CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205208Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 205208	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: None Established/Proper Name: : Desvenlafaxine (Fumarate) Extended-Release Dosage Form: Tablets Strengths: 50 mg and 100 mg		
Applicant: Teva Pharmaceuticals, USA		
Date of Receipt: December 13, 2012		
PDUFA Goal Date: October 13, 2013	Action Goal Date (if different): **10/11/2013**	
RPM: CDR Kofi B. Ansah		
Proposed Indication(s): Major Depression Disorder (MDD)		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 021997 - PRISTIQ Tablets Prescribing Information, manufactured by Wyeth (now owned by Pfizer)	FDA's previous finding of safety and effectiveness (e.g., pharmacokinetic data, or specific sections of labeling)

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Bioavailability and Bioequivalence studies comparing Teva's Desvenlafaxine ER to Pristiq

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
PRISTIQ (desvenlafaxine Succinate) Tablets	NDA 021992	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for the use of desvenalfaxine Fumarate (salt) as the active ingredient in their extended-release 50mg & 100mg tablets formulation as opposed to the desvenalfaxine Succinate (salt) in the innovator's (RLD) tablet formulation, i.e., Fumarate vs. Succinate.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☒ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all*

of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): ***1) NDA 204150 desvenlafaxine extended release tablets 50mg and 100mg from Alembic, 2) NDA 204683 desvenlafaxine extended release tablets 50mg and 100mg from Osmotica, and 3) RLD – NDA 021992, desvenlafaxine succinate extended release tablets 50mg and 100mg (base) from Wyeth (Pfizer).***

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 6673838 and 8269040

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the

NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

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

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

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): *6673838 and 8269040*
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): *02/26/13 (for both patent # 6673838 & patent # 8269040)*

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☒ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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

/s/

KOFI B ANSAH
10/10/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	**DESVENLAFAXINE extended-release tablets for oral use**
Applicant	Teva USA
Application/Supplement Number	NDA 205208
Type of Application	Original
Indication(s)	treatment of major depressive disorder (MDD)
Established Pharmacologic Class[1]	serotonin and norepinephrine reuptake inhibitor (SNRI)
Office/Division	ODE I/DPP
Division Project Manager	Kofi Ansah
Date FDA Received Application	December 13, 2012
Goal Date	October 13, 2013
Date PI Received by SEALD	October 2, 2013
SEALD Review Date	October 3, 2013
SEALD Labeling Reviewer	Elizabeth Donohoe
SEALD Division Director	Laurie Burke

PI = prescribing information

[1] The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item **(deficiency)**.
- **YES:** The PI **meets** the requirement for this item **(not a deficiency)**.
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

N/A 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

NO 4. White space must be present before each major heading in HL.

Comment: *White space is missing prior to the Product Title.*

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*****

Selected Requirements of Prescribing Information

• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment: *The name of the drug product should be in UPPER CASE.*

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

YES 12. All text must be **bolded**.

Comment:

YES 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

Selected Requirements of Prescribing Information

YES 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." in *italics* and centered immediately beneath the heading.

Comment:

YES 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

YES 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

YES 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

NO 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment: *Revision date is missing. This date should be in all "final agreed-upon PI" prior to SEALD review (see draft Labeling Review MAPP on the SEALD internal website). Also, the "revision date" currently at the end of the FPI should be removed; the only revision date in the PI should appear at the end of HL.*

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

NO 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: *The TOC lists "Medication Guide"; this should be deleted. Per LRT (page 11):Do not include FDA-approved patient labeling (e.g., Medication Guide or Patient Package Insert) as a subsection heading in the TOC.*

YES 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE

Selected Requirements of Prescribing Information

11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

NO 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "*[see Warnings and Precautions (5.2)]*".

Comment: *The preferred format is to italicize the entire cross-reference, including the outer brackets; all cross-references currently do not have italicized outer brackets.*

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

YES 42. All text is **bolded**.

Comment:

YES 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

YES 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

Selected Requirements of Prescribing Information

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

YES 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

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/s/

ELIZABETH A DONOHOE
10/03/2013

LAURIE B BURKE
10/03/2013

PeRC PREA Subcommittee Meeting Minutes
September 18, 2013

PeRC Members Attending:
Lynne Yao
Hari Cheryl Sachs
Karen Davis-Bruno (Did not review (b) (4) Desvanlafaxine)
Patricia Dinndorf
Tom Smith
Julia Pinto (Did not review (b) (4) Desvanlafaxine)
Ethan Hausman
Wiley Chambers
Lily Mulugeta
Daiva Shetty
Martha Nguyen
Dianne Murphy
Gregory Reaman
Jane Inglese
William Rodriguez
George Greeley
Coleen LoCicero
Robert "Skip" Nelson
Rachel Whitten
Maura O'Leary

Guests Attending:
Nichella Simms (PMHS)
Erica Radden (PMHS)
Courtney Suggs (OCP)
Donna Snyder (PMHS)
Linda Onaga (DAVP)
Brian Chow (OCP)
Jung Lee (DNCE)
Leslie Chinn (OCP)
Nikolay Nikolov (DPARP)
Karen Hull (DPARP)
L. Fossom (DPP)
Aliza Thompson (DCRP)
Glenn Mannhan (DCRP)
Kofi Ansah (DPP)
Donna Snyder (PMHS)
Amy Talor (PMHS)
Terri Crescenzi (OPT)
Lesley Furlong (DNCE)
Linda Hu (DNCE)
Gilbert Burckart (OCP)
Yodit Belew (OAP)
Gerald Tran (OCP)
Martin Nevit (DTOP)
Jade Pham (DNCE)
Sarah Connelly (DAVP)
Robert Yim (DPARP)
Jing Zhang (DPP)
Nancy Xu (DCRP)
Russell Fortney (DCRP)
Rawa Dwivedi (DCRP)
Jessica Boehmer (DHP)
GT Wharton (OPT)
Angela Men (OCP)

