed to be marketed.

[Redacted]

b(4)

The applicant has compared dissolution profiles (10, 20, 30, 45, and 60 minutes) of clinical 30 mg tablet and proposed commercial 30 mg tablet and they are super-imposable. Similarly, the dissolution profile for 2 x 15 mg tablets is super-imposable to that of the 30 mg tablet. The dissolution profiles for the proposed commercial 15, 30, and 60 mg tablets are similar. Based on this information, the sponsor requested a bio-waiver for the proposed commercial formula. Therefore, the reviewer consulted OCP to review the bio-waiver request. Based on the OCP consult the applicant was requested to provide the discriminatory ability of the dissolution method, and a justification for the amount of sodium lauryl sulfate in the dissolution medium. The sponsor's justified the dissolution medium adequately and a bio-waiver may be granted as recommended by the OCP/ONDQA reviewer.

The stability of the proposed commercial tablets was generated under room temperature and accelerated conditions. Based on the satisfactory stability data for the 15 and 30 mg



CHEMISTRY REVIEW



Executive Summary Section

tablets a shelf life of 36 months shelf life can tentatively be granted. For the 60 mg strength a shelf life of 24 was requested by the sponsor and it may be granted.

Based on the DMET's review, the trademark was changed from "Samska" to "Samsca". All the carton, blister, _____ labels were revised accordingly and those are satisfactory

b(4)

The OC's recommendation for the facilities is pending.

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

The drug product is packaged in blisters _____ The tablets of 15, 30 and 60 mg strengths are designated as immediate release tablets. The recommended starting dose of Samsca is 15 mg/day to a maximum of 60 mg/day, as tolerated.

b(4)

C. Basis for Approvability or Not-Approval Recommendation

The application is approvable pending OC's "Acceptable" recommendation of the facilities.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Amit K. Mitra, Ph.D/6-JUN-2008
Ramesh Sood, Ph.D/
Blair Fraser, Ph.D/
ProjectManagerName/Date

C. CC Block

22 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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

/s/

Amit K. Mitra
7/28/2008 09:56:45 AM
CHEMIST

Ramesh Sood
7/28/2008 10:33:22 AM
CHEMIST



CHEMISTRY REVIEW

NDA 22-275

Samsca (tolvaptan) tablets

**Otsuka Pharmaceutical Co. Ltd
Amit K. Mitra, Ph.D
Office of New Drug Quality Assessment**

**Reviewed for the Division of Cardiovascular and Renal
Products**



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Chemistry Review Data Sheet

1. NDA 22-275
2. REVIEW #:2
3. REVIEW DATE: 28-JUL-2008
4. REVIEWER: Amit K. Mitra, Ph.D

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
22-OCT-2007	22-OCT-2007

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
30-MAY-2008	30-MAY-2008
06-JUN-2008	06-JUN-2008
10-JUN-2008	10-JUN-2008
30-JUN-2008	18-JUL-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Otsuka Pharmaceutical Development & Commercialization, Inc.
Address: 2440 Research Blvd., Rockville, MD 20850
Representative: George Hemsworth, Ph.D

CHEMISTRY REVIEW

Chemistry Review Data Sheet

Telephone:

240-780-4131

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Samsca
- b) Non-Proprietary Name (USAN): Tolvaptan
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Selective vasopressin V₂ receptor antagonist

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 15, 30 and 60 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

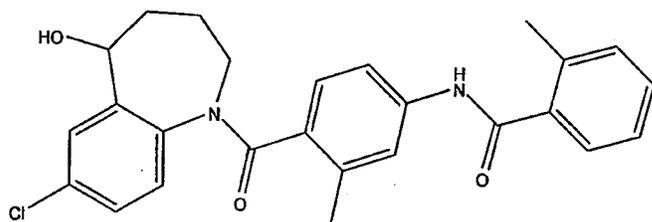
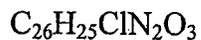
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



