CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204441Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 204441 Resubmission
Review #1

Drug Name/Dosage Form	Tolvaptan Tablets
Strength(s)	15 mg, 30 mg, 45 mg, 60 mg, 90 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Otsuka Pharmaceutical Company Ltd
US agent, if applicable	Otsuka Pharmaceutical Development & Commercialization, Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Resubmission	24-OCT-2017
Amendment	03-NOV-2017
Amendment	06-NOV-2017
Amendment	11-DEC-2017
Amendment	15-DEC-2017
Amendment	01-FEB-2018
Amendment	23-FEB-2018
Amendment	26-FEB-2018
Amendment	14-MAR-2018
Amendment	20-MAR-2018

Quality Review Team

DISCIPLINE	PRIMARY/SECONDARY REVIEWER	OPQ OFFICE/DIVISION
Drug Substance	Thomas Wong/Wendy Wilson-Lee	ONDP/DNDP1
Drug Product		
Process		
Environmental Analysis		
Facilities	Steve Hertz/Zhihao Peter Qiu	OPF/DIA
Biopharmaceutics	Zhuojun Zhao/Jing Li	ONDP/DB
Regulatory Business Process Manager	Grafton Adams	OPRO/DRBPM1
Application Technical Lead	Wendy Wilson-Lee	ONDP/DNDP1

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

None.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
(b) (4)		
IND	54200	Tolvaptan for treatment of hyponatremia in euvolemic and hypovolemic patients
IND	72975	Tolvaptan to (b) (4) prevent progression of ADPKD
IND	107847	Tolvaptan for treatment of polycystic kidney disease
NDA	22275	Tolvaptan Tablets (15 mg, 45 mg, 90 mg)

2. CONSULTS

None.

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends approval of Tolvaptan Tablets (15 mg, 30 mg, 45 mg, 60 mg, and 90 mg) when manufactured in accordance with the NDA, packaged in the proposed commercial packaging, and stored at the recommended storage condition.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	***Slow kidney function decline*** (b) (4) ***adults at risk of rapidly progressing Autosomal Dominant Polycystic Kidney Disease (ADPKD)***
Duration of Treatment	***Chronic***
Maximum Daily Dose	***120 mg***
Alternative Methods of Administration	***None***

B. Quality Assessment Overview

Tolvaptan is a vasopressin V2 receptor antagonist approved in May 2009 under NDA 22-275 (Samsca® (tolvaptan) 15 mg, 30 mg, and 60 mg tablets)) indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia. The current NDA seeks approval to market tolvaptan for the treatment of ADPKD with additional strengths of 45 mg and 90 mg tablets, of which the composition is quantitatively proportional to the approved strengths (15 mg, 30 mg, and 60 mg).

This NDA was initially submitted in November 2012. The CMC portion of the initial submission was reviewed in July and August 2013 with an approval recommendation. A complete response letter was sent to the applicant in August 2013 due to insufficient evidence of efficacy in the pivotal clinical trial. The applicant resubmitted this NDA in October 2017. The applicant stated that no new quality information was included in the resubmission. All quality information is referred to the initial submission. All facilities in NDA 204441 are acceptable for the listed responsibilities (Overall Facilities Recommendation dated March 15, 2018).

In response to a March 12, 2018 information request, the applicant provided an elemental impurities risk assessment in accordance with ICH Q3D Elemental Impurities, evaluating the potential for elemental impurities contamination of the final drug product from the drug substance, inactive ingredients, raw materials, manufacturing equipment, and container closure components. The applicant updated Module 3.2.P.5.5 to reflect the risk

assessment and outcome. Based on the risk assessment and test results, the applicant determined little or no risk of the presence of Class 1 and 2A elemental impurities in tolvaptan tablets. Based on this assessment, tests for the elemental impurities were not included in the specification of tolvaptan tablets. We agree with the risk assessment and conclusion. No controls for elemental impurities in the final drug product are needed.

C. Special Product Quality Labeling Recommendations

None.

Wendy
Wilson- Lee

Digitally signed by Wendy Wilson- Lee
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BIOPHARMACEUTICS

Product:

NDA: 204441 (Resubmission of New Drug Application-505 (b)(1)

Drug Product Name / Strength: Samsac® (Tolvaptan) Immediate Release Tablets, 15, 30, 45, 60 and 90 mg

Route of Administration: Oral

Applicant Name: Otsuka Pharmaceutical Development and Commercialization, Inc.

Background:
Tolvaptan is a vasopressin V2 receptor antagonist approved in May 2009 under NDA 22-275 (Samsca® (tolvaptan) 15-, 30-, and 60-mg tablets)) indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia. This NDA 204441 is to market tolvaptan to slow kidney disease in adults at risk of rapidly progressing ADPKD with additional strengths of 45 mg and 90 mg tablets, of which the composition is quantitatively proportional to the approved strengths (15-, 30-, and 60-mg). During the first review cycle, Division of Biopharmaceutics reviewed[1] and approved the dissolution method and acceptance criteria (shown in Table 1) for Tolvaptan tablets, 15, 30, 45, 60 and 90 mg. A bioequivalence study was conducted between the approved 30-mg tablets and the proposed commercial 90-mg tablets, and bio-waiver for the 45-mg strength was granted.

The original NDA 204441 submission received a "Complete Response (CR)" letter on August 28, 2013, primarily due to concerns with the clinical studies. The CR letter did not include any Biopharmaceutics deficiencies or comments. However, the letter commented on the Applicant's failure (b) (4) for the BE study, and the BE study was the basis for the biowaiver of the 45-mg strength.

The current submission is the resubmission of NDA 204441 received on October 24, 2017, in response to the deficiencies identified in the "Complete Response" letter.

Dissolution Method and Acceptance Criterion:
There is no new quality information included in the resubmission. The dissolution method and acceptance criteria remain the same and adequate (Table 1).

Table 1. Approved Dissolution Method and Acceptance Criterion

USP Apparatus	Speed (RPMs)	Medium	Volume	Cumulative % of Drug Dissolved (Label Claim)
II (Paddle)	50	0.22% SLS in water	900 mL	15,30, 45, 60 mg: Q (b) (4)% in 30 minutes 90 mg: Q= (b) (4)% in 45 minutes

[1] DARRTS: REV-QUALITY-21 (Primary Review), final date 07/10/2013

Biowaiver Request:

During the review of the original NDA 204441 submission, FDA noted that (b) (4) (b) (4) for the bioequivalence trial 156-11-295. FDA subsequently advised that the BE trial conducted on the 90-mg tablets would need to be repeated because of this deficiency.