Agenda

10:40	NDA	(b) (4)
11:00	NDA	205208 Desvenlafaxine (fumarate) Partial Wavier/Deferral
11:20	NDA	(b) (4)
11:30	NDA	(b) (4)
	BLA	(b) (4)
	NDA	(b) (4)

(b) (4)

(b) (4)

Desvenlaxafine (fumarate) Partial Waiver/Deferral/Plan

- NDA 205208 seeks marketing approval for Desvenlafaxine Fumarate ER tablets for the treatment of major depressive disorder (MDD).
- The supplement was submitted on December 13, 2012 and has a PDUFA goal date of October 13, 2013.
- The product triggers PREA as a new active ingredient.
- A waiver is being requested for pediatric patients aged birth to six years because studies are impossible or highly impractical.
- *Division justification for waiver*: MDD is difficult to be diagnosed before age 7 and the prevalence of MDD is quite low in this age group. The necessary studies are impossible or highly impractical. In addition, medication treatment is not the first line treatment recommended for this sub-population due to the efficacy and safety concerns of SSRI/SNRIs.
- A multi-center, randomized, double blind, placebo-controlled study to evaluate the efficacy and safety of devenlafaxine in children and adolescents with MDD.
- The sponsor needs to conduct pediatric studies to assess the safety and effectiveness of desvenlafaxine as a treatment for major depressive disorder in children (7 to 11 years) and adolescents (12 to 17 years). These studies must be 4-8 weeks, placebo-controlled studies. Both children and adolescents will be equally presented in the samples, and there will be a reasonable distribution of both sexes in these age strata.

PeRC Recommendations:

- The PeRC agreed with the Division to grant a partial waiver in pediatric patients aged birth to 6 years because studies are impossible or highly impractical. This is consistent with other products approved to treat MDD.
- The PeRC agreed with the Division to grant a deferral for pediatric patients aged 7 to 17 years because Agency requested the innovator to conduct children and adolescent (7-17 years old) MDD studies to assess the safety and efficacy of desvenlafaxine in these population as a PREA requirement. These studies currently are ongoing. PeRC agreed with the Division's recommendation to defer children and adolescent MDD studies until the innovator completes their pediatric studies.

Additional PeRC Recommendation/s:

- The Division will modify the timelines to account for the studies already underway by Pristiq, the innovator product.

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/s/

GEORGE E GREELEY
10/01/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label Memorandum

Date:	September 24, 2013
Reviewer:	Loretta Holmes, BSN, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z. Chan, PharmD, BCPS Division of Medication Error Prevention and Analysis
Drug Name and Strengths:	Desvenlafaxine Extended-Release Tablets 50 mg and 100 mg
Application Type/Number:	NDA 205208
Applicant:	Teva Pharmaceuticals USA
OSE RCM #:	2013-200

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Contents

1 INTRODUCTION

This memorandum evaluates the revised container labels for Desvenlafaxine Extended-release Tablets submitted by the Applicant on September 20, 2013 (Appendix A) in response to recommendations provided via email on September 17, 2013 (Appendix B). The Division of Medication Error Prevention and Analysis (DMEPA) previously reviewed the following Desvenlafaxine Extended-release Tablets labels and labeling:

- Labels and labeling submitted on December 13, 2012 and February 6, 2013: Recommendations were provided in OSE Review 2013-200 dated August 2, 2013.
- Labels submitted on August 19, 2013: Recommendations were provided via an email sent to the Applicant on September 17, 2013.

2 METHODS AND MATERIALS REVIEWED

DMEPA evaluated the revised container labels submitted on September 20, 2013. We compared the revised labels against our recommendations sent via email on September 17, 20913 to assess whether the revised labels address our concerns from a medication error perspective.

3 CONCLUSIONS AND RECOMMENDATIONS

Our review of the revised container labels determined the Applicant has implemented all of our recommendations and we find the revisions acceptable. Therefore, we have no further recommendations at this time.

If you have further questions or need clarifications, please contact Louis Flowers, OSE Project Manager, at 301-796-3158.

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/s/

LORETTA HOLMES
09/24/2013

IRENE Z CHAN
09/25/2013

M E M O R A N D U M

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

DATE: September 12, 2013

TO: Mitchell Mathis, M.D., CAPT USPHS
Acting Director,
Division of Psychiatry Products
Office of New Drugs
Center for Drug Evaluation and Research

FROM: Jyoti B. Patel, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations
and
William H. Taylor, Ph.D.
Director,
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: **Review of EIR covering NDA 205208,** Desvenlafaxine Fumarate Extended-Release Tablets, sponsored by Teva Pharmaceuticals, USA

At the request of the Division of Psychiatry Products, the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted audits of the clinical and analytical portions for the following bioequivalence studies.

1. Study Number: 53711

Study Title: "A pivotal, open-label, single-center, randomized, single-dose, two-period, two-treatment, two-sequence crossover study to compare the bioequivalence of Desvenlafaxine Fumarate Extended-Release Tablets 100 mg to Pristiq® Extended-Release Tablets, 100 mg under fasted conditions"

2. Study Number: **53811**

Study Title: "A pivotal, open-label, single-center, randomized, single-dose, two-period, two-treatment, two-sequence crossover study to compare the bioequivalence of Desvenlafaxine Fumarate Extended-Release Tablets 100 mg to Pristiq® Extended-Release Tablets, 100 mg under fed conditions"

3. Study Number: **2012-2883**
Study Title: "A single-dose, comparative bioavailability study of one formulation of Desvenlafaxine Fumarate Extended Release Tablets, equivalent to 50 mg Desvenlafaxine and one formulation of Pristiq® Extended Release Tablets, 50 mg under fasting and fed conditions"

The primary objective of these studies was to evaluate bioequivalence under fasted and fed conditions between desvenlafaxine fumarate extended release tablets (test) of Teva Pharmaceuticals, USA and Pristiq® extended release tablets (reference) of Wyeth Pharmaceuticals Inc., USA.

