

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204150Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 204150	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: None		
Established/Proper Name: Desvenlafaxine Extended-Release		
Dosage Form: Tablets		
Strengths: 50mg and 100mg		
Applicant: Alembic Pharmaceuticals Limited		
Date of Receipt: 01/04/13		
PDUFA Goal Date: 03/04/13		Action Goal Date (if different):
Proposed Indication(s): Major Depressive Disorder		

GENERAL INFORMATION

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

YES NO

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



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

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

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
PRISTIQ Tablets Prescribing Information, manufactured by Wyeth (now owned by Pfizer)	Pharmacokinetic data, prescribing information (all sections)

*each source of information should be listed on separate rows

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

Bioavailability and Bioequivalence studies comparing Desvenlafaxine ER to Pristiq and these studies were acceptable/adequate per OCP and Biopharmaceutics reviews.

RELIANCE ON PUBLISHED LITERATURE

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

YES NO

If “NO,” proceed to question #5.

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

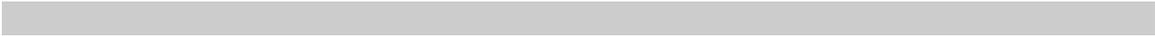
YES NO

If “NO,” proceed to question #5.

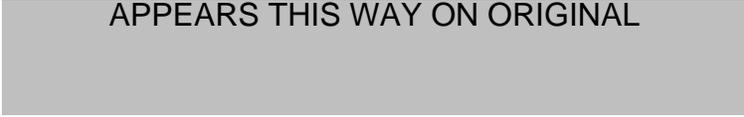
If “YES”, list the listed drug(s) identified by name and answer question #4(c).

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

YES NO



APPEARS THIS WAY ON ORIGINAL



RELIANCE ON LISTED DRUG(S)

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

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

YES NO

If "NO," proceed to question #10.

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

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

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

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

N/A YES NO

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

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

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

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

YES NO

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

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

- b) Approved by the DESI process?

YES NO

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

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

- c) Described in a monograph?

YES NO

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

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

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

YES NO

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

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

This application provides for the use of desvenlafaxine (Base) as the active ingredient in their extended-release 50mg & 100mg tablets formulation as opposed to the desvenlafaxine Succinate (salt) in the innovator's tablet formulation.

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

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

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

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

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

YES NO

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

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
YES NO

If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

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

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

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

YES NO

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

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
YES NO

If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

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

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

No patents listed proceed to question #14

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

YES NO

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

Listed drug/Patent number(s):

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

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

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

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR

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

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

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

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

(a) Patent number(s): *6673838 and 8269040*

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?
YES NO

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

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.
YES NO

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

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

Date(s): 05/10/12 (for Patent # 6673838; & 10/11/12 (for patent # 8269040)

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

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

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

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

/s/

KOFI B ANSAH
03/04/2013

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

Product Title	DESVENLAFAXINE (extended-release tablets, for oral use)
Applicant	Alembic Pharmaceuticals, Limited
Application/Supplement Number	NDA 204150
Type of Application	Original application
Indication(s)	Treatment of major depressive disorder
Established Pharmacologic Class ¹	Serotonin and norepinephrine reuptake inhibitor
Office/Division	ODEI/DPP
Division Project Manager	Kofi Ansah
Date FDA Received Application	January 4, 2013
Goal Date	March 4, 2013
Date PI Received by SEALD	February 28, 2013
SEALD Review Date	February 28, 2013
SEALD Labeling Reviewer	Debra Beitzell
SEALD Division Director	Laurie Burke

PI = prescribing information

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

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

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

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

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

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

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

Comment:

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

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

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *DPP to grant waiver of 1/2 page HL limit in approval letter.*

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

Comment:

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

Comment:

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

Comment:

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

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

Selected Requirements of Prescribing Information

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

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

Comment:

YES

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

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

Comment:

Highlights Limitation Statement

YES

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

Comment:

Product Title

YES

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

Comment:

Initial U.S. Approval

YES

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

Comment:

Boxed Warning

YES

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

Comment:

YES

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

Comment:

Selected Requirements of Prescribing Information

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

Comment:

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

Comment:

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

Comment:

Recent Major Changes (RMC)