In the resubmission, instead of conducting a new BE study, the Applicant requests waiver of bioequivalence study for both 45-mg and 90-mg tablets based on the Teleconference with the Agency on September 11, 2017. The information provided in the resubmission to support the biowaiver request for 45 and 90 mg strengths include:

Composition proportionality: The new 45- and 90-mg strengths were designed to be immediate release tablets that were quantitatively proportional with the currently approved 60-mg tablets. The 45-mg tablet is exactly 0.75 times and the 90-mg tablet is exactly 1.5 times the 60-mg tablet. (b) (4) .

Table 3.2.P.2.2.1-2 Quantitative Composition of Proposed Commercial Tolvaptan 45- and 90-mg Tablets and Approved Samsca 60-mg Tablets

Component	Reference	Function	New Strength				Approved Strength	
			45-mg Tablets		90-mg Tablets		60-mg Tablets	
			mg	% w/w	mg	% w/w	mg	% w/w
(b) (4) Tolvaptan	In-house	Active ingredient	45.0	37.04	90.0	37.04	60.000	37.04
(b) (4)								
Lactose monohydrate	NF							
Corn starch	NF							
Microcrystalline cellulose	NF							
Hydroxypropyl cellulose[c]	NF							
Low-substituted hydroxypropyl cellulose	NF							
FD&C Blue No.2 Aluminum Lake	21 CFR 82.51, 82.102							
Magnesium stearate[d]	NF							
(b) (4								
Total weight			121.5		243.0		162.0	
Tablet description			Blue, square, shallow-convex (b) (4) tablet, debossed with "OTSUKA" and "45" on one side		Blue, pentagon, shallow-convex, (b) (4) tablet, debossed with "OTSUKA" and "90" on one side		Blue, modified rectangle, shallow-convex, (b) (4) (b) (4) tablet, debossed with "OTSUKA" and "60" on one side	

NF = National Formulary; USP = US Pharmacopeia; CFR = Code of Federal Regulations; qs = quantity sufficient

(b) (4)

Dissolution similarity: The similarity factors (f2) calculated for the dissolution profiles for 1 x 45 mg vs 1 x 60 mg and 1 x 90 mg vs 1 x 60 mg obtained using the QC dissolution method were 65 and 57, respectively, demonstrating the dissolution equivalency of the approved 60-mg tablets and the proposed commercial 45- and 90-mg tablets.

[2] \\cdsesub1\evsprod\nda204441\0000\m3\32-body-data\32p-drug-prod\tolvaptan-tablets\32p2-pharm-dev\formulation-development-.pdf

Dose Proportionality: Per Samsca® label, the area under the curve (AUC) increases proportionally with dose after single doses of up to 480 mg and multiple doses up to 300 mg once daily.

Reviewer Note:
Based on the provided supportive information, the bio-waiver request for 45 and 90 mg is granted.

RECOMMENDATION
The resubmission of NDA 204441 for Tolvaptan tablets, 15, 30, 45, 60 and 90 mg is recommended for **APPROVAL** from biopharmaceutics point of view.

Primary Biopharmaceutics Reviewer Name and Date: *Zhuojun Zhao, Ph.D. 3/7/2018*

I concur with Dr. Zhao's recommendation.
Secondary Reviewer Name and Date: *Jing Li, Ph.D. 3/20/2018*

Zhuojun Zhao

Digitally signed by Zhuojun Zhao
Date: 3/20/2018 11:32:13PM
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Jing Li

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Date: 3/20/2018 11:55:27PM
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NDA 204441

Review #2

[redacted] (b) (4) **(tolvaptan) Tablets**

(15 mg, 30 mg, 45 mg, 60 mg and 90 mg)

Otsuka Pharmaceutical Company, Ltd.

Zedong Dong, Ph.D.

Product Quality Reviewer

Office of New Drug Quality Assessment, Division I

CMC REVIEW OF NDA 204441

For the Division of Cardiovascular and Renal Products (HFD-110)

Table of Contents

Chemistry Review Data Sheet

1. NDA 204441

2. REVIEW #: 2

3. REVIEW DATE: August 26, 2013

4. REVIEWER: Zedong Dong, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA 22275	05/19/2009 (AP)
Pre-NDA meeting (IND 72975)	07/06/2012

6. SUBMISSION(S) BEING REVIEWED (CMC):

Submission(s) Reviewed	Document Date
Original Submission 0000	11/15/2012
Amendment 0002 (Drug Product manufacturers)	11/30/2012
Amendment 0022 (Response to CMC/Biopharm IR)	06/11/2013
Amendment 0025 (Response to CMC/Biopharm IR)	06/18/2013
Amendment 0037 (Response to CMC IR)	07/24/2013
Amendment 0039 (Response to CMC IR)	08/13/2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Otsuka Pharmaceutical Company, Ltd.
Address:	2-9 Kanda Tsukasa-cho Chiyoda-ku Tokyo, Japan 101-8535

Chemistry Review Data Sheet

Representative:	Otsuka Pharmaceutical Development and Commercialization, Inc. 1 University Square Drive, Suite 500 Princeton, NJ 08540
Telephone:	(609) 853-2006

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: (b) (4)
b) Non-Proprietary Name (USAN): tolvaptan
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 9
- Submission Priority: P

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

10. PHARMACOL. CATEGORY: slow progressive kidney disease in adults with autosomal dominant polycystic kidney disease (ADPKD)

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 15 mg, 30 mg, 45 mg, 60 mg and 90 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X_Rx ___OTC

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

_____SPOTS product – Form Completed

___X__Not a SPOTS product

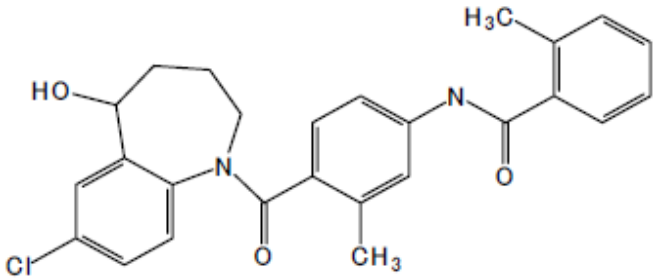
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Names:

(±)-4-[(7-Chloro-2,3,4,5-tetrahydro-5-hydroxyl-1*H*-1-benzazepin-1-yl)carbonyl]-*o*-tolu-*m*-toluidine

Molecular Formula: $C_{26}H_{25}ClFN_2O_3$

Molecular Weight: 448.94



TOLVAPTAN

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				4	Adequate	N/A	N/A
				3	Adequate	06/18/2012	By Raymond P. Frankewich
				4	N/A	N/A	N/A
				4	N/A	N/A	N/A
				4	N/A	N/A	N/A
				3	Adequate	04/24/2012	By George Lunn
				4	N/A	N/A	N/A
				4	N/A	N/A	N/A
				4	N/A	N/A	N/A

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is adequate data in the application, therefore the DMF was not reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	08/26/2013	
Pharm/Tox	N/A		
Biopharm	Approval	07/10/2013	Akm Khairuzzaman
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMEPA	N/A		
EA	Category exclusion (see review)		

The Chemistry Review for NDA 204441

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 204441 is recommended for approval from a Chemistry, Manufacturing and Controls standpoint.