During June 26–July 3, 2013, ORA investigator, Brian R. Cronenwett from the Kansas City District Office, audited the clinical portions of studies 53711 and 53811 at QPS Bio-Kinetic Clinical Applications, Springfield, MO.

During (b) (4), ORA investigator, Susan D. Yuscius from the Chicago District Office, audited the clinical portion of study 2012-2883 and OSI scientist, (b) (4) audited the analytical portions of all three studies (53711, 53811, and 2012-2883) at (b) (4)

The audits included review of business organization, thorough examination of study records, facilities and equipment, interviews, and discussions with the firm's management and staff.

Following the inspections, Mr. Cronenwett issued a Form FDA-483 at QPS Bio-Kinetic Clinical Applications **(Attachment 1)** and Ms. Yuscius (b) (4) issued a Form FDA-483 at (b) (4) (b) (4) **(Attachment 4).** DBGLPC received the firms' responses to the Form FDA-483s **(Attachments 2, 3, and 5).** The

Form FDA-483 observations, firms' responses, and DBGLPC's evaluations of Form FDA-483 observations are discussed below:

QPS Bio-Kinetic Clinical Applications, Springfield, MO:

Clinical Portion: Form FDA-483 observations:

1. **Failure to report to the sponsor, adverse effect that may reasonably be regarded as caused by, or probably caused by, an investigational drug.**
   Specifically, an Adverse Event (A/E) the Principal Investigator (PI) designated as related to investigational product was not reported to the sponsor. Subject #26, (b) (6) (Alternate #3 pre-screen) (Study # 53711) reported an A/E "Headache" to a study monitor. The A/E was incorrectly captured on an inactive A/E raw data record, intended for another subject (b) (6) (#26 pre-screen), created to begin the screening process. Subject (b) (6) did not present to participate, and was documented as "No show" at screening/randomization and "not on study". The raw data A/E log for #26, (b) (6) was blank.

Response:
The firm sent a response on July 26, 2013 **(Attachment 2)** and a follow-up response on August 23, 2013 **(Attachment 3)**. In the responses, the firm agreed to the observation regarding the error in reporting the A/E for subject #26.

As a corrective action, the firm sent a 'Note to File' explaining the error to the sponsor, QPS Netherlands (Data Management), QPS Qualitix Taiwan (Biostatistics), and QPS Bioserve India (Report Writing). A letter detailing the missing A/E was also presented to the IRB at the July 22, 2013 meeting. An erratum was created as an addenda to the Clinical Study Report, which included the A/E of headache for subject #26 ((b) (6)). The erratum was submitted with the response date August 23, 2013.

To ensure integrity of the system, the firm implemented new SOPs and the employees have been trained. Also, the firm's QA Unit conducted a review of all the A/E reporting related to participant/subject movement for studies conducted in 2011, 2012, and 2013.

Evaluation:
DBGLPC reviewer is of the opinion that the firm's corrective actions are acceptable. The Review Division should note the

recording error of A/E for subject #26 ((b) (6)). This error is not likely to impact the overall data integrity of study 53711.

2. **Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation and informed consent. Specifically, for the following subjects, the raw data documented late draw due to "Difficult draw" and the eCRFs indicated the protocol deviation was attributed to "subject's late return to the clinic", which was reported to the sponsor. However, the subjects were actually "checked-in" to the site and under the firm's observation.**
    - **Subject #17, study 53711, Period 2 was documented in raw data as a late draw (11/20/2011, post-dose 6.0 hour data point)**
    - **Subject #18, study 53711, period 1 was documented in raw data as a late draw (11/30/2011, post-dose 7.5, and 14.0 hour data points)**

Response:
The firm sent a response on July 26, 2013 **(Attachment 2)** and a follow-up response on August 23, 2013 **(Attachment 3)**. In the response, the firm agreed to the observation regarding the incorrect records in CRFs.

As a corrective action, the firm's QA Unit conducted a review of all CRFs for study 53711. In addition to the errors discovered during the inspection, an additional error was discovered for a blood sampling time for subject #26, Period 1, 8.5 hours. The sample was taken at 14:55 on November 13, 2011, but it was reported in the CRF as 15:55. A "Note to file" explaining the error was sent to the sponsor, QPS Netherlands (Data Management), QPS Qualitix Taiwan (Biostatistics) and QPS Bioserve India (Report Writing). The IRB was notified of the error by the PI during the July 22, 2013 meeting.
The errata as addenda to the final Study Report with the deviations were submitted to the agency in the response on August 23, 2013 **(Attachment 3).**

Evaluation:
DBGLPC reviewer is of the opinion that the firm's corrective actions are acceptable. The Review Division should note the recording errors in CRF. These errors are unlikely to impact the overall data integrity of study 53711 or human safety.

(b) (4)

Analytical portion: Form FDA-483 observations:

1. **For Validation study PMRI-1285-11 (Desvenlafaxine in human plasma) done to support of studies 2011-2749 (53711), 2011-2750 (53811), and 2012-2883: Failure to use freshly prepared calibrators to evaluate the stabilities of Desvenlafaxine. Specifically, freshly spiked calibration standards were not used to evaluate 'bench-top', 'refrigerated', 'freeze-thaw', and 'post-preparative' (autosampler/processed sample) stabilities of Desvenlafaxine.**

Response:
In the response dated August 21, 2013 **(Attachment 5)**, the firm acknowledged that freshly spiked calibration standards were not used for the above cited stability studies. However, the firm performed the 82-day long term stability at -25^{0}C using freshly spiked calibration standards. Also, in the response, the firm provided results of the re-evaluated bench-top, freeze-thaw, and post-preparative (refrigerated) stabilities of desvenafaxine using freshly spiked calibration standards.

