CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205208Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 205208 SUPPL # HFD # 130

Trade Name

Generic Name Desvenlafaxine Fumarate Extended-Release 50mg & 100mg Tablets

Applicant Name Teva Pharmaceuticals, USA

Approval Date, If Known 10-11-13

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The sponsor solely used PRISTIQ as a RLD and submitted bioequivalence data comparing their product to the innovator's product to support approval.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

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

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 021922 PRISTIQ (desvenlafaxine succinate extended-release tablets)

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☒

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Kofi B. Ansah, Pharm.D., CDR USPHS
Title: Senior Regulatory Project Manager
Date: 10/09/13

Name of Office/Division Director signing form: Mitchell V. Mathis, M.D., CAPT USPHS
Title: Director (acting), Division of Psychiatry Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

MITCHELL V Mathis
10/11/2013

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 205208 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Established/Proper Name: Desvenlafaxine Extended-Release Dosage Form: Tablets		Applicant: Teva Pharmaceuticals, USA. Agent for Applicant (if applicable):
RPM: Kofi B. Ansah, Pharm.D.		Division: Division of Psychiatry Products (DPP)

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A 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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

NDA 21992 – PRISTIQ (desvenlafaxine) Extended-Release Tablets

Provide a brief explanation of how this product is different from the listed drug.

This current product (proposed in this application) is the "Desvenlafaxine [Fumarate (salt)] Extended-Release Tablets, i.e., a different salt (Fumarate vs. Succinate).

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☒ This application relies on (explain) The Agency's findings of Safety and Efficacy from the review of the RLD (i.e., PRISTIQ).

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☒ No changes ☐ Updated Date of check: 10/11/13

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 10/13/13	☒ AP ☐ TA ☐ CR

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☒ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☒ Verified

Version: 07/17/2013

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☒ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☒ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☒ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[4]	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s): AP Letter (10-11-13)
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	9/27/13 (archived on 9/30/13)
• Original applicant-proposed labeling	12/12/12 Original Submission Label
• Example of class labeling, if applicable	PRISTIQ & KHEDZLA PI

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	see above
• Original applicant-proposed labeling	see above
• Example of class labeling, if applicable	see above
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	09/20/13 (revised Labels)
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	N/A - None Requested
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM - PLR Format Review (6/24/13) ☐ DMEPA 8/2/13 & 9/25/13 ☒ DMPP/PLT (DRISK) Memo 09/11/13 ☐ ODPD (DDMAC) 9/9/13 ☐ SEALD 10/3/13 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	2/18/13 ☐ Not a (b)(2) 9/3/13 – Cleared ☐ Not a (b)(2) 10/10/13
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC: 9/18/13 (Peds Page/Record in DARRTS as peds entry) If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	Included (see Action Package)
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ No mtg Meeting (scheduled for 10-16-12) but Sponsor cancelled following receipt of FDA Preliminary Comments (10/10/12).
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None N/A
Division Director Summary Review *(indicate date for each review)*	☐ None 10/10/13
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 10/4/13
PMR/PMC Development Templates *(indicate total number)*	☐ None
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	CDTL Review - 10/04/13 (above)
• Clinical review(s) *(indicate date for each review)*	02/01/13 (Filing Checklist); 9/12/13(review); 9/5/13 (review)
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	02/01/13 (Filing Checklist)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☐ Not applicable None

[6] Filing reviews should be filed with the discipline reviews.

❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☒ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 09/20/13 (primary); 02/01/13 (filing checklist)
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None 09/13/13 (BE-EIR); 04/06/13 (initial memo)
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 09/03/13 (primary); 01/31/13 (filing checklist)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None CMC – 10/04/13 (final); 09/30/13 (primary review); 12/26/12 (initial QA) Biopharmaceutics – 09/05/13 (primary review); 02/15/13 (initial)
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	12/26/12 (initial CMC QA)
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: EER Summary Report – 10/03/13 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
(3) **Or** 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) **And** 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.
(3) **And** 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) **Or** 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.
(3) **Or** 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 ODE's ADRA.

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/s/

KOFI B ANSAH
10/11/2013

From:	Ansah, Kofi
To:	"John Derstine"
Cc:	David, Paul A
Subject:	RE: Final Proposed Labeling for Agreement -- NDA 205208/Desvenlafaxine Extended Release Tablets
Date:	Thursday, October 10, 2013 1:10:00 PM

Hi John,

Thank you for confirming that we have agreement on the labeling.

Kofi.

From: John Derstine [mailto:John.Derstine@tevapharm.com]
Sent: Thursday, October 10, 2013 1:02 PM
To: Ansah, Kofi
Cc: David, Paul A
Subject: RE: Final Proposed Labeling for Agreement -- NDA 205208/Desvenlafaxine Extended Release Tablets

Hi Kofi,

Thank you for the clarifications/explanations. I hereby confirm that we have agreement on the labeling.

Regards,
John

From: Ansah, Kofi [mailto:Kofi.Ansah@fda.hhs.gov]
Sent: Thursday, October 10, 2013 12:50 PM
To: John Derstine; FDA SharedMailbox; FDASharedMailboxForwarding
Cc: David, Paul A
Subject: RE: Final Proposed Labeling for Agreement -- NDA 205208/Desvenlafaxine Extended Release Tablets

Hi John,

Thank you for your email. With regard to your two comments on the PI, see our response below.

1) Sponsor's Comment: Although not identified as a revision in the attached draft, it appears that identification of the number of patients in section 6.1 Clinical Studies Experience (Patient Exposure) has reverted back to values contained in a previous version of the PRISTIQ labeling. For instance, the first numerical listing within this section of the number of patients in the provided draft lists 3,292 patients, whereas the current PRISTIQ labeling lists 4,158. We believe that our labeling should reflect the numerical listings for patients contained in the most current PRISTIQ labeling.

FDA Response: This was not identified as a revision because the language/"number of patients" has not changed from the 09/27/13 - PI on which we secured initial agreement with you prior to forwarding that PI to our SEALD team for their review.