CHEMISTRY REVIEW



Chemistry Review Data Sheet



1. Benzamide, *N*-[4-[(7-chloro-2,3,4,5-tetrahydro-5-hydroxy-1*H*-1-benzazepin-1-yl)carbonyl]-3-methylphenyl]2-methyl-

2. (±)-4'-[[(7-Chloro-2,3,4,5-tetrahydro-5-hydroxy-1*H*-1-benzazepin-1-yl)carbonyl]-*o*-tolu-*m*-toluidide

Molecular weight: 448.94

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	T Y P E	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	3	/	/	4			
	3			4			
	3			4			
	3			4			

b(4)

1 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

CHEMISTRY REVIEW

Chemistry Review Data Sheet

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b(4)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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4 – Sufficient information in application

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6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND		
IND		

b(4)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	None		
EES	Pending		None
Pharm/Tox	None		
Biopharm	Bio-waiver may be granted based on the response from consult review (see review notes).	29-MAY-2008	Dr. Patrick Marroum
LNC	N/A		
Methods Validation	N/A		
OPDRA	N/A		
EA	Categorical exclusion is	06-JUN-2008	Dr. Amit K. Mitra



CHEMISTRY REVIEW



Chemistry Review Data Sheet

	granted		
Microbiology	N/A		

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ___ No If no, explain reason(s) below:



The Chemistry Review #2 for NDA 22-275

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

“Approvable”, pending “Acceptable” recommendation from the OC.

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

Otsuka agreed to submit the validation report of [redacted] and consequent replacement of the dissolution test for the [redacted] as a supplement. Full validation data for the [redacted] method will also be included in the supplement. Otsuka committed to the task above within 2 months post approval.

b(4)

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

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b(4)

b(4)

The starting materials for tolvaptan are not common chemical compounds. However, those molecules were agreed as starting materials by the agency since the sponsor agreed on strict control of related substances and other attributes of the starting materials. [redacted]

b(4)

[redacted] The final step of the synthetic process involves recrystallization [redacted]. Therefore, under experimental conditions it is possible to form methyl ester of toluene sulfonic acid. Toluene sulfonic acid methyl ester (a potential genotoxic carcinogen) is not listed as the drug related impurities in section 3.2.S.3.2.1. Therefore, the applicant was requested to determine



CHEMISTRY REVIEW



Executive Summary Section

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b(4)

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The sponsor has conducted accelerated and stressed stability studies with high temperature, relative humidity, and fluorescent light. Those stability studies indicated that the drug substance is stable under the extreme conditions.

Based on 2 years satisfactory long term and separately 6 months of accelerated stability data on three production batches, the sponsor is requesting a retest period of _____ it can be granted.

b(4)

b(4)



CHEMISTRY REVIEW



Executive Summary Section

[REDACTED]

[REDACTED]

b(4)

Drug Product

[REDACTED]

[REDACTED]

The drug product specifications include Identification (Diode array detection, HPLC), Impurities/degradation products (HPLC), Uniformity for dosage units (HPLC for 15 and 30 mg strengths, and weight variation for the 60 mg strength), Dissolution (USP apparatus 2, 50 rpm followed by HPLC), Assay (HPLC).

There are differences in composition between the tablets used in the clinical trials and that of proposed to be marketed.

[REDACTED]

b(4)

The applicant has compared dissolution profiles (10, 20, 30, 45, and 60 minutes) of clinical 30 mg tablet and proposed commercial 30 mg tablet and they are super-imposable. Similarly, the dissolution profile for 2 x 15 mg tablets is super-imposable to that of the 30 mg tablet. The dissolution profiles for the proposed commercial 15, 30, and 60 mg tablets are similar. Based on this information, the sponsor requested a bio-waiver for the proposed commercial formula. Therefore, the reviewer consulted OCP to review the bio-waiver request. Based on the OCP consult the applicant was requested to provide the discriminatory ability of the dissolution method, and a justification for the amount of sodium lauryl sulfate in the dissolution medium. The sponsor's justified the dissolution medium adequately and a bio-waiver may be granted as recommended by the OCP/ONDQA reviewer.