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

N/A

II. Summary of Chemistry Assessments

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

Drug Product:

The proposed drug product in this NDA is an immediate release tablet in the strengths of 15 mg, 30 mg, 45 mg, 60 mg and 90 mg. The 15, 30 and 60 mg tablets were approved in NDA 22-275. Therefore, all the CMC information for these three strengths is cross-referenced to NDA 22-275. This review focuses on the two new strengths, 45 mg and 90 mg tablets.

The formulation composition of the two new strengths is proportional to the currently approved 60 mg tablet. The manufacturing process, equipment and in-process controls are the same except for (b) (4) The specifications of the 45 mg and 90 mg tablets remain the same as the other currently approved strengths, except for dissolution (Q = (b) (4)% at 45 minutes) for the 90 mg strength. The analytical procedures for the 45 mg d 90 mg tablets are also the same as those for approved strengths. Method validation results are provided for the dissolution method to accommodate the two new strengths, which are found satisfactory. Manufactured with the same materials as those for the approved strengths, (b) (4) blisters are used for the container closure for primary stability studies. Stability data under long term (18 months) and accelerated (6 months) conditions were submitted for the two strengths to support the determination of the shelf life. No significant trend of change was observed in appearance, assay, dissolution, friability or disintegration under both storage conditions. As supported with stability data, per ICH Q1E, a thirty-month expiry is granted.

The proposed marketing package configurations are (b) (4) blister combination cards for 60 mg/30 mg, 45 mg/15 mg, and 90 mg/30 mg strengths. (b) (4) The labeling for blister backing, the proposed weekly pack and monthly carton for the two-strength blister combination cards are found acceptable.

The tablets are recommended to be stored at 25°C (77°F), with excursions permitted between 15°C - 30°C (59°F - 86°F).

A thirty-month expiry at the proposed storage conditions will be granted for the 45 mg and 90 mg tolvaptan tablets based on the provided stability data. This is to be communicated to the applicant in the action letter.

Claim for category exclusion is granted per 21 CFR Part 25.31 (b).

Drug Substance:

The CMC information for tolvaptan drug substance is cross-referenced to NDA 22-275.

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

Tolvaptan tablets are available in (b) (4) ombined strengths blisters for 60 mg/30 mg, 45 mg/15 mg and 90 mg/30 mg strengths. Based on the package insert, the initial dose is 60 mg per day as a split-dose regimen of 45 mg/15 mg (45 mg taken on waking and 15 mg taken 8 hours later). The initial dose should be titrated upward to a split-dose regimen of 90 mg (60 mg/30 mg) per day then to a target split-dose regimen of 120 mg (90 mg/30 mg) per day if tolerated with at least weekly intervals between titrations. Patients may down-titrate to lower doses based on tolerability. Patients should be maintained on the highest tolerable dose.

C. Basis for Approvability or Not-Approval Recommendation *(Harmonized with DS review)*

This new drug application (NDA 204441) is recommended to be approved from the CMC perspective. The recommendation for approval is based upon the acceptable

identity, strength, quality, purity and stability upon the evaluation of the drug product (45 mg and 90 mg strengths).

III. Administrative

A. Reviewer's Signature

(*see appended electronic signature page*)

Zedong Dong, Ph.D.
Chemistry Reviewer
Division I, ONDQA

B. Endorsement Block

(*see appended electronic signature page*)

Hasmukh Patel, Ph.D.
Branch Chief
Brach III, Division I, ONDQA

C. CC Block: entered electronically in DARRTS

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/s/

ZEDONG DONG
08/27/2013

HASMUKH B PATEL
08/27/2013

NDA 204441

[redacted] (b) (4) (tolvaptan) Tablets

(15 mg, 30 mg, 45 mg, 60 mg and 90 mg)

Otsuka Pharmaceutical Company, Ltd.

Zedong Dong, Ph.D.

Product Quality Reviewer

Office of New Drug Quality Assessment, Division I

CMC REVIEW OF NDA 204441

For the Division of Cardiovascular and Renal Products (HFD-110)

Table of Contents

Chemistry Review Data Sheet

1. NDA 204441

2. REVIEW #: 1

3. REVIEW DATE: July 5, 2013

4. REVIEWER: Zedong Dong, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA 22275	05/19/2009 (AP)
Pre-NDA meeting (IND 72975)	07/06/2012

6. SUBMISSION(S) BEING REVIEWED (CMC):

Submission(s) Reviewed	Document Date
Original Submission 0000	11/15/2012
Amendment 0002 (Drug Product manufacturers)	11/30/2012
Amendment 0022 (Response to CMC/Biopharm IR)	06/11/2013
Amendment 0025 (Response to CMC/Biopharm IR)	06/18/2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Otsuka Pharmaceutical Company, Ltd.
Address:	2-9 Kanda Tsukasa-cho Chiyoda-ku Tokyo, Japan 101-8535

Chemistry Review Data Sheet

Representative:	Otsuka Pharmaceutical Development and Commercialization, Inc. 1 University Square Drive, Suite 500 Princeton, NJ 08540
Telephone:	(609) 853-2006

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: JINARC
b) Non-Proprietary Name (USAN): tolvaptan
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 9
- Submission Priority: P

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

10. PHARMACOL. CATEGORY: slow progressive kidney disease in adults with autosomal dominant polycystic kidney disease (ADPKD)

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 15 mg, 30 mg, 45 mg, 60 mg and 90 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X_Rx ___OTC

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

_____SPOTS product – Form Completed

___X__Not a SPOTS product

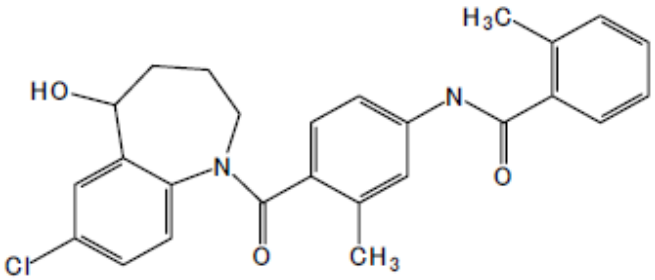
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Names:

(±)-4-[(7-Chloro-2,3,4,5-tetrahydro-5-hydroxyl-1*H*-1-benzazepin-1-yl)carbonyl]-*o*-tolu-*m*-toluidine