The patient exposure number changed because we removed patients who were exposed to Pristiq in the maintenance studies. Because the data related to the maintenance studies are still protected by marketing exclusivity, this patient exposure information has to be removed from your label. This is consistent with what we did with other recently approved b(2) Desvenlafaxine.

2) Sponsor's Comment: It is necessary for us to maintain the revision statement (Revised: MM/YYYY) at the end of our PI for internal labeling purposes, as this is what is used to differentiate between the different labeling revisions. Additionally, based upon the inclusion of this revision statement at the end of the PI for the recently approved (and posted) labeling for KHEDEZLA (another Desvenlafaxine ER product), we respectfully request that this revision statement at the end of our PI be permitted to be retained.

FDA Response: We have to follow the labeling regulations plus guidelines provided by our SEALD team. The revision date at the end of HL replaces the "revision" or "issued" date at the end of the FPI and should not appear in both places. A revision date may appear at the end of FDA-approved patient labeling. A Medication Guide must have a revision date because it is required by regulation (see 21 CFR Part 208).

Please let us know, as soon as possible, if you have any more questions or if we have agreement on labeling.

Best Regards,
Kofi.

From: John Derstine [mailto:John.Derstine@tevapharm.com]
Sent: Thursday, October 10, 2013 11:45 AM
To: Ansah, Kofi
Cc: David, Paul A
Subject: RE: Final Proposed Labeling for Agreement -- NDA 205208/Desvenlafaxine Extended Release Tablets

Hi Kofi,

We've reviewed the provided labeling and have two comments with respect to the PI.

1) Although not identified as a revision in the attached draft, it appears that identification of the number of patients in section 6.1 Clinical Studies Experience (Patient Exposure) has reverted back to values contained in a previous version of the PRISTIQ labeling. For instance, the first numerical listing within this section of the number of patients in the provided draft lists 3,292 patients, whereas the current PRISTIQ labeling lists 4,158. We believe that our labeling should reflect the numerical listings for patients contained in the most current PRISTIQ labeling.
2) It is necessary for us to maintain the revision statement (Revised: MM/YYYY) at the end of our PI for internal labeling purposes, as this is what is used to differentiate between the different labeling revisions. Additionally, based upon the inclusion of this revision statement at the end of the PI for the recently approved (and posted) labeling for KHEDEZLA (another Desvenlafaxine ER product), we respectfully request that this revision

statement at the end of our PI be permitted to be retained.

With regard to the MG and the container labeling we are accepting of the provided labeling. I also hereby confirm that the issue date on the container labeling will be revised to reflect the month/year of FDA action.

Please feel free to contact me if there are any questions on the above.

Regards,
John

John Derstine
Teva Pharmaceuticals USA
Director, Regulatory Affairs
(215) 591-8702

From: Ansah, Kofi [mailto:Kofi.Ansah@fda.hhs.gov]
Sent: Wednesday, October 09, 2013 6:29 PM
To: John Derstine; FDA SharedMailbox; FDASharedMailboxForwarding
Cc: David, Paul A
Subject: Final Proposed Labeling for Agreement -- NDA 205208/Desvenlafaxine Extended Release Tablets

Dear John,

Attached is our final FDA proposed Labeling (i.e., PI, MG, and Container/Bottle Label) for your review and agreement.

PI: As you can tell from the marked-up version of the PI (also attached), most of the changes we have made following our 10/01/13 discussion are formatting changes except noting Revision Date at the end of Highlights & NDCs under Section 16.

MG: No additional changes have been made since our 10/01/13 discussion except noting the Revision Date at the end as: 10/2013.

Container/Bottle Label: No changes have been made to what you submitted on 09/20/13. But please confirm that the Issued Date of 9/2013, currently indicated on the Container/Bottle Labels, will be revised to reflect the month/year of FDA Action (i.e., changed to 10/2013). Provide this confirmation in your response.

[Note: A clean copy of the PI & MG (in pdf) for you to see – Once we have agreement, I will provide you a word copy of the PI & MG with a copy of our Action Letter.]

Please provide your response affirming agreement or non-agreement with our final proposed labeling (i.e., PI, MG, and Container/Bottle Label), as soon as possible – Preferably by noon tomorrow; 10/10/13.

Thanks,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA
CDR, US Public Health Service

Senior Regulatory Health Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

Fax: (301) 796-9838

Email: Kofi.Ansah@fda.hhs.gov

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/s/

KOFI B ANSAH
10/10/2013

From: Ansah, Kofi
To: "John Derstine"
Subject: RE: Information Request (PEDS Plan) -- NDA 205208/Desvenlafaxine ER/MDD
Date: Thursday, October 10, 2013 4:25:00 PM

Hi John,

Thank you for providing this confirmation.

Kofi.

From: John Derstine [mailto:John.Derstine@tevapharm.com]
Sent: Thursday, October 10, 2013 4:09 PM
To: Ansah, Kofi
Subject: RE: Information Request (PEDS Plan) -- NDA 205208/Desvenlafaxine ER/MDD

Hi Kofi,

Please consider this response as an acknowledgement/acceptance of the FDA's proposed deferral dates.

Regards,
John

From: Ansah, Kofi [mailto:Kofi.Ansah@fda.hhs.gov]
Sent: Thursday, October 10, 2013 1:05 PM
To: John Derstine; FDA SharedMailbox; FDASharedMailboxForwarding
Subject: RE: Information Request (PEDS Plan) -- NDA 205208/Desvenlafaxine ER/MDD

Hi John,

We acknowledge your suggested deferral dates but below are the proposed dates for our action letter.

Final Protocol Submission Date: July 2015
Study/Trial Completion Date: June 2019
Final Report Submission: December 2019

Please let us know, as soon as possible, if you have any issues with these dates or if the dates are okay as proposed.

Thanks,
Kofi.