Evaluation:
The firm's long term stability study (82 days) and revalidated stability studies performed using freshly spiked calibration standards are acceptable. With the provided information, this observation has no impact on the overall quality and integrity of the data for studies 53711, 53811, and 2012-2883.

2. **Failure to document all aspects of study conduct. Specifically, for study 2011-2749 (53711), unresolved interference peak was observed in the chromatograms of both periods for the following subjects (Attachment 6):**
   - **Subject 15 (analytical run: 2749-CR03-DEC0511RS)**
   - **Subject 34 (analytical run: 2749-CR07-DEC0611RS)**

A similar occurrence in a different study was addressed (Attachment 7); however, for study 2011-2749, the occurrence of the unresolved interference peak was not documented with proper justification.

Response:
In the response, the firm acknowledged that the presence of the interference peak in chromatograms of subject 15 and 34 should have been documented in the data. However, the firm did not perform any resolution of interference peak or impact analysis

of the interference peak for study 53711. Instead, during the FDA inspection, the firm excluded the data of subjects 15 and 34, and re-analyzed pharmacokinetic parameters for bioequivalence. The result showed that the two formulations are still bioequivalent **(Attachment 5)**.

Evaluation:
This reviewer is of the opinion that the firm should have resolved the interference peak and addressed its impact on accuracy of the sample analysis. In the absence of proper evaluation of impact of the interference peak observed in chromatograms of subjects 15 and 34, the accuracy of the sample analysis cannot be assured. DBGLPC reviewer recommends that subjects 15 and 34 should be excluded from the statistical data analysis and that the Review Division should verify the statistical analysis performed by the firm excluding subjects 15 and 34 **(Attachment 5)**.

Conclusion:

Following review and evaluation of the Form FDA-483 observations and the firms' responses, DBGLPC reviewer recommends that the **clinical and analytical data from studies 53711, 53811 and 2012-2883 are acceptable for further agency review with the following exceptions for study 53711.**

1. **The Review Division should take note of the discrepancy in reporting clinical data for subjects 17, 18 and 26.**
2. **For the analytical portion, subjects 15 and 34 should be excluded from the statistical data analysis.**

Jyoti B. Patel, Ph.D.
Pharmacologist
Bioequivalence Branch,
DBGLPC, OSI

Classification:

VAI: QPS Bio-Kinetic Clinical Applications, Springfield, MO
FEI: 1000511105
VAI: (b) (4)
FEI: (b) (4)

cc:
CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Haidar/Patel/Choi/Dejernett/CF
HFC-130/ORA HQ OMPTO DMPTI MPTTPB BIMO
CDER/OND//DPP/Ansah, Kofi/Kumi, Kofi/Zhang, Jing/Mannheim, Glenn/Zhu, Hao/Mathis, Mitchell
HFR-SW350/Bromley, Gerald (DIB)/Lopicka, Warren (BIMO)/Cronenwett, Brian
Yuscius, Susan
Draft: JBP 9/09/2013
Edit: YMC 9/11/2013, WHT 9/12/2013
OSI file #: 6418; O:\BE\assigns\205208.pha.des.doc
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/Electronic Archive/BEB
FACTS: 1511883

ATTACHMENTS:

Attachment 1: Form FDA-483 (Bio-Kinetic Clinical Applications)
Attachment 2: Response 1 from Bio-Kinetic Clinical Applications
Attachment 3: Response 2 from Bio-Kinetic Clinical Applications
Attachment 4: Form FDA-483 (b) (4)
Attachment 5: Response from (b) (4)
Attachment 6: Interference peak observed for subjects 15 and 34 (Study 53711)
Attachment 7: Impact analysis for interference peak done in a different Desvenlafaxine study

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/s/

JYOTI B PATEL
09/13/2013

WILLIAM H TAYLOR
09/13/2013

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: **8/30/13**

To: Kofi Boadu Ansah, R.Ph, Pharm.D, MBA
Senior Regulatory Project Manager
Division of Psychiatry Products (DPP)

From: Nazia Fatima, Pharm.D, MBA
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, Pharm.D
Team Leader, OPDP

Subject: OPDP Comments on desvenlafaxine fumarate extended-release tablets NDA 205208

OPDP has reviewed the draft product labeling (PI) and medication guide (MG) for desvenlafaxine fumarate extended-release tablets as requested in the consult from DPP dated January 16, 2013.

OPDP's comments, which are based on the draft version of the PI sent via email on August 22, 2013, by Kofi Ansah, are provided directly on the marked-up version of the label attached below. Combined OPDP and the Division of Medical Policy Programs (DMPP) comments on the proposed MG will be provided under separate cover.

If you have any questions, please feel free to contact me, Nazia Fatima at 240 – 402 – 5041or at Nazia.Fatima@fda.hhs.gov

Thank you! OPDP appreciates the opportunity to provide comments on these materials.

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/s/

NAZIA FATIMA
09/09/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 3, 2013
To:	Mitchell Mathis, M.D. Acting Director **Division of Psychiatry Products (DPP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Robin Duer, MBA, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Mathilda Fienkeng, Pharm.D Team Leader Office of Prescription Drug Promotion (OPDP)
From:	Twanda Scales, RN, MSN/Ed. Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Nazia Fatima, Pharm.D., MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	desvenlafaxine extended-release tablets
Dosage Form and Route:	Oral tablets
Application Type/Number:	NDA 205208
Applicant:	Teva Pharmaceuticals, USA

1 INTRODUCTION

On December 12, 2012, Teva Pharmaceuticals, USA submitted for the Agency's review a 505(b)(2) New Drug Application, NDA 205208, for Desvenlafaxine extended-release tablets. Desvenlafaxine extended-release tablets are indicated for the treatment of major depressive disorder (MDD). The referenced listed drug (RLD) for Desvenlafaxine extended-release tablets is Pristiq (desvenlafaxine) extended-release tablets. This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the DPP on January 16, 2013, and August 22, 2013, respectively, for DMPP and OPDP to review the Applicant's proposed MG for Desvenlafaxine extended-release tablets.