Molecular Formula: $C_{26}H_{25}ClFN_2O_3$

Molecular Weight: 448.94



TOLVAPTAN

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				4	Adequate	N/A	N/A
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				4	N/A	N/A	N/A
				4	N/A	N/A	N/A
				4	N/A	N/A	N/A
				3	Adequate	04/24/2012	By George Lunn
				4	N/A	N/A	N/A
				4	N/A	N/A	N/A
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6 – DMF not available
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[2] Adequate, Inadequate, or N/A (There is adequate data in the application, therefore the DMF was not reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending	07/10/2013	
Pharm/Tox	N/A		
Biopharm	Approval	07/10/2013	Akm Khairuzzaman
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMEPA	N/A		
EA	Category exclusion (see review)		

The Chemistry Review for NDA 204441

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 204441 is recommended for approval from a Chemistry, Manufacturing and Controls standpoint, pending an acceptable overall EES status of the manufacturers and satisfactory resolution of the labeling issues.

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

N/A

II. Summary of Chemistry Assessments

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

Drug Product:

The drug product in this NDA are 15 mg, 30 mg, 45 mg, 60 mg and 90 mg immediate release tablets. The 15, 30 and 60 mg tablets were approved in NDA 22-275. Therefore, all the CMC information for these three strengths is cross-referenced to NDA 22-275. This review focuses on the two new strengths, 45 mg and 90 mg tablets.

The formulation composition of the two new strengths are proportional to the currently approved 60 mg tablet. The manufacturing process, equipment and in-process controls are the same except for (b) (4) The specifications of the 45 mg and 90 mg tablets remain the same as the other currently approved strengths, except for dissolution (Q = (b) (4)% at 45 minutes) for the 90 mg strength. The analytical procedures for the 45 mg and 90 mg tablets are also the same as those approved strengths. Method validation results are provided for the dissolution method to accommodate the two new strengths, which are found satisfactory. Manufactured with the same materials as those for the approved strengths, (b) (4) blisters are used for the container closure for primary stability studies. Stability data under long term (18 months) and accelerated (6 months) conditions were submitted for the two strengths to support the determination of the shelf life. No significant trend of change was observed in appearance, assay, dissolution, friability or disintegration under both storage conditions. As supported with stability data, per ICH Q1E, a thirty-month expiry is granted.

The proposed marketing package configurations are [redacted] (b) (4) blister combination cards for 60 mg/30 mg, 45 mg/15 mg, and 90 mg/30 mg strengths. [redacted] (b) (4) The labeling for the proposed weekly pack and monthly carton for the two-strength blister combination cards are found acceptable. However, additional drug information needs to be added on the blister backing.

Claim for category exclusion is granted per 21 CFR Part 25.31 (b).

Drug Substance:

The CMC information for tolvaptan drug substance is cross-referenced to NDA 22-275.

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

Tolvaptan tablets are available in [redacted] (b) (4) combined strengths blisters for 60 mg/30 mg, 45 mg/15 mg and 90 mg/30 mg strengths. The tablets are recommended to be stored at 25°C (77°F), with excursions permitted between 15°C - 30°C (59°F - 86°F).

A thirty-month expiry at the proposed storage conditions will be granted for the 45 mg and 90 mg tolvaptan tablets based on the provided stability data. This is to be communicated to the applicant in the action letter.

C. Basis for Approvability or Not-Approval Recommendation *(Harmonized with DS review)*

This new drug application (NDA 204441) is recommended to be approved from the CMC perspective pending an overall recommendation of the cGMP status of the manufacturing and testing facilities from the Office of Compliance and successful resolution of the labeling issues. The recommendation for approval is based upon the acceptable identity, strength, quality, purity and stability upon the evaluation of the drug product (45 mg and 90 mg strengths).

III. Administrative

A. Reviewer's Signature

(*see appended electronic signature page*)

Zedong Dong, Ph.D.
Chemistry Reviewer
Division I, ONDQA

B. Endorsement Block

(*see appended electronic signature page*)

Hasmukh Patel, Ph.D.
Branch Chief
Brach III, Division I, ONDQA

C. CC Block: entered electronically in DARRTS

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Labeling

The proposed marketing package configurations are (b) (4) blister combination cards for 60 mg/30 mg, 45 mg/15 mg, and 90 mg/30 mg strengths.

(b) (4)

(b) (4)

[redacted]

Combined-strengths blisters are proposed for 60 mg/30 mg tablets, 45 mg/15 mg tablets, and 90 mg/30 mg tablets. Labeling information for the blister backing, monthly carton and weekly carton are provided in the application. The labeling for the monthly and weekly cartons appear to carry the appropriate drug product information. However, the blister backing does not contain any drug product information. Information request was communicated to the applicant:

> *Provide the following drug product information on the blister backing as an immediate container label: proprietary name and established name, strength, net contents, "Rx only" statement, NDC number, lot number and expiration date, storage conditions, bar code, name of manufacturer/distributor. Provide justification for the exclusion of any above information in case of limited available space.*

(b) (4)

[redacted]

(b) (4)

Deficiency #2: Per 21 CFR 201.10(i), include essential drug product information on the blister backing.

(b) (4)

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

B. Environmental Assessment Or Claim Of Categorical Exclusion

Otsuka Pharmaceutical Co., Ltd. claims a categorical exclusion to the environmental assessment requirements in compliance with categorical exclusion criteria 21 CFR Part 25.31 (b). Per their best knowledge, no extraordinary circumstances exist [21 CFR 25.15 (d)]. This drug is manufactured using a synthetic process and is not 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 based on the calculation.

Based on the above information provided by Otsuka, the request for categorical exclusion may be granted.

III. List Of Deficiencies To Be Communicated

(b) (4)

Deficiency #2: Per 21 CFR 201.10(i), include essential drug product information on the blister backing.