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

Comment:

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

Comment:

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

Comment:

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

Comment:

Indications and Usage

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

Comment:

Dosage Forms and Strengths

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

Comment:

Contraindications

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

Comment:

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

Selected Requirements of Prescribing Information

Comment:

Adverse Reactions

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

Comment:

Patient Counseling Information Statement

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

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

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

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

Comment:

Revision Date

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

Comment: *Insert month and year of approval.*

Contents: Table of Contents (TOC)

GENERAL FORMAT

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

Comment:

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

Comment:

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

Comment:

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

Comment:

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

Comment:

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

Selected Requirements of Prescribing Information

Comment:

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

Comment:

- NO** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment: Move statement to end of TOC (i.e., below section 17 heading).

Full Prescribing Information (FPI)

GENERAL FORMAT

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

Comment:

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

Comment:

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

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)

Selected Requirements of Prescribing Information

12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- NO** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment: *Attach Medication Guide to the end of the FPI.*

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

Comment: *Subsection 2.1, 3rd paragraph, change numerical identifier in cross reference to Warnings and Precautions to "(5.7)" and under subsection 2.4, change numerical identifier to "(5.7)". Subsection 5.1, 8th paragraph, remove additional text within brackets after cross reference to (5.7). Subsection 5.9, 1st paragraph, change numerical identifier in cross reference to Clinical Pharmacology to "(12.3)".*

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

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

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

Comment:

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

Comment:

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

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

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

Selected Requirements of Prescribing Information

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

Comment:

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

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

Comment:

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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

/s/

DEBRA C BEITZELL
02/28/2013

LAURIE B BURKE
02/28/2013

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

Label, Labeling and Packaging Memorandum

Date: December 13, 2012

Reviewer: Loretta Holmes, BSN, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, PharmD, BCPS
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Desvenlafaxine Extended-release Tablets
50 mg and 100 mg

Application Type/Number: NDA 204150

Applicant: Alembic Pharmaceuticals Limited

OSE RCM #: 2012-1546

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the revised labels and labeling for Desvenlafaxine Extended-release Tablets, NDA 204150, for areas of vulnerability that could lead to medication errors. DMEPA previously reviewed labels and labeling for this product in OSE Review 2012-1546, dated November 2, 2012.

2 METHODS AND MATERIALS REVIEWED

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the container labels, blister labels, and carton labeling received on November 29, 2012 (see Appendices A, B, and C). We compared those labels and labeling against the recommendations contained in OSE Review 2012-1546 to determine whether the revisions adequately address our concerns from a medication error perspective.

3 CONCLUSIONS AND RECOMMENDATIONS

Our review of the labels and labeling received on November 29, 2012 determined that the Applicant has implemented all of our previous recommendations. We have no additional recommendations at this time.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Sandra Rimmel, OSE Project Manager, at 301-796-2445.

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/s/

LORETTA HOLMES
12/13/2012

IRENE Z CHAN
12/13/2012

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****PRE-DECISIONAL AGENCY MEMO****

Date: December 3, 2012

To: Kofi Ansah, PharmD
Regulatory Project Manager
Division of Psychiatric Products (DPP)

From: Jessica Cleck Derenick, PhD
Regulatory Review Officer
Division of Professional Promotion (DPP)
Office of Prescription Drug Promotion (OPDP)

Susannah Hubert, MPH
Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)
OPDP

Subject: NDA 204150
OPDP labeling comments for Desvenlafaxine extended-release tablets

OPDP has reviewed the proposed product labeling (PI) and Medication Guide for Desvenlafaxine extended-release tablet as requested in the consult dated July 3, 2012.

The following comments are provided below, directly on the attached labeling.

Please feel free to contact Jessica Cleck Derenick at 301-796-0390 or Susannah Hubert at 301-796-3245, or via email, with any questions or clarifications.

Thank you for the opportunity to comment on this proposed labeling.

