CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205208Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

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

DATE: October 4, 2013

TO: File

THROUGH: Ramesh K. Sood, Ph.D., Acting Division Director, ONDQA

FROM: Mohan K. Sapru, Ph.D., Senior CMC Reviewer

SUBJECT: Final CMC Approval Recommendation for NDA 205208 (Desvenlafaxine Extended-Release Tablets)

Background: The applicant, Teva Pharmaceuticals Ltd., has sought U.S. marketing approval for desvenlafaxine extended-release tablets under the provisions of Section 505(b)(2) of the Federal Food and Cosmetic Act and 21 CFR §314.54. Based on the Chemistry, Manufacturing and Controls (CMC) review for this NDA (refer to Quality Review by Dr. Mohan Sapru, dated 9/30/2013), there were no pending CMC deficiencies. However, from the CMC perspective, the NDA 205208 could not be recommended for approval because the Office of Compliance had not issued an overall 'acceptable' recommendation for the relevant manufacturing and testing facilities.

Update: Based on the updated Establishment Evaluation Request Summary, dated October 3, 2013, the Office of Compliance has revised the assessment of the facilities, and has made an overall "acceptable" recommendation for all the listed manufacturing and testing facilities (refer to Establishment Evaluation Summary at the end of this memo).

Conclusion: In view of the overall "acceptable" recommendation by the Office of Compliance for all the listed manufacturing and testing facilities, from the CMC perspective, the new drug application (NDA 205208) for desvenlafaxine extended-release tablets (50 mg and 100 mg) is recommended for approval.

Note: Establishment Evaluation Summary is on the next page.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 205208/000	**Sponsor:**	TEVA PHARMS
Org. Code:	130		425 PRIVET RD
Priority:	5		HORSHAM, PA 19044
Stamp Date:	13-DEC-2012	**Brand Name:**	DESVENLAFAXINE FUMARATE EXTENDED RELEASE
PDUFA Date:	13-OCT-2013	**Estab. Name:**	
Action Goal:		**Generic Name:**	DESVENLAFAXINE FUMARATE EXTENDED RELEASE
District Goal:	14-AUG-2013	**Product Number; Dosage Form; Ingredient; Strengths**	
		001; TABLET, EXTENDED RELEASE; DESVENLAFAXINE FUMARATE; 50MG 002; TABLET, EXTENDED RELEASE; DESVENLAFAXINE FUMARATE; 100MG	

FDA Contacts:	M. SAPRU	Prod Qual Reviewer	3017961718
	T. BOUIE	Product Quality PM	3017961649
	K. ANSAH	Regulatory Project Mgr	3017964158
	C. TELE	Team Leader	3017961762

Overall Recommendation:	ACCEPTABLE	(b) (4)	by J. WILLIAMS	()	3017964196
	PENDING	on 17-AUG-2013	by EES_PROD		
	PENDING	on 17-AUG-2013	by EES_PROD		
	ACCEPTABLE	(b) (4)	by R. SAFAAI-JAZI	()	3017964463
	PENDING	on 31-JAN-2013	by EES_PROD		
	PENDING	on 31-JAN-2013	by EES_PROD		
	PENDING	on 31-JAN-2013	by EES_PROD		

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/s/

MOHAN K SAPRU
10/04/2013

RAMESH K SOOD
10/04/2013

NDA 205208 (Desvenlafaxine Fumarate Extended-Release Tablets (50 mg and 100 mg)

Teva Pharmaceuticals Limited

Mohan K. Sapru, Ph.D.

Office of New Drug Quality Assessment
Division I/Branch I
Reviewed for the Division of Psychiatry Products, HFD-130.

Table of Contents

Chemistry Review Data Sheet

1. NDA: 205208

2. REVIEW #: 1

3. REVIEW COMPLETION DATE: 02-September-2013

4. REVIEWER: Mohan K. Sapru, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	N/A

6. SUBMISSION(S) REVIEWED:

Submission (s) Reviewed	Document Date
Original Submission	13-December-2012
SN-0005	30-July-2013

7. NAME & ADDRESS OF APPLICANT:

Name and Address: Teva Pharmaceuticals USA
425 Privet Road, Horsham, PA 19044

Telephone: 215-591-8702

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None

b) Non-Proprietary Name (USAN): Desvenlafaxine (b) (4) Extended-Release Tablets

c) Code Name/ # (ONDQA only): N/A

d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 2
- Submission Priority: S