APPENDIX: EES REPORT

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 204441/000	**Sponsor:**	OTSUKA PHARM
Org. Code:	110		2440 RESEARCH BLVD
Priority:			ROCKVILLE, MD 20850
Stamp Date:	15-NOV-2012	**Brand Name:**	TOLVAPTAN
PDUFA Date:	01-SEP-2013	**Estab. Name:**	
Action Goal:		**Generic Name:**	TOLVAPTAN
District Goal:		**Product Number; Dosage Form; Ingredient; Strengths**	
		001; TABLET; TOLVAPTAN; 15MG 002; TABLET; TOLVAPTAN; 30MG 003; TABLET; TOLVAPTAN; 45MG 004; TABLET; TOLVAPTAN; 60MG 005; TABLET; TOLVAPTAN; 90MG	
Application:	NDA 204441/000	**Sponsor:**	OTSUKA PHARM
Org. Code:	110		2440 RESEARCH BLVD
Priority:			ROCKVILLE, MD 20850
Stamp Date:	01-MAR-2013	**Brand Name:**	TOLVAPTAN
PDUFA Date:	01-SEP-2013	**Estab. Name:**	
Action Goal:		**Generic Name:**	TOLVAPTAN
District Goal:		**Product Number; Dosage Form; Ingredient; Strengths**	
		001; TABLET; TOLVAPTAN; 15MG 002; TABLET; TOLVAPTAN; 30MG 003; TABLET; TOLVAPTAN; 45MG 004; TABLET; TOLVAPTAN; 60MG 005; TABLET; TOLVAPTAN; 90MG	

FDA Contacts:	Z. DONG	Prod Qual Reviewer	3017963885
	T. BOUIE	Product Quality PM	3017961649
	A. PARK	Regulatory Project Mgr	3017961129
	K. SRINIVASACHAR	Team Leader	3017961760

Overall Recommendation: PENDING on 20-MAR-2013 by EES_PROD

Establishment: (b) (4)

DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE PACKAGER		
Profile:	TABLETS, PROMPT RELEASE	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	28-NOV-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	POTENTIAL OAI
Last Milestone:	ASSIGNED INSPECTION TO IB		
Milestone Date:	03-MAY-2013		

Establishment:	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	02-DEC-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** 9612794 **FEI:** 3002809299 OTSUKA PHARMACEUTICAL CO LTD 463-10 KAGASUNO TOKUSHIMA, , JAPAN		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
Profile:	POWDERS (INCLUDES ORAL (b) (4))	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	19-MAR-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:**	**FEI:** 3003656524	
	OTSUKA PHARMACEUTICAL CO. LTD. - ITANO FACTORY 13 MINAMI, SHISHITOKI, MATSUTANI ITANO, TOKUSHIMA, , JAPAN 7790195		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
Profile:	TABLETS, PROMPT RELEASE	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	17-DEC-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** 9613571	**FEI:** 3003808559	
	OTSUKA PHARMACEUTICAL CO., LTD. 5006-5 AZA HIGASHIYAMA OMAGARI YOSHINOGARI-CHO KANZAKI-GUN, SAGA, JAPAN		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	30-NOV-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** 9611255	**FEI:** 3002807834	
	OTSUKA PHARMACEUTICAL CO., LTD. - SECOND TOKUSHIMA FACTORY 224-18 HIRAISHI, EBISUNO KAWAUCHI, TOKUSHIMA, , JAPAN		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	14-FEB-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE PACKAGER		
Profile:	TABLETS, PROMPT RELEASE	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	02-DEC-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE PACKAGER		
Profile:	TABLETS, PROMPT RELEASE	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	30-NOV-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

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

/s/

ZEDONG DONG
07/11/2013

HASMUKH B PATEL
07/11/2013

BIOPHARMACEUTICS INITIAL ASSESSMENT and FILING REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 204-441	**Reviewer**: Akm Khairuzzaman, Ph.D.	
Submission Date:	03/01/2013		
Division:	Division of Cardiorenal Products	**Team Leader:** Angelica Dorantes, PhD	
Sponsor:	Otsuka Pharmaceutical Development and Commercialization, Inc. I University Square Drive, Suite 500, Princeton, NJ 08540		
Trade Name:	(b) (4)	**Date Assigned:**	03/05/2013
Established Name:	Tolvaptan	**Date of Review:**	06/19/2013
Indication:	Indicated to slow progressive kidney disease in adults with autosomal dominant polycystic kidney disease (ADPKD)	**Type of Submission:** Original NDA 505(b)1, addition of new strengths to the approved product with new indication.	
Formulation/strengths	Tablets, 45 mg & 90 mg		
Route of Administration	Oral		

FILING EXECUTING SUMMARY:

The immediate release formulation of Samsca® (tolvaptan) 15-, 30-, and 60-mg tablets was approved on 19 May 2009 in NDA 22-275 for the treatment of hyponatremia, developed by the same company. This NDA is just for additional strengths: 45 mg and 90 mg tablets with the same formulation (quantitatively proportional). (b) (4) Therefore, no additional risks were found from biopharmaceutics point of view. A bioequivalence trial was conducted between the approved 30-mg tablets and the proposed commercial 90-mg tablets. The applicant has asked for a biowaver for the lower strength 45 mg tablet, the bio-waver can be granted. Dissolution method has not been changed from the one submitted under the original approved NDA. At this stage there is no biopharmaceutics related deficiency for this application and the application is recommended for approval from biopharmaceutics point of view.

RECOMMENDATION

The NDA is recommended for APPROVAL from the Biopharmaceutics perspective.

Akm Khairuzzaman, Ph.D.
Biopharmaceutics Reviewer, ONDQA

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader, ONDQA

BIOPHARMACEUTICS ASSESSMENT – REVIEWER NOTES

1. The Reviewer's analyses on the formulation development:

Evaluation: Acceptable.

This NDA is just for an extension of new strengths (two additional strengths to support new indication) of an approved product under the NDA-22-275 (Samsca® (tolvaptan) 15-, 30-, 60-mg tablets). (b) (4) . The formulation composition of these two new additional strengths and the originally approved product are shown below in tables:

Table. 1. Quantitative Composition of Proposed Commercial Tolvaptan 45- and 90-mg Tablets

Component	Quality Standard	Function	New Strengths			
			45-mg		90-mg	
			mg	% w/w	mg	% w/w
Tolvaptan	In-house	Active ingredient	45.0	37.04	90.0	37.04
(b) (4)						(b) (4)
Lactose monohydrate[c]	NF					
Corn starch	NF					
Microcrystalline cellulose	NF					
Hydroxypropyl cellulose[d]	NF					
Low-substituted hydroxypropyl cellulose	NF					
FD&C blue No.2 aluminum lake	21 CFR 82.51, 82.102					
Magnesium stearate[e]	NF					
(b) (4)						
Total tablet weight			121.5		243.0	
Tablet description			Blue, square, shallow-convex, (b) (4) (b) tablet, debossed with "OTSUKA" and "45" on one side		Blue, pentagon, shallow-convex, (b) (4) tablet, debossed with "OTSUKA" and "90" on one side	

Table. 2. Formulation composition of the approved product, Samsca® (tolvaptan).