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/s/

JESSICA N CLECK DERENICK
12/03/2012

SUSANNAH HUBERT
12/03/2012

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion

****PRE-DECISIONAL AGENCY MEMO****

Date: December 3, 2012

To: Kofi Ansah, PharmD
Regulatory Project Manager
Division of Psychiatric Products (DPP)

From: Jessica Cleck Derenick, PhD
Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 204150
DPDP comments on the draft carton and container labeling
for Desvenlafaxine extended-release tablets

DPDP has reviewed the draft carton and container labeling for Desvenlafaxine extended-release tablets (Desvenlafaxine) as requested in the consult from DPP dated July 3, 2012. DPDP's comments are based on the draft version of the carton and container labeling emailed by Kofi Ansah on November 30, 2012 (see attached).

We do not have any comments on the draft carton and container labeling for Desvenlafaxine at this time.

DPDP appreciates the opportunity to provide comments on these materials. If you have any questions, please feel free to contact me:

Jessica Cleck Derenick: 301-796-0390; Jessica.Cleck-Derenick@fda.hhs.gov

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/s/

JESSICA N CLECK DERENICK
12/03/2012

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

PATIENT LABELING REVIEW

Date: November 30, 2012

To: Thomas Laughren, MD
Director
Division of Psychiatry Products (DPP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Melissa Hulett, MSBA, BSN, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): desvenlafaxine

Dosage Form and Route: Extended release tablets

Application Type/Number: NDA 20-4150

Applicant: Alembic Pharmaceuticals Limited

1 INTRODUCTION

On February 29, 2012, Alembic Pharmaceuticals Limited submitted for the Agency's review an original NDA Application for Desvenlafaxine Extended Release Tablets indicated for the treatment of major depressive disorder. On November 20, 2012 the Division of Psychiatry Products (DPP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG).

This review is written in response to a request by DPP for DMPP to review the Applicant's proposed Medication Guide (MG) for Desvenlafaxine Extended Release Tablets.

2 MATERIAL REVIEWED

- Draft Desvenlafaxine MG, received on February 29, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on November 20, 2012.
- Draft Desvenlafaxine Prescribing Information (PI) received on February 29, 2012 revised by the Review Division throughout the review cycle, and received by DMPP on November 20, 2012.
- Approved PRISTIQ (desvenlafaxine) comparator labeling dated March 7, 2012.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

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

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
11/30/2012

MELISSA I HULETT
11/30/2012

LASHAWN M GRIFFITHS
11/30/2012

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

Label, Labeling and Packaging Review

Date: November 2, 2012

Reviewer: Loretta Holmes, BSN, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, PharmD, BCPS
Division of Medication Error Prevention and Analysis

Associate Director: Scott Dallas, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Desvenlafaxine Extended-release Tablets
50 mg and 100 mg

Application Type/Number: NDA 204150

Applicant: Alembic Pharmaceuticals Limited

OSE RCM #: 2012-1546

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1 INTRODUCTION

This review evaluates the proposed container labels, carton and insert labeling for Desvenlafaxine (Base) Extended-release Tablets, NDA 204150, for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

NDA 204150 for Desvenlafaxine Extended-release Tablets is a 505(b)(2) application. The reference listed drug (RLD) is Pristiq Extended-release Tablets (NDA 21992) which was approved on February 29, 2008.

1.2 PRODUCT INFORMATION

The following product information was provided in the February 29, 2012 submission.

- Active Ingredient: Desvenlafaxine (Base)
- Indication of Use: Treatment of major depressive disorder (MDD)
- Route of Administration: Oral
- Dosage Form: Extended-release Tablets
- Strengths: 50 mg and 100 mg
- Dose and Frequency of Administration: 50 mg once daily, with or without food. Tablets should be taken whole; do not divide, crush, chew, or dissolve.
Moderate renal impairment: 50 mg per day
Severe renal impairment and end-stage renal disease: 50 mg every other day
Hepatic impairment: (b) (4)
- How Supplied: Bottles containing 14, 30, 90, 100, or 1000 tablets; Cartons containing 10 blister cards with 10 blisters per card. Each blister contains one tablet.
- Storage: Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F-86°F)

Container and Closure System: HDPE bottles; all bottles (except the 1000-count bottles) have (b) (4)

2 METHODS AND MATERIALS REVIEWED

Pristiq, the RLD for this NDA, is a currently marketed product. Thus, DMEPA searched the FDA Adverse Event Reporting System (AERS) database for Pristiq medication error reports that may inform this review. We also reviewed the proposed labels and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA AERS database using the strategy listed in Table 1.