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: The Application was Submitted under Section 505(b)(2) of the Federal Food Drug and Cosmetic Act and 21 CFR §314.54

10. PHARMACOL. CATEGORY/INDICATION: A Serotonin-Norepinephrine Reuptake Inhibitor (SNRI) for the Treatment of Major Depressive Disorder (MDD)

11. DOSAGE FORM: Extended-Release Tablets

12. STRENGTH/POTENCY: Equivalent to 50 mg and 100 mg Desvenlafaxine

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, MOLECULAR FORMULA, MOLECULAR MASS, STRUCTURAL FORMULA:

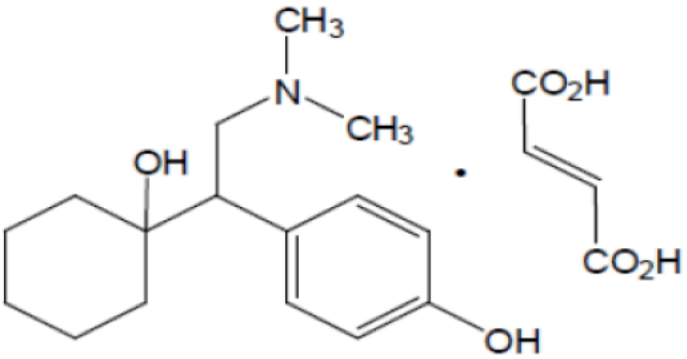
Chemical Name: 4-[2-(dimethyl amino)-1-(1-hydroxycyclohexyl) ethyl] phenol fumarate

Molecular Formula: $C_{20}H_{29}NO_6$

Molecular Mass: 379.45

CAS No.: 130198-08-2

Structure:



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17. RELATED/SUPPORTING DOCUMENTS:

A. DMF(s):

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED
26379	II	Teva Pharmaceuticals Industries Ltd	O-Desmethyl Venlafaxine Drug Substance	1	Adequate	30-Aug-2013
SN-0005		Teva Pharmaceuticals Industries Ltd	O-Desmethyl Venlafaxine Drug Substance	1	Adequate	01-Sept-2013

[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	113629	Treatment of major depressive disorder.

18. STATUS:

ONDQA:

CONSULTS/ CMC-RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	PENDING	30-Sept-2013	
Methods Validation	Not requested. The methods are conventional and don't qualify for internal validation by the FDA laboratories.	02-Sept-2013	Mohan K. Sapru, Ph.D.
Environmental Assessment	Categorical Exclusion	02-Sept-2013	Mohan K. Sapru, Ph.D.
Biopharmaceutics	ACCEPTABLE	04-Sept-2013	Banu S. Zolinik, Ph.D.
Microbiology	N/A	N/A	N/A

The Executive Summary (NDA 205208)

I. Recommendations.

A. Recommendation and Conclusion on Approvability.

From the chemistry, manufacturing and controls (CMC) perspective, the new drug application (NDA 205208) for desvenlafaxine extended-release tablets (50 mg and 100 mg) is not recommended for approval at this stage because the Office of Compliance has not issued an overall 'acceptable' recommendation for all the relevant manufacturing and testing facilities. A follow up memorandum, which specifies the final CMC recommendation, will be submitted if the Office of Compliance issues a final recommendation for the relevant manufacturing and testing facilities.

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

Not applicable at this stage.

II. Summary of Chemistry Assessments.

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

Drug Substance: Desvenlafaxine is the major active metabolite of the antidepressant venlafaxine, and functions as a serotonin-norepinephrine reuptake inhibitor (SNRI). For CMC details regarding drug substance, the applicant has referred to Type II DMF #26379, which has been reviewed and found to be adequate (refer to DMF# 26379 review by Dr. Mohan Sapru, dated September 9, 2013). Briefly, desvenlafaxine fumarate exists in (b) (4) crystalline forms (b) (4), and as amorphous form. Teva's product is desvenlafaxine fumarate (b) (4) The DMF holder has adequately provided details of manufacturing process, including the strategy for control of impurity levels. Regarding drug substance specification, identification is appropriately carried out both by HPLC, and infrared spectroscopy. The acceptance limit for assay values (HPLC, 98.0-102% (b) (4)) is adequate. ICH Q3A-compliant acceptance limit of NMT 0.15% for specified individual impurities is acceptable. Levels of heavy metals, which are reflective of a variety of upstream operations and quality of materials used in the synthesis, are appropriately controlled at not-more-than (NMT) 0.002%. The acceptance limits for residual solvents have been appropriately

set in compliance with ICH Q3C limits. HPLC-based methods for determination of (b) (4) as well as gas chromatography (GC) assays for residual solvents have been adequately validated, as per ICH recommendations, for specificity, linearity, accuracy, method precision, ruggedness, and stability-indicating characteristics involving forced degradation. Furthermore, the stability data support DMF holder's proposed (b) (4) month retest period.