2 MATERIAL REVIEWED

- Draft Desvenlafaxine extended-release tablets MG received on December 12, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on January 16, 2013
- Draft Desvenlafaxine extended-release tablets MG received on December 12, 2012, revised by the Review Division throughout the review cycle, and received by OPDP on August 22, 2013
- Draft Desvenlafaxine extended-release tablets Prescribing Information (PI) received on December 12, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on January 16, 2013
- Draft Desvenlafaxine extended-release tablets Prescribing Information (PI) received on December 12, 2012, revised by the Review Division throughout the review cycle, and received by OPDP on August 22, 2013
- Approved Pristiq (desvenlafaxine) extended-release Tablets comparator labeling dated February 14, 2013

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG documents using the Verdana font, size 11.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible

- ensured that the MG is consistent with the Prescribing Information (PI)
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- removed unnecessary or redundant information
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
09/03/2013

NAZIA FATIMA
09/03/2013

ROBIN E DUER
09/03/2013

LASHAWN M GRIFFITHS
09/03/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	August 2, 2013
Reviewer:	Loretta Holmes, BSN, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z. Chan, PharmD, BCPS Division of Medication Error Prevention and Analysis
Associate Director:	Scott Dallas, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strengths:	Desvenlafaxine Extended-Release Tablets 50 mg and 100 mg
Application Type/Number:	NDA 205208
Applicant:	Teva Pharmaceuticals USA
OSE RCM #:	2013-200

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Contents

1 INTRODUCTION

This review evaluates the proposed container labels and insert labeling for Desvenlafaxine Extended-Release Tablets, NDA 205208, for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

NDA 205208 for Desvenlafaxine Extended-Release Tablets is a 505(b)(2) application relying on clinical and preclinical data for Pristiq Extended-Release Tablets (NDA 021992), which was approved on February 29, 2008.

1.2 PRODUCT INFORMATION

The following product information is provided in the February 6, 2013 submission.

- Active Ingredient: Desvenlafaxine
- Indication of Use: Treatment of major depressive disorder (MDD)
- Route of Administration: Oral
- Dosage Form: Extended-Release Tablets
- Strengths: 50 mg and 100 mg
- Dose and Frequency: The recommended dose is 50 mg orally once daily, with or without food. Tablets must be swallowed whole with fluid and not divided, crushed, chewed, or dissolved.
  Moderate renal impairment: 50 mg/day
  Severe renal impairment or end-stage renal disease: 50 mg every other day. The doses should not be escalated in patients with moderate or severe renal impairment.
  Hepatic impairment: 50 mg/day. Dose escalation above 100 mg/day is not recommended
- How Supplied: 14-count, 100-count, and 500-count bottles
- Storage: Store at 20ºC to 25ºC (68ºF to 77ºF)
- Container and Closure System: 14-count and 100-count bottles have child-resistant closures (CRC).

2 METHODS AND MATERIALS REVIEWED

NDA 205208 for Desvenlafaxine was filed as a 505(b)(2) application. The referenced drug is Pristiq, a currently marketed product. Thus, searching the FDA Adverse Events Reporting System (FAERS) database for Pristiq medication error cases may inform this review. The Division of Medication Error Prevention and Analysis (DMEPA) is simultaneously completing a label and labeling review for Osmotica's Desvenlafaxine product in OSE Review 2013-307. Thus, we referred to the medication error cases evaluated in that review to determine if any of the recommendations contained in OSE Review 2013-307 are applicable to this review.

Additionally, using the principals of human factors and Failure Mode and Effects Analysis,[1] along with postmarketing medication error data, DMEPA evaluated the following:

- Container Labels submitted on February 6, 2013 (Appendix A)
- Insert Labeling submitted on December 13, 2012 (no image)
- Medication Guide

We compared the Desvenlafaxine proposed labels and labeling against the currently marketed Pristiq labels (Appendix B) and labeling to identify any potential safety issues.

Additionally, we reviewed Alembic Pharmaceuticals Limited's Desvenlafaxine (NDA 204150) in OSE Review 2012-1546, dated November 4, 2012. It is another 505(b)(2) Desvenlafaxine product approved on March 4, 2013. We looked at that review to determine if there were recommendations that would also be applicable to this review.

3 MEDICATION ERROR RISK ASSESSMENT

Our evaluation of DMEPA's previous reviews and our risk assessment of the proposed Desvenlafaxine labels and labeling identified areas of concern which can be improved for clarity and to increase the readability and prominence of important information on the labels to promote the safe use of the product. These areas of concern include the presentation of established name, the prominence of certain labeling statements, inadequate strength differentiation, and the use of error-prone symbols. We provide recommendations for the labels and labeling in Section 4 below.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product, to mitigate any confusion, and to clarify information.

4.1 COMMENTS TO THE DIVISION

DMEPA provides the following comments for consideration by the review division prior to the approval of this NDA:

A. General Comment for All Labels and Labeling

As currently presented, the established name reads (b) (4) ". Per consultation with ONDQA, the word (b) (4) should be removed and the active ingredient revised to read "Desvenlafaxine".

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

B. Insert Labeling

1. The error-prone symbol "<" which means "less than" is used in the Full Prescribing Information, *Dosage and Administration*, *Patients with renal impairment* section of the insert labeling (i.e., "<30 mL/min"). This symbol may be misinterpreted to mean "greater than", the opposite of the intended meaning. Consider replacing the symbol "<" with the words "less than".