Component	Quality Standard	Function	Approved Strengths (Samsca Tablets)					
			15-mg		30-mg		60-mg	
			mg	% w/w	mg	% w/w	mg	% w/w
Tolvaptan	Non compendial	Active ingredient	15.000	17.24	30.000	17.24	60.000	37.04
(b) (4)								(b) (4)
Lactose monohydrate[c]	NF							
Corn starch	NF							
Microcrystalline cellulose	NF							
Hydroxypropyl cellulose[d]	NF							
Low-substituted hydroxypropyl cellulose	NF							
FD&C blue No.2 aluminum lake	21 CFR 82.51, 82.102							
Magnesium stearate[e]	NF							
(b) (4)								
Total tablet weight			87.000		174.000		162.000	
Tablet description			Blue, triangular, shallow-convex, (b) (4) tablet, debossed with "OTSUKA" and "15" on one side		Blue, round, shallow-convex, (b) (4) tablet, debossed with "OTSUKA" and "30" on one side		Blue, modified rectangular, shallow-convex, (b) (4) tablet, debossed with "OTSUKA" and "60" on one side	

As shown in the above tables, the formulation composition of the two new proposed strengths are quantitatively proportional with that of the highest strength of the approved product, 60 mg tablets. Therefore, this reviewer believes that no further review on the formulation is necessary.

2. **The Reviewer's analyses on the manufacturing process development using dissolution test:** No additional process development was done.
   Evaluation: Acceptable.

3. **The Reviewer's analyses on dissolution method:**

   Evaluation: Acceptable.

   The dissolution method development was done under the approved NDA- 22-275 and the same method will be used for these two new additional strengths. The developed dissolution method is as follows:

   Apparatus: USP apparatus 2 (paddle)
   Dissolution medium: 0.22% SLS, 900mL
   Paddle speed: 50rpm
   SLS = sodium lauryl sulfate

   Since the applicant is using the same approved method, therefore no further review is necessary.

4. **The Reviewer's analyses on the data supporting the dissolution limit:**

   Evaluation: Acceptable.

   Dissolution limit proposed in the specification:

45 mg Tablets	90 mg Tablets	Approved product (15, 30, and 60-mg tablets)
Q = (b) (4) % in 30 minutes	Q = (b) (4)	Q = (b) (4) % in 30 minutes[a]

[a] tightened from Q = (b) (4) at FDA's request, dated July 8, 2008

The Applicant used the dissolution test results for 3 batches of 45- and 90-mg (used for the primary studies) for setting up the dissolution limit. These raw data are provided below:

Tab.3. Dissolution of Tolvaptan 45-mg Tablets

Lot No.	Sampling Time (min)	Percent Tolvaptan Dissolved														
		Vessel 1	2	3	4	5	6	7	8	9	10	11	12	Max	Min	Mean
11F82A045A	10	(b) (4)													(b) (4)	62.4
	20															81.6
	30															87.3
	45															90.2
	60															91.6
11F82A045B	10															62.3
	20															83.2
	30															89.2
	45															91.8
	60															92.7
11F82A045C	10															63.3
	20															83.8
	30															88.8
	45															90.9
	60															91.7

Tab. 4.. Dissolution of Tolvaptan 90-mg Tablets

Lot No.	Sampling Time (min)	Percent Tolvaptan Dissolved														
		Vessel 1	2	3	4	5	6	7	8	9	10	11	12	Max	Min	Mean
11F82A090A	10	[redacted]													(b) (4)	60.5
	20															78.5
	30															84.0
	45															87.5
	60															89.7
11F82A090B	10															61.7
	20															81.2
	30															86.7
	45															89.9
	60															91.2
11F82A090C	10															57.9
	20															78.1
	30															84.6
	45															88.3
	60															90.0

Note 1: Bold presents the dissolution less than [redacted] (b) (4)
Note 2: Twelve tablets were tested in order to set the specification.

Additionally, the applicant has also used the following stability data to set up the dissolution limit.

Table. 5. Dissolution of 90-mg Tablets in [redacted] (b) (4) Blister Under Long-term Condition

Storage Condition		25°C/60% RH														
Lot No.		11F82A090A					11F82A090B					11F82A090C				
Time (Months)		0	3	6	9	12	0	3	6	9	12	0	3	6	9	12
30 min	max	[redacted]														(b) (4)
	min															
	mean	87	91	92	89	91	86	93	89	89	91	87	90	89	90	90
45 min	max	[redacted]														(b) (4)
	min															
	mean	90	94	95	92	94	90	95	93	93	94	91	93	92	92	92
60 min	max	[redacted]														(b) (4)
	min															
	mean	90	95	96	94	94	91	95	94	93	94	93	94	93	92	92

Note 1: Bold presents the dissolution less than [redacted] (b) (4)
Note 2: Twelve tablets were tested in order to set the specification.

Table. 6. Dissolution of 90-mg Tablets in [redacted] (b) (4) Blister Under Accelerated Condition

Storage Condition			40°C/75% RH											
Lot No.			11F82A090A				11F82A090B				11F82A090C			
Time (Months)			0	1	3	6	0	1	3	6	0	1	3	6
Dissolution (%) (n = 12)	30 min	max	[redacted]											(b) (4)
		min												
		mean	87	87	88	85	86	89	89	89	87	89	85	85
	45 min	max	[redacted]											(b) (4)
		min												
		mean	90	92	94	91	90	92	92	92	91	92	91	91
	60 min	max	[redacted]											(b) (4)
		min												
		mean	90	94	96	93	91	93	93	93	93	93	92	93

Note 1: Bold presents the dissolution less than [redacted] (b) (4)
Note 2: Twelve tablets were tested in order to set the specification.

It is to be noted here that Batch # 11F82A090A was used for bioequivalence study. As provided in the above table, the mean dissolution for 3 primary batches of 90-mg tablets (including the bioequivalence batch) was 84.0%−86.7% (individual: min [redacted] (b) (4) %, max [redacted] (b) (4) %) at 30 minutes. The 90-mg tablets showed a lower dissolution at 30 minutes compared to that of other strengths of tablets. This reviewer believes that this is due to a larger tablet size and higher content of tolvaptan drug substance. However, this reviewer noted that the mean dissolution for 3 primary batches of 90-mg tablets at 45 min was 87.5% – 89.3%. Although it is likely that the applicant [redacted] (b) (4) but the reviewer believes that the dissolution limit could be tighten to Q= [redacted] (b) (4) % in 45 min for the 90 mg tablets.