Drug Product: The proposed drug product consists of desvenlafaxine fumarate extended-release (ER) tablets for oral administration. The clinical formulation will be available in 50 mg and 100 mg tablet strengths. Desvenlafaxine (brand name: Pristiq®), also known as O-desmethylvenlafaxine, is an antidepressant of the serotonin-norepinephrine reuptake inhibitor class, which has been originally developed and marketed by Wyeth (now part of Pfizer). Unlike the innovator drug Pristiq®, which uses the salt form of desvenlafaxine i.e., desvenlafaxine succinate, the applicant has proposed to use desvenlafaxine fumarate in the clinical formulation. The inactive ingredients used in the formulation are commonly used excipients, and no interaction amongst these excipients has been reported. It is noted that all excipients in the unit dose are below the IIG limits for oral route of administration. A risk assessment of formulation has been conducted by the applicant by identifying and evaluating drug product critical quality attributes (assay, impurities, content uniformity, and dissolution). The manufacturing process includes (b) (4) main steps. Specifically, (b) (4) in-process tests (hardness and friability) have been identified as critical to product quality. Robustness of the process, influence of critical process parameters on dissolution and content uniformity have been verified in the pivotal size scale-up batches. In addition, a risk assessment of manufacturing process has been conducted by the applicant by identifying and evaluating drug product critical quality attributes (CQAs). Two of the in-process tests (hardness and friability) have been identified as critical to product quality. The proposed regulatory specification for desvenlafaxine E.R. tablets involves testing for description, appearance, dissolution, content uniformity, assay, impurities/degradation product, (b) (4) In addition, certificates of analysis for the excipients from excipient manufacturers have been provided, and are acceptable. The proposed acceptance limits for degradation impurities have been set as per recommendations in ICH Q3B (R2) and in view of comparison of the impurity profiles of Pristiq Tablets and the desvenlafaxine E.R. tablets. All the tested batches have complied with the relevant release specification at the time of testing and release for use. The levels of individual impurities are at (b) (4) % in the tested drug product batches (50 mg and 100 mg tablets). There are no impurities that are unique to the drug product. The container/closer system for desvenlafaxine fumarate extended-release tablets 50 mg and 100 mg consists of high density polyethylene (HDPE) bottles (60cc and 300cc) and complies with USP <661>and USP <671>requirements. The drug product is stable under long-term and accelerated conditions for periods of 18 months and 6 months, respectively. The updated

stability data supports an expiry period of 24 months for the drug product stored under the recommended room temperature storage conditions.

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

The proposed drug product, desvenlafaxine extended-release tablets (50 mg and 100 mg), is to be used for the treatment of major depressive disorder (MDD) in adults. The 50 mg tablets will be light pink, film-coated round shaped, debossed with "T" on one side and with "N1" on other side. The 100 mg tablets will be reddish orange, film-coated round shaped, debossed with 'T' on one side and with "N2" on other side. Desvenlafaxine extended-release tablets 50 mg and 100 mg tablets will be packaged in 60cc and 300cc HDPE bottles.

C. Basis for Approvability or Not-Approval Recommendation.

Based on the review of the original submission, several deficiencies were identified in the DMF # 26379 and NDA submissions, and communicated to the applicant via mid-cycler review deficiency letters. The deficiencies concerning DMF # 26379 have been satisfactorily addressed by the DMF holder. Specifically, based on Agency recommendation, the DMF holder has agreed to change the designation of starting materials. Furthermore, the identified NDA deficiencies concerning drug product specification and stability have been adequately addressed by the applicant. The applicant has committed to carry out stability studies on the first three commercial batches under both long-term storage conditions as well as accelerated storage conditions. The Biopharmaceutical aspects of this NDA have been reviewed and found adequate by the Biopharmaceutics review team (refer to the Biopharmaceutics review refer to Biopharmaceutics review by Dr. Banu S. Zolnik. Regarding labeling, since the use of the salt name is not a standard approved nomenclature, the CMC recommended that the word (b) (4) be omitted, and the label should read as 'Desvenlafaxine Extended-Release Tablets' and not (b) (4) as initially proposed by the applicant. This recommended change has been incorporated in the latest version of labeling. From the CMC perspective, there are no outstanding labeling-related issues. However, the Office of Compliance has not, as yet, issued an 'acceptable' recommendation for all the relevant manufacturing and testing facilities.