From: John Derstine [mailto:John.Derstine@tevapharm.com]
Sent: Monday, September 09, 2013 12:28 PM
To: Ansah, Kofi
Subject: RE: Information Request (PEDS Plan) -- NDA 205208/Desvenlafaxine ER/MDD

Dear Kofi,

In light of the limited time we have to present a pediatric plan, I was wondering whether you could take a look at the attached draft which outlines our proposal for a pediatric study. I would appreciate any feedback you could provide as to whether the information contained in the attached document would be sufficient or whether additional info is needed. If additional information is needed, would you be able to detail the minimum information that is required.

Depending upon your response to the above will influence how quickly we can submit a response to this request.

I look forward to hearing from you.

Regards,
John

John Derstine
Teva Pharmaceuticals USA
Director, Regulatory Affairs
(215) 591-8702

From: Ansah, Kofi [mailto:Kofi.Ansah@fda.hhs.gov]
Sent: Wednesday, September 04, 2013 1:00 PM
To: John Derstine; FDA SharedMailbox; FDASharedMailboxForwarding
Subject: Information Request (PEDS Plan) -- NDA 205208/Desvenlafaxine ER/MDD

Dear John:

Regarding your NDA currently under review, we need you to provide the following information.

REQUIRED PEDIATRIC ASSESSMENTS
Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

A draft guidance on the implementation of PREA was issued by FDA in September 2005 and is available at http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079756.pdf .

As such, a pediatric plan needs to be submitted to address this NDA.

We note that your 03/26/13 response to (this request in) our filing Letter did not include a Pediatric Plan (b) (4) (b) (4) request. We also note that for this application, and at this time, we only intend to grant (i) a Partial-Waiver for patients ages 0-6 years and (ii) Defer Pediatric Studies for patients ages 7-17 years (hence the need for a Peds Plan).

Your pediatric plan must contain elements that will allow the Agency to determine whether the plan is sufficient to provide adequate data for dosing, safety, and efficacy for use in the appropriate pediatric populations. A synopsis of your proposed studies is to include the final report submission date as well as the relevant age ranges to be studied.

All requests for pediatric waivers must include a scientific rationale to support the waiver request.

Please amend your application address this deficiency as soon as possible since we are schedule to take this application to Pediatric and Exclusivity Review Committee (PeRC) next week.

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA
CDR, US Public Health Service
Senior Regulatory Health Project Manager, Division of Psychiatry Products
FDA/Center for Drug Evalua ion and Research, Office of Drug Evalua ion-I
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112
Silver Spring, MD 20993 - 0002
Phone: (301) 796-4158
Fax: (301) 796-9838
Email: Kofi.Ansah@fda.hhs.gov

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/s/

KOFI B ANSAH
10/10/2013

From:	Ansah, Kofi
To:	John Derstine (John.Derstine@tevapharm.com)
Subject:	DPP proposed PI & MG for Agreement -- NDA 205208/desvenlafaxine ER - Labeling
Date:	Friday, September 27, 2013 4:30:00 PM
Attachments:	09-27-13_DPP_proposed_PI__NDA 205208_DSV ER_(based on Sponsor"s 08-19-13 draft) (3).doc 09-27-17_DPP_proposed_MG__NDA 205208_DSV ER_(based on Sponsor"s 08-19-13 draft) (3).doc
Importance:	High

Dear John,

Attached is our proposed PI and MG. Please let us know if we have agreement in principle on this PI & MG so that DPP can move it forward to the SEALD team for their final review and input. If you have any edits/counter-proposal please track those changes in the attached documents and email them back to us.

Please note that we might have some last minute formatting/minor edits that may need to be incorporated, depending on the input we get from SEALD, before finalization of this label.

In the interest of time, we ask that you try and get back to us as soon as possible, preferable by COB Monday; 9/30/13. But certainly let us know if you require more time so that we can with you to get this done asap. Thank you !

Best Regards,

Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA
CDR, US Public Health Service
Senior Regulatory Health Project Manager, Division of Psychiatry Products
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/s/

KOFI B ANSAH
09/30/2013

From: Ansah, Kofi
To: John Derstine (John.Derstine@tevapharm.com)
Subject: DMEPA Information Request - 2 -- NDA 205208 - Desvenlafaxine ER Tablets/Container Labels
Date: Tuesday, September 17, 2013 4:56:00 PM

Dear John,

We have reviewed the revised container labels submitted on August 19, 2013 . We note the product name is in upper case font. Please revise to title case font as previously requested (i.e., "Desvenlafaxine Extended-Release Tablets").

Please provide your response by close-of-business on Friday, September 20, 2013.

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA
CDR, US Public Health Service

Senior Regulatory Health Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112

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Phone: (301) 796-4158

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Email: Kofi.Ansah@fda.hhs.gov

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/s/

KOFI B ANSAH
09/17/2013

From: Ansah, Kofi
To: "John Derstine"
Subject: OCP Information Request (amended) -- NDA 205208/Desvenlafaxine ER/MDD
Date: Friday, September 13, 2013 1:38:00 PM

Hi John,

Your response (email dated 9/9/13) didn't quite address OCP's concerns – See their amended request below and provide the requested information, as soon as possible.

Please submit to the Division of Psychiatry Drug Products (DPP) the recalculated bioequivalence data (excluding subjects 15 and 34) with the statistical analysis for Study 2011-2749 (53711) you included in your response to the 483 issued as result of the Office of Scientific Investigation (OSI) inspection of the Analytical Site for Study 53711. The title of Study 53711 is "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".

Include in your submission to DPP, a mean plasma concentration time profile and a summary of descriptive statistics of pharmacokinetic parameters based on the data of the patients used in the recalculation (i.e., exclude patients 15 and 34 in study 53711).

Please submit the requested information via email to the DPP by 9/18/13; and follow that email with a formal submission to the NDA no later than 9/30/13.