Question to the Applicant: *The agency does not agree with the dissolution limit proposed for the higher strength tablet, 90 mg. Based on the data provided in the application package (batch release and stability data), the agency recommends to tighten the dissolution limit of the 90 mg tablet to Q= (b) (4)% in 45 minutes.*

Applicant's Response: *On June 18th, the applicant has responded to this deficiency. The applicant agreed to tighten the dissolution limit of the 90-mg tablets to Q= (b) (4)% in 45 minutes from Q= (b) (4). Batch analysis data was reassessed by the applicant under the revised dissolution limit and were found to be acceptable within (b) (4). Applicant also updated the stability data (long-term and accelerated conditions) to include the dissolution data at 45 minutes. These updates are provided in this amendment.* (b) (4)

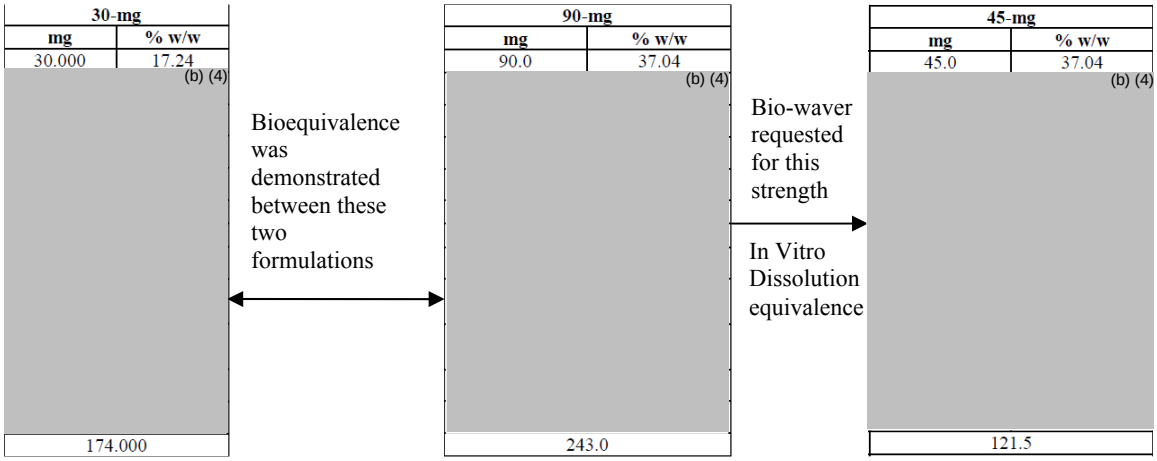
Reviewer's Final Evaluation: *Acceptable.*

5. The Reviewer's analyses on the data supporting the biowaiver request for the lower strength (45 mg):

Evaluation: Acceptable.

Based on the information provided under the formulation composition (see Table 7 in this review) the low strength (45 mg tablet) is exactly proportional (wt/wt) to the highest strength (90 mg) used for the BE study. Therefore, as per the ***Guidance for Industry: Bioavailability and Bioequivalence Study for Orally Administered Drug Products – General Consideration: "****When the drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to the strength on which BA or BE testing has been conducted, an in vivo BE demonstration of one or more lower strengths can be waived based on dissolution tests and an in vivo study on the highest strength",* Applicant's request for bio-waver can be granted for the lower strength.

Table. 7. Comparative formulation composition of the approved strength vs. new strengths.



Bioequivalence trial was conducted between approved 30-mg and proposed commercial 90-mg tablets with a dosing group of 3 x 30 mg vs 1 x 90 mg (Trial 156-11-295). As a result, a single 90-mg tablet was bioequivalent to 3 × 30-mg tablets. Geometric mean ratios (90% CIs) were 1.00 (0.93, 1.08) and 0.98 (0.92, 1.04) for C_{max} and AUC_{inf}, respectively. This is subject to be reviewed by the Office of Clinical Pharmacology. The Applicant has provided the following dissolution data in support of bio-waver.

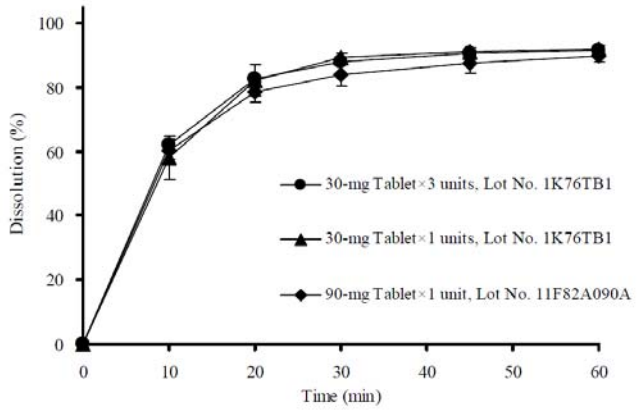


Fig.1. Dissolution Profiles of Approved 30-mg Tablets and Proposed Commercial 90-mg Tablets

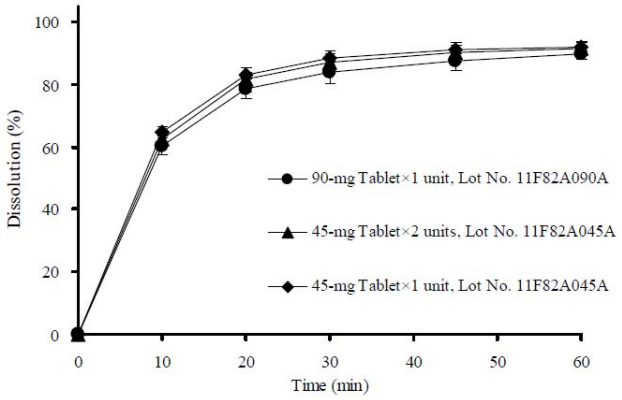


Fig.2. Dissolution Profiles of Proposed Tolvaptan 90-and 45-mg Tablets

6. Reviewer's evaluation on disintegration stability during product shelf life :

Evaluation: Acceptable.

See data provided in Table 5 & 6 in this review.

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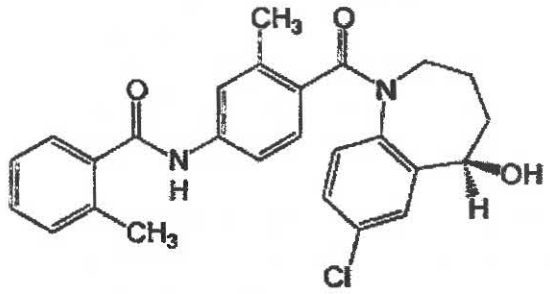
/s/

AKM KHAIRUZZAMAN
07/02/2013
Recommended for approval from biopharmaceutics point of view.