In conclusion, from CMC perspective, this new drug application (NDA 205208) will not be recommended for approval at this stage because the Office of Compliance has not issued an overall 'acceptable' recommendation for all the relevant manufacturing and testing facilities.

III. Administrative.

A. Reviewer's Signature

Mohan Sapru

B. Endorsement Block

Senior Review Chemist: Mohan K. Sapru, Ph.D.

Acting Branch Chief: Olen Stephen, Ph.D.

C. CC Block

Project Manager: Kofi Ansah

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/s/

MOHAN K SAPRU
09/30/2013

RAMESH K SOOD
09/30/2013

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	NDA 205-208
Submission Date	12/12/2012
Product name, generic name of the active	Desvenlafaxine Fumarate
Dosage form and strength	Extended Release Tablets, 50 mg & 100 mg base
Applicant	Teva Pharmaceutical USA
Clinical Division	Division of Psychiatry Products
Type of Submission	505 (b) (2)
Biopharmaceutics Reviewer	Banu S. Zolnik, PhD
Biopharmaceutics Team Leader (Acting)	Sandra Suarez Sharp, PhD

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS
A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING

	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?	X		The applicant submitted dissolution data with the following method. (b) (4), USP 1 at 100 rpm, 900 mL. In addition, the applicant provided dissolution data in pH (b) (4), 4.5 (b) (4) buffer conditions.
2.	Is the dissolution test part of the DP specifications?	X		1 hour: NMT (b) (4)%, 4 hour: (b) (4)%, 8 hour: (b) (4)%, 12 hour: (b) (4)% and 24 hour: NLT (b) (4)%
3.	Does the application contain the dissolution method development report?	X		However, the applicant did not provide dissolution data with varying method developmental parameters (*i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.*) to select the proposed dissolution method as the optimal test for their product
4.	Is there a validation package for the analytical method and dissolution methodology?	X		
5.	Does the application contain in vitro alcohol induced dose dumping studies?	X		Alcohol induced dose dumping studies are conducted in 0.1 N HCl and in the proposed dissolution method for 50 mg and 100 mg strengths

6.	Does the application include a biowaiver request?		X	The applicant is not requesting a biowaiver, because the applicant submitted BE studies on both strengths. BE studies will be reviewed by OCP.
7.	Is there information provided to support the biowaiver request?			N/A
8.	Does the application include an IVIVC model?		X	N/A
9.	Is information such as BCS classification mentioned, and supportive data provided?	X		The Applicant stated that Desvenlafaxine Fumarate can be considered BCS III drug and provided Caco-2 Permeability studies.
10.	Is information on mixing the product with foods or liquids included?		X	N/A
11.	Is there any in *vivo* BA or BE information in the submission?	X		The application contains three BE studies comparing Desvenlafaxine Fumarate ER Tablets Eq. to 100 mg to the RLD, Pristiq ER Eq. to 100 mg Tablets under fasting and fed conditions. In addition Desvenlafaxine Fumarate ER Tablets Eq. to 50 mg to Pristiq ER, Re. to 50 mg under fasting conditions. In addition this study included a fed arm to determine the food effect. OCP will review the BE studies.

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
12.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	X		
13.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.		X	N/A
14.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.		X	N/A
15.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X		Comments will be sent to the Applicant in the 74-day letter. The comments are outlined under the Recommendation section of this filing review.

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

BIOPHARMACEUTICS INITIAL ASSESSMENT

SUMMARY

This 505(b)(2) NDA application contains an approved active ingredient of a different salt. An approved product Pristiq® contains desvenlafaxine succinate whereas the applicant is seeking approval for Desvenlafaxine Fumarate ER tablets Eq. 50 mg and 100 mg. The Applicant is pursuing this 505(b)(2) application on the findings of safety and effectiveness of Pristiq® Extended-Release Tablets (NDA 21992, approved 29-FEB-08) for the treatment of MDD.