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA
CDR, US Public Health Service
Senior Regulatory Health Project Manager, Division of Psychiatry Products
FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112
Silver Spring, MD 20993 - 0002
Phone: (301) 796-4158
Fax: (301) 796-9838
Email: Kofi.Ansah@fda.hhs.gov

From: John Derstine [mailto:John.Derstine@tevapharm.com]
Sent: Thursday, September 12, 2013 9:52 AM
To: Ansah, Kofi
Subject: FW: OCP Information Request -- NDA 205208/Desvenlafaxine ER/MDD

Dear Kofi,

I just wanted to follow-up on the response provided below, as your original contact had requested the submission of recalculated bioequivalence data via email by September 11, 2013. Has the information the CRO provided addressed the request for recalculated data, or is the CRO's response still under evaluation?

Any update you could provide would be appreciated.

Regards,
John

From: John Derstine
Sent: Monday, September 09, 2013 4:40 PM
To: Ansah, Kofi
Subject: RE: OCP Information Request -- NDA 205208/Desvenlafaxine ER/MDD

Dear Kofi,

Please see the response from the CRO (provided below) as well as the referenced errata (see attached).

Based on the 483, and subsequent internal QA audit, five errors were noted (see attached errata).
Of the errors noted; only one of these (the blood draw time entered incorrectly) could have potentially affected the BE results. This however is not the case:

The sample was collected on time per the protocol. The correct sample time was relayed to (b) (4) for PK analysis. The error was in recording the time in the CRF.

- **Subject 26 dosed at 6:25.**
- **The 8.5 hour blood draw occurred at 14:55** (this is reflected in the subject source documents and PK sampling time provided to (b) (4) for PK analysis).
- **The 8.5 hour blood draw was recorded in the CRF as 15:55**. (in error)

Considering the facts above, there was no need for the BE to be recalculated. We believe that the errata provides the necessary information.

Please let me know whether this addresses the FDA's request regarding recalculated data. Based on the CRO's response, it doesn't appear that recalculating data is necessary. Please let me know if further information is needed or what is required in order to ensure this request is considered addressed.

Regards,
John

From: Ansah, Kofi [mailto:Kofi.Ansah@fda.hhs.gov]
Sent: Friday, September 06, 2013 11:45 PM
To: John Derstine; FDA SharedMailbox; FDASharedMailboxForwarding
Subject: OCP Information Request -- NDA 205208/Desvenlafaxine ER/MDD

Importance: High

Dear John:

Regarding your NDA currently under review, we need you to provide the following clinical pharmacology information, as soon as possible.

Please submit to the Division of Psychiatry Drug Products (DPP) the recalculated bioequivalence data for Study 53711 (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) that you included in your response to the 483 issued by the Office of Scientific Investigation (OSI). Please include in your submission to DPP, a mean (+/-SD) plasma concentration time profile and a summary of descriptive statistics of pharmacokinetic parameters based on the data of the patients used in the recalculation (i.e. exclude patients not used in the recalculation).

Please submit the data via e-mail by 9/11/13 and follow the email with an official submission to the DPP by 9/30/13.

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA
CDR, US Public Health Service

Senior Regulatory Health Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

Fax: (301) 796-9838

Email: Kofi.Ansah@fda.hhs.gov

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/s/

KOFI B ANSAH
09/13/2013

From: Ansah, Kofi
To: John Derstine (John.Derstine@tevapharm.com)
Subject: OCP Information Request -- NDA 205208/Desvenlafaxine ER/MDD
Date: Friday, September 06, 2013 11:44:00 PM
Importance: High

Dear John:

Regarding your NDA currently under review, we need you to provide the following clinical pharmacology information, as soon as possible.

Please submit to the Division of Psychiatry Drug Products (DPP) the recalculated bioequivalence data for Study 53711 (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) that you included in your response to the 483 issued by the Office of Scientific Investigation (OSI). Please include in your submission to DPP, a mean (+/-SD) plasma concentration time profile and a summary of descriptive statistics of pharmacokinetic parameters based on the data of the patients used in the recalculation (i.e. exclude patients not used in the recalculation).

Please submit the data via e-mail by 9/11/13 and follow the email with an official submission to the DPP by 9/30/13.

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA
CDR, US Public Health Service
Senior Regulatory Health Project Manager, Division of Psychiatry Products
FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112
Silver Spring, MD 20993 - 0002
Phone: (301) 796-4158
Fax: (301) 796-9838
Email: Kofi.Ansah@fda.hhs.gov
Commissioned Corps of the United States Public Health Service- "Protecting, promoting, and advancing the health and safety of the Nation"

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/s/

KOFI B ANSAH
09/06/2013

Bouie, Teshara

From: Bouie, Teshara
Sent: Thursday, August 22, 2013 9:36 AM
To: 'John Derstine'
Cc: Ansah, Kofi
Subject: RE: NDA 205208

Hi John,

Please see our responses below in red.

Teshara G. Bouie

From: John Derstine [mailto:John.Derstine@tevapharm.com]
Sent: Thursday, August 15, 2013 2:03 PM
To: Bouie, Teshara
Cc: Ansah, Kofi
Subject: RE: NDA 205208

Hi Teshara,

Would it be possible for you to provide clarification on a couple of items?

1) Does this indicate that our proposal to use the revised dissolution method (900 mL of 0.05M Buffer Acetate pH 4.5, Apparatus I (Basket), 100 rpm) is acceptable?

   Yes, the FDA is willing to consider the revised dissolution method for 50 mg strength. If appropriate, we are willing to consider different dissolution methods for your propose two strengths (e.g. (b) (4) USP 1 (basket), 100 rpm for the 100 mg strength). We remind you that you need to implement the new dissolution method in batches under stability testing.

   In addition, include data supporting the selection of the new method. Note that to increase the discriminating ability of the new method, it may be necessary to tighten the acceptance criteria beyond (b) (4) for the 50 mg strength.