The stability of the proposed commercial tablets was generated under room temperature and accelerated conditions. Based on the satisfactory stability data for the 15 and 30 mg



CHEMISTRY REVIEW



Executive Summary Section

tablets a shelf life of 36 months shelf life can tentatively be granted. For the 60 mg strength a shelf life of 24 was requested by the sponsor and it may be granted.

Based on the DMET's review, the trademark was changed from "Samska" to "Samsca". All the carton, blister, _____ labels were revised accordingly and those are satisfactory

b(4)

The OC's recommendation for the facilities is pending.

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

The drug product is packaged in blisters _____ The tablets of 15, 30 and 60 mg strengths are designated as immediate release tablets. The recommended starting dose of Samsca is 15 mg/day to a maximum of 60 mg/day, as tolerated.

b(4)

C. Basis for Approvability or Not-Approval Recommendation

The application is approvable pending OC's "Acceptable" recommendation of the facilities.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Amit K. Mitra, Ph.D/6-JUN-2008
Ramesh Sood, Ph.D/
Blair Fraser, Ph.D/
ProjectManagerName/Date

C. CC Block

62 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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Amit K. Mitra
6/26/2008 03:11:28 PM
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Ramesh Sood
6/27/2008 07:20:20 AM
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Initial Quality Assessment

OND Division:	Division of Cardiovascular and Renal Products
NDA:	22-275
Applicant:	Otsuka Pharmaceutical Company, Ltd
Letter Date:	22-OCT-2007
Stamp Date:	23-OCT-2007
PDUFA Date:	22-AUG-2008
Trademark:	Samska
Established Name:	Tolvaptan
Dosage Form:	Tablets
Route of Administration:	Oral
Indication:	Short-term improvement of signs and symptoms of worsening heart failure beyond that achieved with standard of care and for the treatment of hypervolemic and euvolemic hyponatremia (including patients with heart failure, cirrhosis, SIADH, etc.) and for the prevention of worsening hyponatremia.
Assessed by:	Amit K. Mitra

ONDQA Fileability:

Yes

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Summary:

This is a 505(b) 1 submission for an immediate release tablet dosage form of a new molecular entity, tolvaptan for short-term improvement of signs and symptoms of worsening heart failure beyond that achieved with standard of care and for the treatment of hypervolemic and euvolemic hyponatremia (including patients with heart failure, cirrhosis, SIADH, etc.) and for the prevention of worsening hyponatremia. Tolvaptan is a selective arginine vasopressin (AVP) V2 receptor and belongs to a class of compounds generally called vaptans.

The submission is in eCTD format. Tolvaptan is synthesized as a racemate and the established and chemical name are in the USAN. _____

substance from the drug product. There was an End-of-Phase II CMC meeting between the agency and the sponsor where the assignment of starting materials, specific information regarding drug substance specifications, drug product specifications, and stability protocol were discussed. According to the sponsor (see the summary of Biopharmaceutics and Associated Analytical methods section, m2-7-1) tolvaptan is a BCS class IV drug.

Drug Substance: Tolvaptan drug substance is synthesized as a _____. The sponsor has reported _____ form of the drug substance. Tolvaptan has an asymmetric center and can exist in two enantiomers. Since drug substance is a racemate it exhibits no optical rotation. Each optical isomer was characterized separately. The drug substance is insoluble in water and its solubility is not pH dependent. It is non hygroscopic and has a melting point of approximately 224°C. The sponsor has conducted risk analysis of process parameters and came to the conclusion that there is no critical process parameters for the manufacturing process of tolvaptan drug substance. The sponsor proposed to control the following attributes for quality control: Description, ID, melting point, heavy metals, related

substances, residual solvents (for ICH class II solvent only), LOD, residue on ignition, and assay. The drug substance is substantially stable under accelerated conditions and 30°C/65%RH at solid state.