The dissolution information in this submission is included in the pharmaceutical development section. It should be noted however, that the firm adopted the FDA's OGD recommended dissolution method as the proposed dissolution method, and they did not investigate any other dissolution methods as part of their development. The next tables include the proposed dissolution method and acceptance criteria.

Proposed Dissolution method for Desvenlafaxine Fumarate ER Tablets				
USP Apparatus	**Rotation Speed**	**Medium Volume**	**Temp**	**Medium**
I (basket)	100 rpm	900 ml	37°C ± 0.5 °C	(b) (4)

Proposed Acceptance Criteria for Desvenlafaxine Fumarate ER tablets (% of the labeled amount dissolved)
1 hour: NMT (b) (4) %
4 hour: (b) (4) %
8 hour: (b) (4) %
12 hour: (b) (4) %
24 hour: NLT (b) (4) %

In addition, the firm submitted data on risk assessment of the formulation variables on the dissolution where they investigated the effect of extended release (b) (4) type and quantity, coating, lubricant quantity and other process parameters on dissolution. The firm submitted the following dissolution profiles:

1) Dissolution profile of the Teva's product for eq. 50 and 100 mg to Pristiq® (50 and 100 mg) in the proposed method.
2) Dissolution profile of the Teva's product for eq. 50 and 100 mg to Pristiq® (50 and 100 mg) in (b) (4) Acetate Buffer (pH 4.5), (b) (4)
3) Dissolution profile of the Teva's product for eq. 50 and 100 mg to Pristiq® (50 and 100 mg) in the proposed method with 0%, 5%, 10%, 20 % and 40% alcohol.
4) Dissolution profile of the Teva's product for eq. 50 and 100 mg to Pristiq® (50 and 100 mg) in 0.1 N HCl with 0%, 5%, 10%, 20 % and 40% alcohol.

The Biopharmaceutics review will be focused on **1)** the evaluation and acceptability of the proposed dissolution method and acceptance criteria, and **2)** the evaluation of the dissolution data included in the in vitro alcohol induced dose dumping study.

RECOMMENDATION:
From the ONDQA-Biopharmaceutics perspective, NDA 205208 for Desvenlafaxine Fumarate Tablets is fileable. The following comments should be conveyed to the Applicant in the 74-Day Letter.

Provide a copy of the dissolution method development report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:

Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (*i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.*) used to select the proposed dissolution method as the optimal test for your product. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable.

{See appended electronic signature page}
Banu S. Zolnik, PhD — 02/15/13
Biopharmaceutics Reviewer — Date
Office of New Drug Quality Assessment

{See appended electronic signature page}
Sandra Suarez Sharp, Ph.D. — 02/15/13
Biopharmaceutics Team Leader (Acting) — Date

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

Office of New Drug Quality Assessment

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/s/

BANU S ZOLNIK
02/15/2013

SANDRA SUAREZ
02/15/2013

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I (Branch I)

Initial Quality Assessment
NDA: 205208

OND Division:	Division of Psychiatry Products
Applicant:	Teva Pharmaceuticals USA
NDA Filing Category:	505(b)(2)
Letter Date:	12-DEC-12
Stamp Date:	13-DEC-12
PDUFA Date:	12-OCT-13
Proposed Trade Name:	Tradename has not been proposed
Established Name:	Desvenlafaxine Fumarate Extended-Release Tablets
Dosage Form:	Tablet (Extended-Release)
Strengths:	Equivalent to 50 mg and 100 mg Desvenlafaxine
Route of Administration:	Oral
Indication:	Treatment of major depressive disorder [MDD]
Assessor:	Chhagan G. Tele, Ph.D.
ONDQA Fileability:	Yes