Table 1: AERS Search Strategy	
Date	03/30/11 (date of our most recent Pristiq review) to 08/08/12
Drug Names	<u>Active ingredient</u> : Desvenlafaxine; Desvenlafaxine Succinate; Desvenlafaxine Anhydrous <u>Tradename</u> : Pristiq <u>Verbatim Term</u> : Desvenlaf%; Prist%
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues (HLT) Product Label Issues (HLT) Product Quality Issues NEC (HLT)

The AERS database search identified 222 reports. Each report was reviewed for relevancy and duplication. After individual review, 68 reports were not included in the final analysis for the following reasons:

- Accidental dose omission
- Drug use without a prescription
- Wrong frequency (error not attributed to the labels or labeling)
- Adverse drug event not related to medication error
- Intentional overdose
- Duplicate report
- Product complaint not related to the labels or labeling

2.2 LABELS AND LABELING

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the following Desvenlafaxine Extended-release Tablets labels and labeling submitted by the Applicant on February 29, 2012:

- Container Labels (Appendix C)
- Blister Labels (Appendix D)
- Carton Labeling for Blisters (Appendix E)
- Insert Labeling (no image)
- Medication Guide (no image)

Additionally, we compared the Desvenlafaxine proposed labels and labeling against the currently marketed Pristiq labels (Appendices F, G, and H) and insert labeling to identify any potential safety issues.

2.3 PREVIOUSLY COMPLETED REVIEWS

DMEPA most recently reviewed Pristiq (NDA (b) (4)) in the following reviews:

- OSE Review 2011-207 (Label and Labeling Review), dated April 19, 2011
- OSE Review 2009-776 (915 Review), dated April 26, 2010

We looked at these reviews to determine if there were recommendations that were not yet implemented or addressed that would also be applicable to this review and should be included in our recommendations.

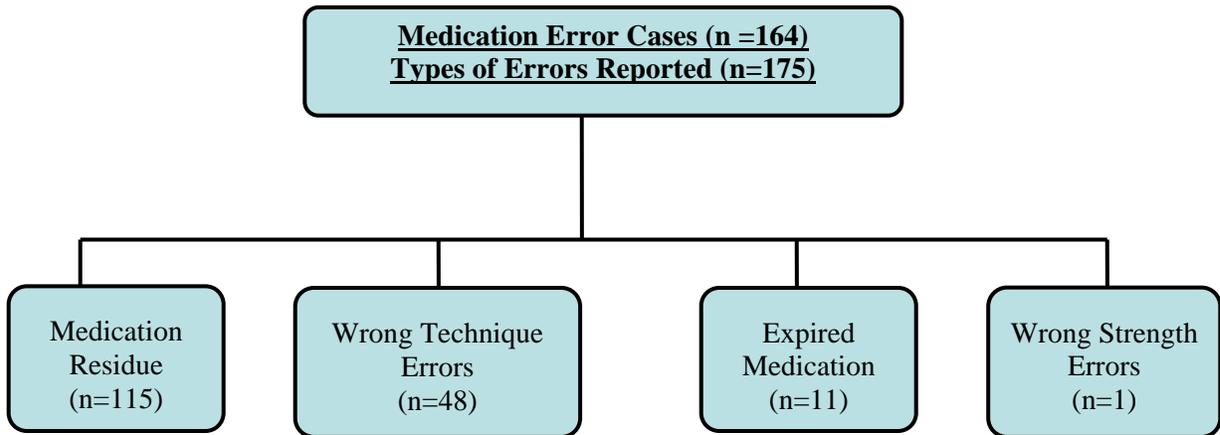
3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our AERS search and the risk assessment of the labels and labeling.

3.1 MEDICATION ERROR CASES

Following exclusions as described in Section 2.1, one hundred sixty-four (n=164) Pristiq medication error cases remained for our detailed analysis. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter². Figure 1 provides a stratification of the number of errors (by type of error) identified in the 164 cases reviewed. The types of errors (n=175) exceeds the number of cases analyzed because some cases reported more than one type of error. Appendix I provides a listing of all ISR numbers for the cases summarized in this review.