2) If so, I assume the dissolution profile data that is being requested should be representative of product tested with the revised method. Is this correct? Should the requested information be submitted as an official response or via email, similar to the previous requests for information from the bio review? Should documentation reflecting the revised dissolution method be provided as part of this response?

   Please see response #1. Requested information should be sent via email; however, official documentation reflecting the revised dissolution method should follow the email.

3) In order to ensure that we are providing you with the requested dissolution profile data ("bio-batches and registration batches") could you confirm that this only refers to those batches for which demonstrated batches were presented in the application [50 mg: K-46724, K-46725, K-46726 and 100 mg: K-46406, K-46313, K-46314, K-46315, K-47646 (Scale-up)].

   Yes, provide the dissolution data for 50 mg strength batches 46724, K-46725, K-46726 in the revised dissolution media. Provide dissolution data for K-46406, K-46313, K-46314, K-46315, K-47646 in the original media, or the revised media depending on your decision about adopting the revised method for 100 mg strength.

4) Would you be able to clarify what is meant by "tabular and graphical form in QC media"? I'm not familiar with this terminology. Would this refer to tables and graphs presented in MS Word format?

   Tabular format refers to all dissolution data from each batch per strength in one table and graphical refers to the dissolution profiles of each batch in a graph.

5) Depending upon some of the clarification/responses to the above will determine how quickly we can respond. Is there any wiggle room in the requested response date of August 20, 2013?

   We extended the date to August 22, 2013

I realize I've presented a lot of questions above, however I want to ensure that what we provide you is in accord with your expectations.

I look forward to your response. If you feel it might be easier to talk through these questions, please let me know and I can give you a call.

Best regards,
John

John Derstine
Teva Pharmaceuticals USA
Director, Regulatory Affairs
(215) 591-8702

From: Bouie, Teshara [mailto:Teshara.Bouie@fda.hhs.gov]
Sent: Thursday, August 15, 2013 12:33 PM
To: John Derstine; FDA SharedMailbox; FDASharedMailboxForwarding
Cc: Ansah, Kofi
Subject: NDA 205208

Hi John,

The biopharmaceutics reviewer has the following request:

Provide the dissolution profile data from the bio-batches and registration stability batches in a tabular and graphical form in QC media for the setting of the dissolution acceptance criteria (i.e., specification-sampling time points and specification values) for 50 mg and 100 mg strengths.

Please provide a response by August 20, 2013.

Regards,

Teshara G. Bouie, MSA, OTR/L
CDR, United States Public Health Service
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment I
Phone (301) 796-1649
Fax (301) 796-9749

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/s/

TESHARA G BOUIE
08/22/2013

From:	Ansah, Kofi
To:	John Derstine (John.Derstine@tevapharm.com)
Subject:	DMEPA Comments & Request for revised Labeling -- NDA 205208/Desvenlafaxine Extended-Release Tablets
Date:	Wednesday, August 14, 2013 12:45:00 PM
Attachments:	07-15-13_revised_draft-PI__NDA 205208_DSV_(from Sponsor) with DPP"s initial edits.doc 07-2013_Sample PI - KHEDEZLA.pdf
Importance:	High

Dear John,

DMEPA advises the comments and 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 regarding these comments, specifically, please contact CDR Louis Flowers (OSE/DMEPA Project Manager) at 301-796-3158 or email: Louis.Flowers@fda.hhs.gov.

C. In light of these comments/recommendations, please submit revised labeling for your NDA as follows:

Prescriber Information (PI): Working off your 7-15-13 revised draft PI, and incorporating the general comment from A above, please adapt your PI to the KHEDEZLA PI (as applicable), i.e., a recently approved DSV product/labeling (July 2013), and resubmit your draft PI as soon as possible, preferably by 08/19/13. Refer to the attached.

Container Labels: Please also submit revised container Labels based on the comments under A & B above, as soon as possible.

[Note: The resubmitted PI and Labels will be used for further labeling review/discussions.]

Please feel free to contact me if you have any questions with regard to this information and email me copies of these revised labeling once they are submitted – Thank you.

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA
CDR, US Public Health Service

Senior Regulatory Health Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112

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Phone: (301) 796-4158

Fax: (301) 796-9838

Email: Kofi.Ansah@fda.hhs.gov

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

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/s/

KOFI B ANSAH
08/14/2013

Bouie, Teshara

From: Bouie, Teshara
Sent: Wednesday, July 17, 2013 5:54 PM
To: john.derstine@tevapharm.com
Cc: Ansah, Kofi
Subject: NDA 205208 - Information Request

Hi John,

The CMC reviewer has the following request for information:

1. Include microbiological testing in drug product specification or provide justification, with supporting data, for excluding microbiological testing from proposed drug product specification.

2. The drug product stability data, involving 9-month and 6-month stability testing under long-term and accelerated storage conditions, respectively, don't adequately support the proposed expiry period. Provide additional stability data in support of your proposed expiry period of 24 months.

3. Regarding labeling, we recommend you change the name (b) (4) to 'Desvenlafaxine Extended-Release Tablets'.

4. We have reviewed Type II DMF 26379 and found it deficient. We have issued a DMF deficiency letter to the DMF holder, dated July 10, 2013. Approval of the NDA is contingent upon adequate information being provided in a supporting DMF.

We request a response to these requests asap, but no later than **July 30, 2013**.

Regards,

Teshara G. Bouie, MSA, OTR/L
CDR, United States Public Health Service
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment I
Phone (301) 796-1649
Fax (301) 796-9749

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/s/

TESHARA G BOUIE
07/17/2013

From:	Ansah, Kofi
To:	"John Derstine"
Cc:	Grewal, Renmeet
Subject:	Request for PI info following SRPI Review -- NDA 205208 - desvenlafaxine Fumarate ER
Date:	Monday, July 01, 2013 9:58:00 AM
Importance:	High

Dear Mr. Derstine,

During our preliminary review of your submitted labeling, we have identified the labeling format issues listed below. Please correct these deficiencies and resubmit the PI in Word within 2 weeks of receiving this correspondence. The resubmitted PI will be used for further labeling review.