Background

Desvenlafaxine fumarate extended-release tablets for oral administration contain desvenlafaxine fumarate, a selective inhibitor of the human serotonin and norepinephrine reuptake inhibitor (SNRI) for the treatment of MDD. Desvenlafaxine (O-desmethylvenlafaxine) is the major active metabolite of the antidepressant venlafaxine, a medication used to treat major depressive, generalized anxiety, social anxiety, and panic disorders. The applicant pursued this 505(b)(2) application on the findings of safety and effectiveness of Pristiq® Extended-Release Tablets (desvenlafaxine succinate salt Eq. to 50 mg & 100 mg base) manufactured by Wyeth Pharmaceuticals Inc. (NDA 21992, approved 29-FEB-08) for the treatment of MDD. The route of administration, dosage form, and strengths of Desvenlafaxine Fumarate ER Tablets 50 mg and 100 mg of Teva Pharmaceuticals are same as that of the Reference Listed Drug, Pristiq® (desvenlafaxine succinate) ER Tablets 50 mg and 100 mg. The application contains a full report of three (3) *in vivo* bioequivalence studies. These studies compared Desvenlafaxine Fumarate Extended-Release Tablets, Eq. to 100 mg base to the reference listed drug, Pristiq® Extended-Release Tablets, Eq. to 100 mg base under both fasting and post-prandial conditions. In addition, Desvenlafaxine Fumarate Extended-Release Tablets, Eq. to 50 mg base was compared to Pristiq® Extended-Release Tablets, Eq. to 50 mg base under fasting conditions. This study included a post-prandial arm to compare Desvenlafaxine Fumarate Extended-Release Tablets, Eq. to 50 mg base to the fasted study in order to determine the food effect for their product. Electronic submission is provided for the CMC information for the review. The applicant provided Quality Overall Summary in the submission. The applicant had Pre-IND meetings (IND 113629, Type B, (b) (4)) with the clinical division to discuss CMC, biopharmaceutics, and clinical biopharmacetics issues. Minutes of these meetings can be found in DARRTS and should be read by the respective reviewers. No CMC specific meetings have been held with the sponsor; however the reviewers need to bridge any changes and agreements evolved from this meeting, amendments, and annual reports submitted during the drug development. Since Teva submitted a 505(b)(2) application for a new active ingredient of a currently approved drug, Pristiq®, this change in the active ingredient may be subject to the pediatric studies requirement. Accordingly, the applicant requested a full waiver of that requirement for the proposed product under the Federal Food, Drug, and Cosmetic Act, Section 505B. The labeling proposed for the Teva Pharmaceuticals USA drug product is the same as the labeling for the listed drug except for changes required because (1) the drugs are produced and distributed by different manufacturers, (2) differences in package configurations, (3) differences in the salt form of the active ingredient, including differences in the molecular weight and equivalency statements, (4) inactive ingredients are not identical, and (5) differences in the tablet descriptions.

Drug Substance

The drug substance, Desvenlafaxine Fumarate will be manufactured commercially by Teva API India Ltd. in Ghirongi Malanpur (Bhind, Madhya Pradesh, India). It is also noted that the future Desvenlafaxine Fumarate batches could be manufactured at (b) (4) Teva-Tech site, Ramat Hovav Emek Sara, Israel. Desvenlafaxine Fumarate information is cross-referenced to DMF #26379 [Holder: Teva Pharmaceuticals Industries Ltd. in Petah Tiqva, Israel] regarding chemistry, manufacture, control, reference standards, stability, and packaging. The applicant provided a LoA dated 19-SEP-12 to refer DMF #26379 for the drug substance CMC information. DMF #26379 will need to be found adequate to support NDA. In NDA submission, the applicant provided Desvenlafaxine Fumarate release specification, release data of the drug substance batches used in manufacture of drug product batches for NDA submission batches, and summary of the analytical method verification reports. Desvenlafaxine Fumarate is a white to off-white crystalline powder. The melting point of the Desvenlafaxine Fumarate is approximately 153° C. Desvenlafaxine Fumarate manufactured by Teva API India Ltd. is (b) (4) monohydrate. (b) (4)

Drug Product

Desvenlafaxine Fumarate extended release oral tablets will be available in 50 mg and 100 mg (equivalent to desvenlafaxine) tablet strengths (a generic version of Pristiq® Tablets 50 mg and 100 mg, listed as the RLD). The 50 mg tablets will be light pink, film coated round shaped, debossed with 'T' on one side and with "N1" on other side. The 100 mg tablets will be reddish orange, film coated round shaped, debossed with 'T' on one side and with "N2" on other side. They are supplied in 60cc and 300cc HDPE bottles of 14, 100, and 500 tablets with 1 g silica gel desiccant in each bottle.