Figure 1: Pristiq medication errors (n =164) categorized by type of error



² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>. Accessed June 1, 2011.

3.1.1 Medication Residue (n=115)

- In nearly all cases, concern that the Pristiq tablet was not being absorbed was expressed.
- In eight cases patients reported seeing the Pristiq tablet in their stool and as a result manipulated the tablets (e.g., piercing, breaking, or chewing) in order to get the tablet to dissolve after administered.
- In seven cases, it was reported that the medication was not working.
- In five cases, the medication was discontinued by the patient or the prescriber.
- In two cases the dose was increased.
- In the remaining cases the outcome was not reported or there were singular reports of not feeling well, no medication level in blood, medication seems to be helping, and no adverse event.

Although reports of medication residue are not considered medication errors, we identified 115 reports that related to Pristiq tablets appearing in stool. Additionally, some of the reporters were healthcare professionals who did not appear to be aware that the inert matrix tablet may appear in stool and the active medication has already been absorbed by the time the patient sees the inert matrix tablet. As a result of the matrix appearing in stool, there were instances reported where the tablets were manipulated, the dose increased, or the medication discontinued.

Our review of the insert labeling noted that Section 17.17 *Residual Inert Matrix Tablet* of the insert labeling of both products and the section entitled “*How should I take Pristiq*” and “*How should I take desvenlafaxine*” in the Medication Guide (MG) of Pristiq and Desvenlafaxine Extended-release Tablets, respectively, state the inert matrix or tablet may appear in stool. Although this information is found in these two locations, it appears that healthcare providers and patients are not well aware of the issue. Therefore, it may be helpful to consider giving it more prominence by including the information in the *Dosage and Administration* section of the insert labeling.

3.1.2 Wrong Technique (n=48)

- Twenty cases described patients who manipulated the tablets (e.g., cutting, breaking, chewing) on their own in order to take a different dose for reasons such as dose too high, cannot afford the medication, wired jaw, and suffering an adverse reaction/event.
- In 13 cases, the prescriber instructed the patient to cut or break the tablet or it appeared that it was prescribed in this manner and in most of these cases the patient was being tapered down to a lower dose.
- In 8 cases the patients saw the tablet matrix in their stool (see Section 3.1.1) and manipulated the tablets to help ensure they would be absorbed.
- In 7 cases it was not clear why the tablets were manipulated.

- Some of the adverse reactions/events reported in these cases included dizziness, lethargy, drowsiness, nausea, weakness, headache, and in one case, chest pain and shortness of breath although the patient in this one case had a previous history of cardiovascular disease.

Pristiq is an extended-release tablet. The name does not contain a modifier to indicate that it is an extended-release product but there are no immediate-release desvenlafaxine products from which it needs to be distinguished so it is difficult to quantify the impact this has on the potential for wrong technique errors to occur with this product. The Applicant for Desvenlafaxine Extended-release Tablets has not proposed a proprietary name. Therefore, the dosage form “extended-release” will have to convey to practitioners that the tablets (which are not scored) should be swallowed whole and not manipulated.

Our review of the insert labeling for information regarding administration of the tablets noted the *Dosage and Administration* section of the insert labeling and the “*How Should I Take...*” section of the Medication Guide of both products state that the tablets should be swallowed whole and should not be divided, crushed, chewed or dissolved.

Additionally, our review of these wrong technique cases noted that in many cases the tablets were manipulated in an attempt to reduce the dose during tapering. Healthcare providers desiring to taper patients off the drug appear to have limited options because these are extended-release tablets and they are only available in 50 mg and 100 mg strengths. Therefore, patients who require 75 mg or 25 mg or less do not have that dosing option without cutting or breaking the tablet, which is not recommended. Our review of the insert labeling for instructions on how to taper the medication noted that it states “When discontinuing therapy, gradual dose reduction is recommended whenever possible to minimize discontinuation symptoms.” However, there are no instructions provided on how to reduce the dose. Per DPP, there is no data currently available to support a specific regimen for discontinuing therapy; therefore, at this time we cannot add information on how to properly reduce the dose of this product for discontinuation.