2. In the *Dosage and Administration* sections of Highlights of Prescribing Information and Full Prescribing Information, there are instances where the numerical strength or dose is not followed by their unit of measure each time they are mentioned (e.g., 50 and 100 mg tablets). We recommend revising the numerical strength or dose so it is followed by the appropriate unit of measure (e.g., 50 mg and 100 mg tablets). Dashes are also used in the *Dosage and Administration* section of Full Prescribing Information to indicate dosage ranges (e.g., 50-400 mg/day). When dashes are used along with numbers in a sequence, they may be overlooked or misinterpreted as a period, especially if the print font is small. Consider deleting the dashes when dosage ranges are specified. For example, revise the statement 50-400 mg/day to read: "50 mg to 400 mg/day".

4.2 COMMENTS TO THE APPLICANT

DMEPA advises the recommendations below be implemented prior to approval of this NDA:

A. General Comment

The established name is presented as (b) (4) . The active ingredient is Desvenlafaxine. Thus, revise the established name to read "Desvenlafaxine Extended-Release Tablets".

B. Container Labels

1. The active ingredient "Desvenlafaxine Fumarate" is presented in upper case font and the dosage form is presented in title case font. Use the same title case font for the active ingredient and the dosage form since both represent the established name in its entirety.

2. The yellow font color used for the statement of strength on the 50 mg strength labels is difficult to read because it lacks sufficient contrast against the white background. For the statement of strength consider color boxing, outlining the text with a dark color, or some alternate means to provide sufficient contrast against the white background.

3. Increase the font size utilized for the statement of strength.

4. The statement of strength lacks prominence. Relocate the strength directly below the established name. To accommodate this, consider minimizing the "TEVA" logo at the bottom of the principal display panel (PDP). As currently presented, the company logo is too prominent.

5. Revise the text in yellow font on the side panel to a darker font to improve the readability of this information.
6. The "Rx only" statement is too prominent. Decrease its prominence by debolding the font.

If you have further questions or need clarifications, please contact Louis Flowers, Project Manager, at 301-796-3158.

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

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

/s/

LORETTA HOLMES
08/02/2013

IRENE Z CHAN
08/02/2013

SCOTT M DALLAS
08/02/2013

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 205208

Application Type: Original 505(b)(2) NDA

Name of Drug: Desvenlafaxine fumarate extended-release tablets, 50 mg and 100 mg

Applicant: Teva Pharmaceuticals

Submission Date: 2/12/13

Receipt Date: 2/13/13

1.0 Regulatory History and Applicant's Main Proposals

This is a 505b2 original NDA with the innovator RLD being Pristiq (desvenlafaxine HCl), NDA 21992

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant. The applicant will be asked to correct these deficiencies and resubmit the PI in Word within 2 weeks. The resubmitted PI will be used for further labeling review.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

NO 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

YES

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

12. All text must be **bolded**.

Comment:

YES 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

YES 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

YES 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

YES 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment:

Dosage Forms and Strengths

YES 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

YES 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

NO 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

NO 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

YES

30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

YES 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

Selected Requirements of Prescribing Information (SRPI)

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

YES 42. All text is **bolded**.

Comment:

YES 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

YES 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

N/A 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

NO 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

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

/s/

PAUL A DAVID
06/24/2013

M E M O R A N D U M

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

DATE: April 16, 2013

TO: Chief,
Medical Products and Tobacco Trip Planning Branch
Division of Medical Products and Tobacco Inspections
Office of Medical Products and Tobacco Operations

Director, Investigations Branch
(b) (4)

FROM: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

SUBJECT: FY 2013, **CDER High Priority User Fee NDA, Pre-Approval Data Validation Inspection**, Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: NDA 205208
DRUG: Desvenlafaxin Fumarate Extended-Release Tablets 50 mg and 100 mg
SPONSOR: Teva Pharmaceuticals, USA Horsham, PA

This memo requests that you arrange for inspections of clinical and analytical portions of the following bioequivalence studies. Once an **ORA investigator is identified, please contact the DBGLPC point of contact (POC) listed at the end of this memo for background materials. A DBGLPC scientist with specialized knowledge may participate in the inspection of the analytical site to provide scientific and technical expertise. Please contact DBGLPC POC upon receipt of this assignment to arrange scheduling of the analytical inspection. Please complete the inspections prior to** (b) (4)**.**

Do not notify the sites of the application number, the studies to be inspected, drug name, or the study investigators prior to the start of the inspection. The information will be provided to

the site(s) at the inspection opening meeting. **Please note that this inspection will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).**

At the completion of the inspection, please send a scanned copy of the completed sections A and B of this memo to Dr. Sam Haidar and the DBGLPC POC.

1. Study Number: **53711**
Study Title: "A pivotal, open-label, single-center, randomized, single-dose, two-period, two-treatment, two-sequence crossover study to compare the bioequivalence of Desvenlafaxine Fumarate Extended-Release Tablets 100 mg to Pristiq® Extended-Release Tablets, 100 mg under fasted conditions"
Subjects enrolled: 34

2. Study Number: **53811**
Study Title: "A pivotal, open-label, single-center, randomized, single-dose, two-period, two-treatment, two-sequence crossover study to compare the bioequivalence of Desvenlafaxine Fumarate Extended-Release Tablets 100 mg to Pristiq® Extended-Release Tablets, 100 mg under fed conditions"
Subjects enrolled: 24

Clinical Site: Bio-Kinetic Clinical Applications
1816 W. Mt. Vernon
Springfield, MO 65802
TEL: (417)831-0456
FAX: (417)831-0715

Investigators: Thomas J. Legg, D.O. (Study: 53711)
Email: Thomas.legg@qps-usa.com

Donald Burkindine, D.O. (Study: 53811)
Email: Donald.burkindine@qps-usa.com

3. Study Number: **2012-2883**
Study Title: "A single-dose, comparative bioavailability study of one formulation of Desvenlafaxine Fumarate Extended Release Tablets, equivalent to 50 mg Desvenlafaxine and one formulation

of Pristiq® Extended Release Tablets, 50 mg under fasting and fed conditions"
Subjects enrolled: 30

Clinical Site: Pharma Medica Research, Inc.
4770 Sheppard Avenue East
Toronto, Ontario, Canada MIS 3V6
TEL: (416) 759-4111
FAX: (416) 759-2869

Investigator: Xueyu (Eric) Chen, M.D., Ph.D.
Email: echen@pharmamedica.com

SECTION A

RESERVE SAMPLES: Because these are bioequivalence studies subject to 21 CFR 320.38 and 320.63, the site conducting the study (i.e., each investigator site) is responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided by the sponsor for subject dosing.