Highlights (HL)

1. 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). If not previously done; please request *a waiver if unable to meet the ½-page requirement.*
2. Patient Counseling Information Statement - Must include one of the following three bolded verbatim statements, as applicable (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."**
3. Revision Date - Bolded revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Full Prescribing Information (FPI)

1. **Patient Counseling Information**

   Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements, as applicable, 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)"

We request that you resubmit labeling that addresses these issues by July 15, 2013, or sooner. The resubmitted PI will be used for further labeling review/discussions.

[Note: Please email me a copy of the revised PI once it's submitted – Thanks.]

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA
CDR, US Public Health Service

Senior Regulatory Health Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

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Email: Kofi.Ansah@fda.hhs.gov

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/s/

KOFI B ANSAH
07/01/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205208

FILING COMMUNICATION

Teva Pharmaceuticals, USA
Attention: John Derstine
Director, Regulatory Affairs
425 Privet Road
Horsham, PA 19044

Dear Mr. Derstine:

Please refer to your New Drug Application (NDA) dated December 12, 2012, and received December 13, 2012, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Desvenlafaxine (b) (4) Extended-Release Tablets 50mg and 100mg.

We also refer to your amendment dated February 6, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 13, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by **September 20, 2013**.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

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

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

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for (b) (4) pediatric studies for this application. Your request has been reviewed and it has been denied at this time given that there are no clinical trials using desvenlafaxine in the pediatric population with major depressive disorder (MDD). However, we would, most likely, waive the pediatric study requirement for ages 0 to 6 years old in the treatment of MDD because studies are highly impractical due to the low prevalence of this disorder in this age range. For pediatric major depressive disorder, we consider the relevant age groups to include children (ages 7 through 11) and adolescents (ages 12 through 17).

As such a pediatric drug development plan is required to be submitted to this NDA to address this issue.

A draft guidance on the implementation of PREA was issued by FDA in September 2005 and is available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079756.pdf.

Your pediatric plans must contain elements that will allow the Agency to determine whether the plan is sufficient to provide adequate data for dosing, safety, and efficacy for use in the appropriate pediatric populations. A synopsis of your proposed studies is to include the final report submission date as well as the relevant age ranges to be studied.

Please provide the above requested information within 30 days from the date of this letter.

If you have any questions, contact CDR Kofi Ansah, Pharm.D., Senior Regulatory Project Manager, at (301)796-4158 or email: Kofi.Ansah@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
CAPT USPHS
Director (acting)
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

MITCHELL V Mathis
02/25/2013

From:	Ansah, Kofi
To:	"John Derstine"
Cc:	David, Paul A
Subject:	Agreement to Use FedEx -- RE: Desvenlafaxine Fumarate ER Tablets (NDA # 205208)
Date:	Thursday, February 14, 2013 9:16:00 AM

Hi John,

As a follow-up to my response to your email from yesterday (2/13/13) regarding your request that the Agency approve you to use Federal Express, in lieu of certified mail, to deliver the notice of certification of invalidity or noninfringement of a patent to the applicable patent holder and NDA holder, the Agency, in accordance with 21 CFR 314.52(e), agrees in advance that the use of Federal Express delivery for both notification and receipt documentation of the notice of certification of invalidity or noninfringement of a patent is acceptable.

Best Regards,
Kofi.

From: John Derstine [mailto:John.Derstine@tevapharm.com]
Sent: Wednesday, February 13, 2013 4:44 PM
To: Ansah, Kofi
Subject: RE: Desvenlafaxine Fumarate ER Tablets (NDA # 205208)

Thank you Kofi!

I appreciate the response.

Best Regards,
John

From: Ansah, Kofi [mailto:Kofi.Ansah@fda.hhs.gov]
Sent: Wednesday, February 13, 2013 1:04 PM
To: John Derstine; FDA SharedMailbox
Cc: David, Paul A
Subject: RE: Desvenlafaxine Fumarate ER Tablets (NDA # 205208)

Hi John,

Thank you for your voicemail and subsequent email. Yes; your application was filed as of February 11, 2013. Please expect our 74-day Letter with some comments/ information request by day 74.

With regards to providing your notice of Para IV certification, you may do so utilizing FedEx as you have proposed, as long as the proposed delivery method provides proof of receipt.

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D.
CDR, US Public Health Service
Regulatory Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4109
Silver Spring, MD 20993 - 0002
Phone: (301) 796-4158
Fax: (301) 796-9838
Email: Kofi.Ansah@fda.hhs.gov
Commissioned Corps of the United States Public Health Service- "Protecting, promoting, and advancing the health and safety of the Nation"

From: John Derstine [mailto:John.Derstine@tevapharm.com]
Sent: Tuesday, February 12, 2013 5:17 PM
To: Ansah, Kofi
Subject: Desvenlafaxine Fumarate ER Tablets (NDA # 205208)

Hello Kofi,

This email is a follow-up to a voicemail I left for you today. I realize there was a lot of content in the voicemail, so I thought I would capture the requests in an email and forward to your attention as well.

1) Based upon the information contained in the NDA Acknowledgement letter, I realize that a formal letter of acceptance of the application will not be forthcoming. However, since we have not received notice that the application is not sufficiently complete, can we interpret that to mean that our application has been filed (as of Feb. 11, 2013)?

2) Based on the certification contained within this application, we are required to provide Notice. The CFR requires one to use USPS certified mail, unless given permission by the Agency to do otherwise. We hereby request permission to send Notice by Fed Ex instead of via USPS certified mail.

I look forward to your response to the above.