Drug Product: Tolvaptan tablets have been developed as immediate release tablets of 15, 30 and 60 mg strengths. Tolvaptan drug substance is practically insoluble in water. In order to improve the dissolution and thereby enhance the bioavailability, [REDACTED] is used in the tablet formulation. The tolvaptan tablets contain hydroxypropyl cellulose [REDACTED], [REDACTED], lactose monohydrate, corn starch, microcrystalline cellulose, low substituted hydroxypropyl cellulose [REDACTED], magnesium stearate, and FD&C Blue #2 aluminum lake (colorant). All excipients used in the manufacture of the drug product are compendial, except for the colorant which has CFR listings. The sponsor proposes to control the following attributes for quality control: Description, Identification, Impurities/Degradation products, content uniformity, dissolution, and assay. Based on 18 months long term stability data and 6 months accelerated stability data, the sponsor is proposing a shelf life of [REDACTED]. The drug product chemically is not sensitive to light, temperature fluctuations (freeze/thaw), and under high temperature/ high humidity conditions (40C/75%RH). However, the moisture content increases by approximately 1% over 18 months storage at 25°C/60%RH.

b(4)

Critical Issues for Review

Drug Substance

- Is the characterization of each enantiomer in 3.2.S.3.1 adequate?
- The drug substance is a racemate; i.e. a 50:50 mixture of two optical isomers. The two optical isomers could be different with regard to safety and efficacy profiles. It is also possible for one optical isomer to convert into another optical isomer under in vivo conditions. This inter-conversion may or may not have an impact on the safety and efficacy of the drug product.
- The synthetic scheme in 2.3.S.2 suggests that a drug substance intermediate is formed by a [REDACTED] process. Is there a possibility of residual toluene sulfonic acid to form methyl ester at the final recrystallization step when [REDACTED] [REDACTED] Toluene sulfonic acid methyl ester (a potential genotoxic carcinogen) is not listed as the drug related impurities in 3.2.S.3.2.1. Did the sponsor test for methyl ester of toluene sulfonic acid in the drug substance?
- The sponsor indicated that there are no critical process steps during manufacturing. Is the statement accurate?

b(4)

- Is sponsor's risk analysis appropriate?
- The sponsor has proposed a retest period of [REDACTED] Is it justified?

b(4)

Drug Product

- The sponsor has not adopted any specifications for hardness and friability for the drug product. Is it justified?
- Has the sponsor demonstrated that the [REDACTED] is uniformly [REDACTED] Is dissolution a good test for determining the [REDACTED]

b(4)

- The sponsor proposed to submit an amendment to extend the shelf life to [REDACTED] The adequacy of the data needs to be evaluated.
- The sponsor has not adopted a specification for moisture content in the drug product. The moisture content increases slightly (approximately 1% over 18 month's storage at 25 °C/60%RH). Does the change in moisture affect the hardness, friability or dissolution rate of the tablet?
- Does the drug substance remain in [REDACTED] throughout the shelf life of the drug product?
- Should the sponsor be requested to provide risk assessment for potential [REDACTED] of the [REDACTED] during manufacture and stability, pre and post approval?
- The sponsor claimed that since this is tablet dosage form, specification for microbial limits need not be adopted. The microbial limits test on the tablets, as provided in Table 3.2.P.5.4-2 through Table 3.2.P.5.4-4, showed zero microbial count, yeast and mold count, and absence of Escherichia Coli. The excipients also contain some form of microbial limits specification. Is skip lot testing more appropriate than no testing?

b(4)

b(4)

Labeling

- Is the established name "tolvaptan" on immediate container label is prominent enough per CFR 201.15?

- Does the Division labeling policy allow for not including the inactive ingredients on the carton/immediate container label?
- The Form 356h states that the sponsor is seeking approval for 15, 30 and 60 mg tablets. However, the "How Supplied" section states that tolvaptan is available in 15 and 30 mg strengths. A resolution of the discrepancy should be sought.

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/s/

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