Please note that the final rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) specifically addresses the requirements for bioequivalence studies (http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265.htm). Please refer to CDER's "Guidance for Industry, Handling and Retention of BA and BE Testing Samples" (May 2004), which clarifies the requirements for reserve samples (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf).

Please follow the instructions below:

- ☐ **Verify if reserve samples were retained according to regulations.**
- ☐ **If the reserve samples were stored at a third party site, please verify and collect an affidavit to confirm that the third party is independent from the sponsor, manufacturer, and packager, and that the sponsor was notified in writing of the location. In an event the reserve samples were not retained or are not adequate in quantity, please notify the POC immediately.**
- ☐ **Please obtain a written assurance from the clinical investigator or the responsible person at the clinical**

site that the reserve samples are representative of those used in the specific bioequivalence study, and that they were stored under conditions specified in accompanying records. Document the signed and dated assurance [21 CFR 320.38(d, e, g)] on the facility's letterhead, or Form FDA 463a, Affidavit.

☐ **Samples of the test and reference products in their original containers should be collected and shipped to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening, at the following address:**

Benjamin Westenberger, Ph.D.
Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
US Courthouse and Customhouse Bldg.
1114 Market Street, Room 1002
St. Louis, MO 63101
TEL: (314) 539-2135

SECTION B

Please confirm the informed consent and records for 100% of subjects enrolled at the site. The study records in the NDA submission should be compared to the original documents at the site. Include a description of your findings in the EIR.

Data Audit Checklist:

- Evidence of under-reporting of AEs identified? _____
- Evidence of inaccuracy in electronic data capture? _____
- Presence of 100% of signed and dated informed consent forms:_____
- Reports for the subjects audited:_____
- Number of subject records reviewed during the inspection:_____
- Number of subjects screened at the site:_____
- Number of subjects enrolled at the site:_____
- Number of subjects completing the study:_____
- Verify from source documents that evaluations related to the primary endpoint were accurately reported in case report forms:_____
- Confirm that clinical assessments were conducted in a consistent manner and in accordance with the protocol:_____
- Confirm that SOPs were followed during study conduct:_____

- Examine correspondence files for any sponsor- or monitor-requested changes to study data or reports:_____
- Include a brief statement summarizing your findings (IRB approvals, study protocol and SOPs, protocol deviations, adverse events, concomitant medications, inclusion/exclusion criteria, adequacy of records, drug accountability documents, and case report forms for dosing of subjects, etc.)
- Other Comments:

_____

_____

Collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

ANALYTICAL:
For all the three studies:

Analytical Site: (b) (4)

Contact Person: (b) (4)

Methodology: LC-MS/MS
Analytes: Desvenlaflaxine (O-Desmethylvenlafaxine)
Matrix: Plasma (with K_2EDTA)

Please confirm the following during the inspection:

- Examine all pertinent items related to the analytical methods used for the measurement of **Desvenlafaxine concentrations in human plasma.**
- Compare the accuracy of the analytical data provided in the NDA submission by the applicant with the original documents at the site.
- Determine if the validated analytical method was employed for the subject sample analysis.
- Compare the assay parameters (such as variability between and within runs, accuracy and precision, etc.) observed during the

study sample analysis with those obtained during method validation.

- Confirm that the accuracy and precision in matrix were determined using standards and QCs prepared from separate stocks.
- Determine if the subject samples were analyzed within the validated stability period.
- **Confirm that freshly made calibrators and/or freshly made QCs were used for stability evaluations during method validation.**
- **Confirm that the precision and accuracy was demonstrated at least one time using QCs and calibrators prepared from separate stock solutions.**
- **Scrutinize the number of repeat assays of the subject plasma samples, the reason for such repetitions, the SOP(s) for repeat assays, and if relevant stability criteria such as the number of freeze-thaw cycles sufficiently covered the stability of reanalyzed subject samples.**
- Examine correspondence files between the analytical site and the sponsor for their content.

Additional instructions to ORA Investigator:

In addition to the compliance program elements, other study specific instructions may be provided by the DBGLPC POC prior to the inspection. Therefore, we request that the DBGLPC POC be contacted for further instructions, inspection-related questions or clarifications before the inspection, and also regarding data anomalies or questions noted during review of study records on site.

Please fax/email a copy of Form FDA 483 if issued, as soon as possible. If at close-out of the inspection, it appears that the violations may warrant an OAI classification, please notify the DBGLPC POC as soon as possible. At completion of inspection, please remind the inspected entity of the 15 business-day timeframe for submission of a written response to observations listed on Form FDA 483. Please forward written response as soon as you receive it to Dr. Sam H. Haidar (Fax: 1-301-847-8748 or Email: sam.haidar@fda.hhs.gov) and DBGLPC POC.