Best Regards,

John Derstine
Teva Pharmaceuticals USA
Director, Regulatory Affairs
(215) 591-8702

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/s/

KOFI B ANSAH
02/15/2013

From:	Ansah, Kofi
To:	John Derstine [TEVA]
Cc:	Rimmel, Sandra J
Subject:	OSE/DMEPA Information Request -- NDA 205208 - desvenlafaxine Fumarate ER - MDD
Date:	Tuesday, January 29, 2013 11:10:00 AM

Dear Mr. Derstine,

Regarding your NDA 205208 currently under review, the OSE/DMEPA review team is in need of some additional information to facilitate their review. You only submitted text versions of the container labels with your 12/12//12 NDA submission. This information is insufficient for their review. You need to submit copies of the actual container labels/carton labeling you are proposing for all product strengths and bottle sizes.

Please provide the requested information, as soon as possible, preferably by close-of-business on Wednesday, February 6, 2013.

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D.
CDR, US Public Health Service

Regulatory Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4109

Silver Spring, MD 20993 - 0002

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/s/

KOFI B ANSAH
01/30/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205208

NDA ACKNOWLEDGMENT

Teva Pharmaceuticals, USA
Attention: John Derstine
Director, Regulatory Affairs
425 Privet Road
Horsham, PA 19044

Dear Mr. Derstine:

We have received your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Desvenlafaxine (b) (4) Extended-Release Tablets 50mg and 100mg

Date of Application: December 12, 2012

Date of Receipt: December 13, 2012

Our Reference Number: NDA 205208

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 11, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions please call me at (301)796-4158 or email: Kofi.Ansah@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Kofi Ansah, Pharm.D., CDR USPHS
Senior Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

KOFI B ANSAH
01/15/2013

Pre-IND 113629

MEETING PRELIMINARY COMMENTS

Teva Pharmaceuticals
Attention: John Derstine
Director, Regulatory Affairs
425 Privet Road
Horsham, PA 19044

Dear John:

Please refer to your Pre-Investigational New Drug Application (PIND) file for desvenlafaxine fumarate 50mg and 100mg Extended-Release Tablets for the treatment of Major Depressive Disorder (MDD).

We also refer to your correspondence, dated and received August 21, 2012, requesting a Pre-NDA teleconference and guidance on the future new drug application, to be submitted under 505(b)(2) of the Act. The sponsor intends to rely on the Agency's previous finding of safety and effectiveness for Wyeth Pharmaceuticals Inc.'s approved drug product Pristiq® (desvenlafaxine) Extended-Release Tablets, NDA # 021992.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion during the teleconference scheduled for Tuesday, October 16, 2012, from 11am to 12pm EST between Teva Pharmaceuticals and Division of Psychiatry Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (email me at Juliette.Toure@fda.hhs.gov). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, email me to discuss the possibility of including these items for discussion at the meeting.

FDA Preliminary Responses

Pre-IND 113629 – desvenlafaxine fumarate extended-release tablet
Teva Pharmaceuticals USA
Type B, Face to Face, Pre-NDA Meeting

Participants:

FDA

Thomas Laughren, M.D.	Division Director, DPP
Mitchell Mathis, M.D.	Deputy Division Director
Ni Khin, M.D.	Clinical Team Leader
Kavneet Ripi Kohli-Chhabra, M.D.	Clinical Reviewer
Chhagan Tele, Ph.D.	Chemistry Review Team Leader
Angelica Dorantes, Ph.D.	Biopharmaceutics Team Leader
Houda Mahayni, Ph.D.	Biopharmaceutics Reviewer
Linda Fossom, Ph.D.	Pharmacology/Toxicology Supervisor
Shiny Mathew, Ph.D.	Pharmacology/Toxicology Reviewer
Hao Zhu, Ph.D.	Clinical Pharmacology Team Leader
Kofi Kumi, Ph.D.	Clinical Pharmacology Reviewer
Dhananjay Chhatre, MS, RAC	Operations Research Analyst, Office of Business Informatics, Division of Data Management Solutions and Services Team
Colleen Locicero	Associate Director for Regulatory Affairs, ODE 1
Juliette Touré, Pharm.D.	Senior Regulatory Project Manager

Background:

Desvenlafaxine (4-[2-dimethylamino-1-(1-hydroxycyclohexyl) ethyl] phenol fumarate), a serotonin and norepinephrine reuptake inhibitor (SNRI), is the major active metabolite of the antidepressant, venlafaxine. Desvenlafaxine succinate monohydrate was originally approved by FDA in February 2008 as an extended-release tablet containing 50 mg and 100 mg of desvenlafaxine (as the free base) for the treatment of major depressive disorder (Pristiq®, NDA 21-992). The recommended dose is 50 mg once daily, with or without food, although higher doses are also used (up to 400 mg/day in clinical trials).

In accord with the draft guidance titled *Guidance for Industry: Applications Covered by Section 505(b)(2)*, Teva is planning the submission of a 505(b)(2) for an application which incorporates an active ingredient of a different salt. An approved product (Pristiq®) incorporates desvenlafaxine succinate as the active ingredient, whereas Teva would propose an application which incorporates desvenlafaxine fumarate as the active ingredient. In preparation for submission of an NDA application, Teva requested a Pre-IND meeting on October 12, 2011. The Agency provided preliminary responses to the Sponsor's questions via a December 01, 2011 correspondence. Teva after reviewing the Agency's comments decided to cancel the teleconference meeting scheduled for December 06, 2011.

Based on the information provided in this current meeting package, Teva completed six studies:

- (b) (4)
- (b) (4)
- Study # 53611 - 2-way crossover, fasted pivotal study on the 50 mg strength with 34 subjects
- Study # 53711 - 2-way crossover, fasted pivotal study on the 100 mg strength with 34 subjects
- Study # 53811 - 2-way crossover, fed pivotal study on the 100 mg strength with 34 subjects
- Study # 2012-2883 - 3-way crossover, fasted pivotal study on the 50 mg strength with a fed arm to illustrate food effect with 30 subjects

The Sponsor states that the formulations used in two studies (b) (4) were not considered the same when compared to the final formulation. Study #53611 for the 50 mg was a failed study.