The excipients used in Desvenlafaxine Fumarate ER tablets were selected based on what was used in the RLD including excipient compatibility studies, physico-chemical properties, dosage form requirements, pharmaceutical functionalities, safety, and Inactive Ingredient Guide (IIG) (b) (4). Moreover, all of the RLD excipients (excluding coating) were used in Teva's product. Inactive ingredients used for the 50 mg and 100 mg tablets are hypromellose (USP), microcrystalline cellulose (NF), (b) (4) talc (USP), magnesium stearate (NF) (b) (4) pink (50 mg tablets) and (b) (4) red (100 mg tablets). (b) (4) pink contains (50 mg tablets) inactive ingredients iron oxide red, iron oxide yellow, lecithin, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol-part hydrolyzed, talc, titanium dioxide, xanthan gum, and iron oxide black. (b) (4) red contains (100 mg tablets) inactive ingredients iron oxide red, iron oxide yellow, lecithin, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol-part hydrolyzed, talc, titanium dioxide, and xanthan gum. All excipients are commonly used in the solid dosage forms (no novel excipients). It is noted that all excipients in the unit dose are below the IIG limits for oral route of administration. None of the excipients are of human or animal origin.

The applicant provided calculations for maximum daily dose of elemental iron from inactive ingredient (iron oxide red and iron oxide yellow used in the formulation) that will be getting to the patients (2 doses/day of 50 mg desvenlafaxine tablets: (b) (4) and one dose/day of 100 mg desvenlafaxine tablet: (b) (4)). This amount is well within the FDA limit for elemental Iron of 5 mg/day [CFR 73.1200(c)]. The reviewer need to evaluate the calculations for maximum daily dose of elemental iron that will be getting to the patients.

The applicant provided pharmaceutical and manufacturing process development studies to achieve required scale up, dissolution profile, and content uniformity. The main steps of the manufacturing and packaging of Desvenlafaxine Fumarate ER Tablets are (b) (4) The assigned reviewer will need to review in detail

about these studies for the robust manufacturability of the drug product. The reviewer need to check if [redacted] desvenlafaxine is used in the commercial formulation.

A risk assessment of formulation was conducted by the applicant by identifying and evaluating drug product CQAs. Formulation variables used for determining drug product CQA (assay, impurities, content uniformity, and dissolution) are [redacted] grade and amount, [redacted] amount, talc amount, and magnesium stearate amount. The reviewer needs to evaluate the risk assessment data for the drug product CQAs.

Once the formulation was finalized based on small scale experiments, as described in the previous section, additional experiments were performed to examine the influence of unit operations on drug product CQAs. Most experiments were performed on a small scale and examined the influence of critical process parameters (CPP) and critical material attributes (CMA) on impacted DP CQAs based on initial risk assessment. Robustness of the process, influence of critical process parameters on dissolution and content uniformity (main impacted CQAs) were verified in the pivotal size scale-up batches.

A risk assessment of manufacturing process was conducted by the applicant by identifying and evaluating drug product CQAs. Manufacturing process used for determining drug product CQA (assay, impurities, content uniformity, and dissolution) are [redacted] The reviewer needs to evaluate the risk assessment data of manufacturing process for the drug product CQAs.

Manufacturing, processing, packaging, labeling and handling of Desvenlafaxine Fumarate E.R Tablets will take place at the manufacturing facility, Teva Pharmaceutical Industries Ltd. Jerusalem OSD Form Production Plant, Jerusalem, Israel. The in-process tests performed in tabletting are average weight, individual weight, thickness, hardness, diameter/dimensions, friability, and disintegration. The reviewer needs to evaluate these parameters to ensure the robustness of the manufacturing process.

The proposed regulatory specifications for desvenlafaxine ER tablets involve description, appearance, dissolution, content uniformity, assay, impurities/degradation product, [redacted] Validated analytical methods are provided for the determination of assay and impurities/degradation product, [redacted] and dissolution. The reviewer needs to evaluate the adequacy of the validation parameters.

[redacted]

The batch analyses of the NDA exhibit batches of drug product (50 mg and 100 mg strengths) are provided. The dissolution test method (HPLC) is performed in accordance with USP <711> using the USP Apparatus 1 (Basket) at 100 rpm to determine the amount of drug substance released. The adequacy of the dissolution method and specification limits will need to be determined in conjunction with the ONDQA Biopharmaceutics reviewer.

Exhibit batches of Desvenlafaxine Fumarate Extended-Release Tablets 50 mg and 100 mg are packed in HDPE bottles of 14's, 100's, 500's pack. 6 months Accelerated and 9 months long term stability data for 50 mg strength and 12 months long term stability data for 100 mg strength of Desvenlafaxine Fumarate Extended-Release Tablets are provided. The firm has committed to submit an update (within 4 months of NDA submission) for long-term and accelerated data for the commercial batches to support expiry date. In accordance with our policy, the assigned expiration dating period will be based on the extent and quality of the primary stability data provided. The applicant proposed a tentative 24 month expiry for the product based on the stability data.