ANGELICA DORANTES
07/10/2013

Initial Quality Assessment
Branch I

OND Division:	Division of Cardiovascular and Renal Products
NDA:	204441
Applicant:	Otsuka Pharmaceutical Co.
Letter Date:	Nov 15, 2012
Stamp Date:	Nov 15, 2012
PDUFA Date:	TBD
Tradename:	TBD
Established Name:	Tolvaptan
Dosage Form:	Tablets, 15 mg, 30 mg, 45 mg, 60 mg and 90 mg
Route of Administration:	Oral
Indication:	To slow progressive kidney disease in adults with autosomal dominant polycystic kidney disease (ADPKD)
Assessed by:	Kasturi Srinivasachar
ONDQA Fileability:	Yes



and enantiomer

Summary

This is a 505(b)(1) NDA for a new indication for tolvaptan. Tolvaptan was previously approved under the tradename Samsca for the treatment of hyponatremia (NDA 22275). Tolvaptan was granted orphan drug and fast track designation for ADPKD. This is a partial or "rolling" submission containing complete CMC and non-clinical sections as allowed under the fast track program. The rest of the sections is expected to be submitted by Dec. 31, 2012 when the official clock will start. The only CMC difference between this NDA and the previously approved NDA, 22275, is the addition of 2 new strengths of tolvaptan, 45 and 90 mg. The strengths approved in NDA 22275, 15, 30 and 60 mg are also intended to be marketed in NDA 204441, giving a total of 5 immediate release strengths for the ADPKD indication.

A pre-NDA CMC meeting was held with the firm on July 6, 2012 to discuss issues related to dissolution, shelf-life, a two strength blister combination card and submission strategy. Otsuka inquired if the two new strengths could be submitted in a supplement to the existing NDA 22275 and after approval, the entire CMC section in NDA 22275 cross referenced to the NDA for ADPKD. They were told that the new strengths could not be included in NDA 22275 since these were not studied clinically for hyponatremia.

Drug Substance

Tolvaptan is a synthetic racemic drug substance with one chiral center. It is a white crystalline powder with melting point ~ 224° C. Tolvaptan is insoluble in water and its solubility is pH independent in the range 2-12. Only one morphic form of the drug substance has been reported. All CMC information for the drug substance is cross-referenced to NDA 22275.

Drug Product

The two new strengths, 45mg and 90 mg, have the same excipients as the currently approved strengths in NDA 22275. They are also quantitatively proportional to the 60 mg tablets. The manufacturing process is identical to that previously described and starts with (b) (4) A bioequivalence study was carried out between the approved 30 mg and proposed 90 mg tablets and it is claimed that bioequivalence was established. The Applicant has requested a biowaiver for the 45 mg strength based on quantitative proportionality to the 90 mg strength and comparison of dissolution profiles. (b) (4) A new 2 strength blister combination card for commercial tablets is proposed to enhance patient compliance. The combination blister cards will facilitate the administration of a daily high dose/low dose regimen e.g. 45 mg/15 mg, 60 mg/30 mg, or 90mg /30 mg tablets. The packaging materials for the combination blister card are stated to be the same as those used in the stability studies.

The specifications for the 45 mg and 90 mg tablets are the same as approved in NDA 22275 for the 15, 30 and 60 mg tablets with the exception of description and the dissolution acceptance criterion for the 90 mg tablet which was changed from Q= (b) (4)% in 30 min to Q= (b) (4). This difference has been justified by the slower dissolution of the 90 mg tablets at 30 min as compared to the other strengths, presumably because of the larger tablet size and higher drug substance content.

Stability studies on the new strengths have been carried out on production scale batches packaged in (b) (4) blisters (b) (4). 12 months of long term and 6 months of accelerated data have been provided for 3 batches of each packaging configuration. In addition, stability studies were carried out in bulk tablet packaging. (b) (4) month shelf-life is proposed (b) (4)

APPEARS THIS WAY ON ORIGINAL

Critical Review Issues

Drug Substance

- Although it is acceptable to cross-reference a previously approved NDA if there are no changes to the drug substance, shouldn't the current specification and CoAs of representative batches be provided in this new NDA?

Drug Product

- The biowaiver request and the proposed dissolution specifications for the new strengths should be evaluated by the Biopharmaceutics reviewer.
- Has the manufacturing process in 3.2.P.3.3 been described in sufficient detail? In lieu of this, is there a Master Batch Record?
- Regarding the specification
  - Skip lot testing for microbial quality is proposed. Is this acceptable?
- Regarding Stability
  - Can a (b) (4) month shelf-life for the 45 mg and 90 mg tablets be granted based on 12 months' long term and 6 months' accelerated data and the justification provided in 3.2.P.8.1? It should be noted that the 60 mg strength, although approved in NDA 22275, was never marketed; (b) (4)
- There is not much information regarding the proposed combination blister card. Has Otsuka committed to place the first three marketed batches of this configuration on stability as advised at the pre-NDA meeting?

Labeling

- No labeling has been submitted at this time but will presumably be part of the main submission. Both the package insert and carton and container labels will need to be reviewed for relevant CMC information when submitted.

Comments and Recommendations

The application is fileable -- see attached Filing Check List. Facilities have been entered into EES and the overall recommendation is currently "Pending"; the reviewer should confirm the completeness and accuracy of the entries. A categorical exclusion from environmental assessment has been requested. A Methods Validation request is not deemed necessary for the drug substance or drug product since the same analytical methods are used as in approved NDA 22275. This does not preclude the reviewer from identifying analytical procedures for validation later in the review timeframe based on specific concerns. A single CMC reviewer is recommended since the there is no drug substance section to review and the drug product section consists of just 2 additional strengths manufactured using the same process as the previously approved strengths.

Kasturi Srinivasachar — Dec. 11, 2012
Pharmaceutical Assessment Lead — Date

Hasmukh Patel — Dec. 11, 2012
Branch Chief — Date

PRODUCT QUALITY -- CMC and BIOPHARMACEUTICS
FILING REVIEW FOR NDA

NDA Number:	**NDA Type: 9**	**Established/Proper Name:**
204441	**Original NDA, N-000**	**Tolvaptan/TBD**
Applicant:	**Letter Date: Nov 15, 2012**	
Otsuka Pharmaceuticals	**Stamp Date: Nov 15, 2012**	**PDUFA Goal: TBD depending on Priority or Standard Review**

CMC Reviewer: Zedong Dong

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

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

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

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		

10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

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

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	X		Cross reference to NDA 22275
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Cross reference to NDA 22275
14.	Does the section contain information regarding the characterization of the DS?	X		Cross reference to NDA 22275
15.	Does the section contain controls for the DS?	X		Cross reference to NDA 22275
16.	Has stability data and analysis been provided for the drug substance?	X		Cross reference to NDA 22275
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

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

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			NA

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		See section 1.4.1 for tabular listing of packaging DMFs

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?		X	Rolling submission, labeling expected with main submission
33.	Have the immediate container and carton labels been provided?		X	Rolling submission, labeling expected with main submission

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

37.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		X	

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/s/

KASTURI SRINIVASACHAR
12/11/2012

HASMUKH B PATEL
12/11/2012