The Sponsor claims, according to the PK results of 2 studies (studies #53711, 53811), their DVS fumarate ER 100 mg tablets was bioequivalent to Pristiq® ER 100 mg tablets with respect to C_{max} and AUC for desvenlafaxine under both fasting and fed conditions. The study for the 50 mg tablets (study #2012-2883) showed the food effect; an increase of C_{max} and AUC, by ~19% and ~8%, respectively, under the fed state as compared to drug administration in the fasting state.

No SAEs were reported for any of these studies. The common AE reported among these three studies appeared within the expected profile of this drug. In the fourth quarter of this year, they plan to submit full bioequivalence reports of these 3 BE studies (studies #53711, 53811, & 2012-2883) to support the 505(b)(2) NDA application.

Questions:

Biopharmaceutics and Clinical Pharmacology

Question 1: We are currently planning to submit full bioequivalence reports of the passing studies (#53711, 53811 & 2012-2883) in support of our application. Although the other studies/batches may be referenced as part of the Pharmaceutical Development Report, we are not planning to submit data or abbreviated bioequivalence reports for any of the other referenced studies as the formulations of the drug product evaluated in the other studies are not considered the same/similar as the final proposed formulation. Based on the information included in the briefing package, does the Agency agree with the proposed approach regarding the submission of the bioequivalence studies?

> ***Preliminary Comments:*** *The proposed studies (#52711, 53811 & 2012-2883) to be submitted are reasonable. You are reminded that the clinical trial formulation used in these BE as well as supportive clinical studies must be linked to the To Be Marketed Formulation (TBM) if they are different.*

Discussion at Meeting:

Question 2: We are planning to submit the following studies:

- Study # 53711 (100 mg): 2-way (test: K-46406; reference: E12613) crossover fasted pivotal study
- Study # 53811 (100 mg): 2-way (test: K-46406; reference: E12613) crossover fed pivotal study
- Study # 2012-2883 (50 mg): 3-way (test: K-46726; reference: E99239) crossover fasted pivotal study with a fed arm to illustrate food effect for the product

Based on the information included in the briefing package, does the Agency have any comments with regard to the conducted studies which are planned to be submitted in support of the application?

Preliminary Comments: *On face, the studies appear to be reasonable. However, acceptance of the study results will be a review issue. The Sponsor is reminded of the Clinical Pharmacology and Biopharmaceutics comments as reflected in the meeting minutes dated 12/01/2011 for the Pre-IND Teleconference in Attachment 3 of the current meeting package.*

Discussion at Meeting:

Chemistry, Manufacturing and Controls

Question 3: Based on the information included in the briefing package, will the submission of 9 months of long term stability data for the 50 mg strength be an issue for acceptance of the application?

Preliminary Comments: *Acceptance of the application will not be the issue; however, we recommend that you provide a minimum of 12 months of long-term and 6 months of accelerated stability data on three registration batches of 50 mg tablet strength packaged in the proposed packaging at the time of submission.*

Discussion at Meeting:

Question 4: We are also considering manufacturing and submitting another batch of the 100 mg strength to support the scale-up of the manufacturing process to commercial scale. In the event we manufacture this batch for submission, the following changes may also be included:

- Process change to the API

In order to provide increased control of the API manufacturing process, we propose to perform more of the processing steps in-house at Teva (TAPI). In addition to moving the earlier processing steps in-house, we are also proposing an additional Teva (TAPI) site for the manufacturing of the final API. Please note all proposed facilities have been registered with and inspected by the FDA. Please note that no new impurities are introduced as a result of the proposed back integration of the API. The only revision to the drug substance specification as a result of this change, is the incorporation of additional tests and limits for (b) (4) in order to cover the proposed API manufacturing processes.

• Incorporation of (b) (4) the manufacturing process

(b) (4)

In the event we manufacture this batch for submission purposes and in order to support these changes, we would propose submission of only the corresponding finished product certificate of analysis and comparative dissolution profiles. We will compare this batch to the batch used to conduct the bioequivalence studies via comparative dissolution profiles and by comparing the (b) (4) material. Additionally, we would commit to provide stability data for this batch to the application via the annual report. The intent of this batch would be to demonstrate the proposed changes in support of their incorporation for the manufacture of both strengths of the drug product. Does the Agency agree with the approach outlined to support the above-referenced changes?

Preliminary Comments: *Yes, we agree. However, since you intend to use the 100 mg batch to support the proposed changes, it is requested that you also submit comparative dissolution profiles for the lower 50 mg strength.*

We also ask that you provide:
1) Comparative table of component/composition of 50 mg and 100 mg strengths.
2) (b) (4)

Discussion at Meeting:

Labeling

Question 5: We intend to rely on the information and presentation of the currently approved labeling for Pristiq®. We only intend to change/modify information which would be specific to our product (i.e. information pertaining to the different salt of the drug substance, inactive ingredients, packaging configurations, manufacturer, etc.). Does the Agency have any guidance or feedback regarding our proposed approach to labeling?

Preliminary Comments: *On face, we have no objection to your proposal for labeling; however, this is a matter of review once the NDA application has been submitted.*

Discussion at Meeting:

GENERAL COMMENTS

505(b)(2) APPLICATION

Please refer again to the general advice we have previously sent you regarding the submission of a 505(b)(2) application. We would like to further note that, as described in our guidance for industry, *Applications Covered by Section 505(b)(2)*, **approval** or **filing** of a 505(b)(2) application, like a 505(j) application, may be delayed because of patent and exclusivity rights that apply to the listed drug relied upon (21 CFR 314.50(i), 314.107, and 314.108 and section 505A of the Act).

PREA PEDIATRIC STUDY PLAN

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

MANUFACTURING FACILITIES

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, email me at Juliette.Toure@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Juliette Touré, PharmD
CDR, United States Public Health Service
Senior Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

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

/s/

JULIETTE T TOURE
10/10/2012