The applicant provided comparability protocol (3.2.R Regional Information) for the: 1) use of an alternate source and additional site of manufacturing for drug substance, 2) alternate facilities for the testing of drug substance and drug product release/stability testing, 3) (b) (4) sampling and testing as a routine in-process test to Content Uniformity is required as part of release testing, 4) an additional packaging configuration which is outside the bracket of the currently approved packaging configurations, and 5) Teva proposes the use (b) (4) The reviewer need to evaluate comparability protocol for the minimum supportive information to be provided at the time of submission in support of quality of the drug substance and the drug product.

Critical Issues for Review

Drug Substance

- The NDA applicant references DMF #26379 [Teva Pharmaceuticals Industries Ltd. in Petah Tiqva, Israel] for information on Desvenlafaxine Fumarate. DMF #26379 will need to be evaluated and found acceptable to support this NDA.
- (b) (4)

Drug Product

(b) (4)

(b) (4)

Comments and Recommendation:

The NDA is fileable from a CMC perspective. The NDA does not appear to incorporate elements of QbD. (b) (4) The drug substance is manufactured under DMF #26379. DMF should be reviewed to support this NDA. Assignment of the NDA to a single reviewer is recommended. The dissolution part of the submission should be consulted to the ONDQA biopharm group. Biopharmceutics reviewer has been assigned yet.

A claim for categorical exclusion under 21 CFR §25.31(b) is provided in Module 1. In accordance with 21 CFR §25.31, Teva Pharmaceuticals USA requested a categorical exclusion [25.31(a)] from the requirement for an Environmental Assessment or Environmental Impact Statement based upon two facts indicating that the approval of the drug product will not increase the use of the active moiety and not toxic to organisms in the environment. In addition, Teva Pharmaceuticals USA certified that it will maintain compliance with all appropriate Federal, State, and Local environmental laws and regulations in the manufacture and distribution of Desvenlafaxine Fumarate Extended-Release Tablets, Eq. to 50 mg & 100 mg base.

The list of manufacturing, testing, and packaging sites for drug substance and drug product is provided to enter into EES. The ONDQA PM need to submit all testing, packaging, and manufacturing sites into EES. The reviewer will need to confirm that these sites are correct and that there are no additional sites that need to be entered.

PRODUCT QUALITY: CMC AND BIOPHARMACEUTICS
FILING REVIEW FOR NDA

NDA Number: 205208	**Applicant:** Teva Pharmaceuticals USA	**Stamp Date:** 12-DEC-12
Drug Name: Desvenlafexine Fumarate ER Tablets	**NDA Type:** Standard	**Filing:**

CMC Reviewer: Mohan Sapru, Ph. D.
Biopharmaceuticals Reviewer: not assigned yet

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		
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		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
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?	X		
23.	Have any biowaivers been requested?			Biopharmaceutics reviewer's input needed
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?		X	

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		

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. BIOPHARMACEUTICS				
	Parameter	**Yes**	**No**	**Comment**
34.	Does the application contain dissolution data?	X		
35.	Is the dissolution test part of the DP specifications?	X		
36.	Does the application contain the dissolution method development report?	X		
37.	Is there a validation package for the analytical method and dissolution methodology?	X		
38.	Does the application include a biowaiver request?			Biopharmaceutics reviewer need to review the information if provided in the application
39.	Does the application include a IVIVC model?			Biopharmaceutics reviewer need to review the information if provided in the application
40.	Is information such as BCS classification mentioned, and supportive data provided?		X	
41.	Is there any in *vivo* BA or BE information in the submission?			Biopharmaceutics reviewer's input needed

K. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
42.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	X		
43.	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
44.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Biopharmaceutics reviewer's input needed
45.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		X	

Chhagan Tele 18-DEC-12

Name of Pharmaceutical Assessment Lead or CMC Lead/CMC Reviewer Date
Division of Pre-Marketing Assessment #
Office of New Drug Quality Assessment

Ramesh Sood

Name of Branch Chief Date
Division of Pre-Marketing Assessment #
Office of New Drug Quality Assessment

APPEARS THIS WAY ON ORIGINAL

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

/s/

CHHAGAN G TELE
12/18/2012
IQA

RAMESH K SOOD
12/26/2012