DBGLPC POC:

Foreign: Arindam Dasgupta, Ph.D.
Email: arindam.dasgupta@fda.hhs.gov
TEL: (301)796-3326
FAX: (301)847-8748

Domestic: Jyoti B. Patel, Ph.D.
Email: jyoti.patel@fda.hhs.gov

TEL: (301)796-4617
FAX: (301)847-8748

cc:
CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Haidar/Patel/Choi/Dasgupta/Dejernett/CF
HFC-130/ORA HQ OMPTO DMPTI MPTTPB BIMO
CDER/OND//DPP/Ansah, Kofi/Kumi, Kofi/Zhang, Jing/Mannheim, Glenn/Zhu, Hao/Mathis, Mitchell
HFR-SW350/Bromley, Gerald (DIB)/Lopicka, Warren (BIMO)
Draft: JBP 4/08/2013
Edit: YMC 04/09/2013
OSI file #: 6418; O:\BE\assigns\bio205208.doc
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/Electronic Archive/BEB
FACTS: 1511883

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/s/

JYOTI B PATEL
04/16/2013

SAM H HAIDAR
04/16/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 205208 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: None Established/Proper Name: Desvenlafaxine Fumarate Extended-Release Dosage Form: Tablets Strengths: 50 mg and 100 mg		
Applicant: Teva Pharmaceuticals, USA Agent for Applicant (if applicable):		
Date of Application: December 12, 2012 Date of Receipt: December 13, 2012 Date clock started after UN:		
PDUFA Goal Date: October 13, 2012	Action Goal Date (if different): October 11, 2013	
Filing Date: February 11, 2013	Date of Filing Meeting: January 31, 2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): Major Depressive Disorder		

Type of Original NDA: AND (if applicable)	☐ 505(b)(1) ☒ 505(b)(2)
Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 113629	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	✓			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	✓			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	✓			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		✓		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	✓			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	✓			
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**		✓		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***		✓		
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	✓			

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
NDA 021992	PRISTIQ	NCE	03/01/13

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		✓		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		✓		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		✓		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			✓	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	✓			
Index: Does the submission contain an accurate comprehensive index?	✓			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	✓			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Applications in "the Program" (PDUFA V) (NME NDAs/Original BLAs)	**YES**	**NO**	**NA**	**Comment**
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?		✓		
• If yes, were all of them submitted on time?			✓	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			✓	
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			✓	
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	✓			
Are all establishments and their registration numbers listed on the form/attached to the form?	✓			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	✓			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	✓			

Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)]. ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*				
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	✓			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	✓			
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			✓	Electronic submission

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*: 02/13/13			✓	

Pediatrics	**YES**	**NO**	**NA**	**Comment**

PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	✓			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	✓			
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	✓			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	✓			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]				
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***		✓		Applicant does not intend to request a proprietary name at this time.
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***		✓		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels			

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

	☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	✓			
Is the PI submitted in PLR format?[4]	✓			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			✓	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	✓			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	✓			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	✓			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	✓			
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	✓			
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	✓			

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			✓	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		✓		
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		✓		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** Pre-NDA Meeting was for 10/16/12 ***If yes, distribute minutes before filing meeting***		✓		Meeting cancelled by the Sponsor upon receipt of our 10/10/12 Preliminary Comments .
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		✓		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 01/31/13

BLA/NDA/Supp #: NDA 205208

PROPRIETARY NAME: none

ESTABLISHED/PROPER NAME: Desvenlafaxine Fumarate Extended-Release
DOSAGE FORM/STRENGTH: 50mg and 100mg Tablets

APPLICANT: Teva Pharmaceuticals, USA

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Major Depressive Disorder

BACKGROUND: Teva Pharmaceuticals USA submitted this new 505(b)(2) application that proposes a new desvenlafaxine formulation (i.e. Desvenlafaxine Fumarate Extended-Release Tablets 50mg and 100mg) for the treatment of MDD. The RLD is PRISTIQ (i.e., NDA 021992) and the submission also references IND 113629.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kofi Ansah, Pharm.D.	Y
	CPMS/TL:	Paul David/ Renmeet Grewal	N
Cross-Discipline Team Leader (CDTL)	Jing Zhang, M.D.		Y
Clinical	Reviewer:	Glenn Mannheim, M.D.	Y
	TL:	Jing Zhang, M.D.	Y
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	
	TL:	N/A	

Clinical Pharmacology	Reviewer:	Kofi Kumi, Ph.D.	Y
	TL:	Hao Zhu, Ph.D.	Y
Biostatistics	Reviewer:	N/A	
	TL:	N/A	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Shiny Mathew, Ph.D.	Y
	TL:	Linda Fossom, Ph.D.	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Mohan Sapru, Ph.D.	Y
	TL:	Chhagan Tele, Ph.D.	Y
Quality Microbiology *(for sterile products)*	Reviewer:	N/A	
	TL:	N/A	
CMC Labeling Review	Reviewer:	Mohan Sapru, Ph.D.	Y
	TL:	Chhagan Tele, Ph.D.	Y
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Loretta Holmes, Pharm.D.	Y
	TL:	Irene Z. Chan, Pharm.D.	
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Seongeun (Julia) Cho, M.D.	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers: Biopharmaceutics DMPP/Patient Labeling Team	Banu Zolnik, Ph.D. Twanda Scales, RN, MSN		Y Y
Other attendees: ADRA/ODE-I	Colleen Locicero, Pharm.D.		Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: Yes	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

or efficacy issues ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: Biopharmaceutics comments/ information request to be sent via 74-Day Letter.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Mitchell V. Mathis, M.D., Division Director (acting) DPP

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V):

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments: **MILESTONE DATES:**

Receipt Date:	12/13/12
Day 45:	**01/27/13 (Filing Meeting: 1/31/13)**
Day 60:	02/11/13
Day 74:	**02/25/13**
Mid-Cycle:	**05/13/13**
Month 8:	08/13/13
PDUFA Date:	**10/13/13 (Sunday) therefore; Action Date: 10/11/13**

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by

	Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in "the Program")
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☒	Other: Send Biopharmaceutics Comments/Information Request in 74-day Letter.

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

KOFI B ANSAH
02/18/2013