3.1.3 Expired Medication (n=11)

- Four cases reported the patients were using expired Pristiq samples. One of these four cases stated the physician dispensed expired samples and the adverse event/reaction reported in this case was stomach ache.
- One case stated the patient was “given” expired Pristiq. No explanation was provided.
- The remaining cases do not describe the packaging, a dispensing error, or state why expired medication was used by the patient. The adverse events/drug reactions reported include drowsiness, lightheadedness and dizziness.

Although these reports did not describe the underlying cause of the error, we want to ensure that the expiration dates are clearly displayed on the proposed container labels and carton labeling and not presented in a confusing manner (e.g., day/month/year format) in order to help prevent dispensing or using expired medication. We also acknowledge that it is the healthcare provider’s and patient’s responsibility to check the expiration date

prior to dispensing or using the medication. Our review of the proposed labels and labeling indicate that the space allowed for the expiration date appears to be adequate enough to print the date in a font size that will provide adequate visibility. However, the date format is not shown. The format used should be clearly presented.

3.1.4 Wrong Strength (n=1)

- In this case, a patient was prescribed Pristiq 50 mg tablets but received 100 mg instead. The patient did not realize the error initially, took the medication and complained of depression, forgetfulness and confusion. When she realized the error she cut the tablet in half to get the correct dose. The case did not describe how the error occurred.

Our review of the current Pristiq container labels noted the strengths appear to be adequately differentiated. Our review of the Desvenlafaxine Extended-release Tablets container labels noted the strengths do not appear to be well differentiated from one another.

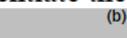
3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

DMEPA identified the following deficiencies in the container labels, carton labeling and insert labeling.

A. General Deficiency

-  (b) (4)

B. Container Labels and Carton Labeling

- A  (b) (4) is used to differentiate the 50 mg strength from the 100 mg strength tablets. However, a  (b) (4) is also used to highlight the strength of Pristiq 100 mg tablets (refer to Appendix F). We note the label of this product may be considered to be different than the Pristiq label, but these containers may appear side by side on a pharmacy shelf. This similarity in colors may lead to confusion between these two product strengths. Therefore, the sponsor should consider the use of a different color for the 50 mg strength, one that does not overlap with any of the colors used for Pristiq strength differentiation, which may help to minimize the potential for confusion.
- Although the two product strengths are outlined in color, they lack adequate differentiation.
- The format to be used for the presentation of the expiration date is not on the container labels or carton labeling.
- The medication guide statement lacks prominence. The use of a bold font will help to increase the prominence of the statement.

C. Blister Labels

- See Comment B, first and second bullet.

D. Insert Labeling

- Error-prone symbols are used in the Dosage and Administration section of the insert labeling.
- Information regarding the residual inert matrix tablet appearing in stool is not prominent in the insert labeling.

We provide recommendations in Section 5 to correct these deficiencies and minimize the risk of medication errors. We did not identify any safety concerns with the Medication Guide (MG) and, therefore, have no recommendations for the MG.

4 CONCLUSIONS

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

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Comments to the Division

1. Insert Labeling, Section 2: Dosage and Administration

- a. In the section *Patients with Renal Impairment*, the error-prone symbol “<” (less than) is used (i.e., “<30 mL/min”). As part of a national campaign to reduce medication errors related to error-prone medical abbreviations, symbols and dose designations, the FDA agreed not to approve labels and labeling that included the use of error prone abbreviations, symbols or dose designations. Thus, we request you revise the statement to read “less than 30 mL/min”.
- b. Information regarding the residual inert matrix tablet appearing in stool is not prominent in the insert labeling. Consider adding this information to the *Dosage and Administration* section of the insert labeling to increase the prominence and visibility of the information in order to help increase healthcare providers’ awareness of the issue.

B. General Comment for All Labels and Labeling

(b) (4)

C. Container Labels and Carton Labeling

1. A (b) (4) is used to differentiate the 50 mg strength from the 100 mg strength tablets. However, a (b) (4) is also used to highlight the strength of Pristiq 100 mg tablets. We note the label of this product may be considered to be different than the Pristiq label, but these containers may appear side by side on a pharmacy shelf. This similarity in colors may lead to confusion

between these two product strengths. Therefore, consider the use of a different color for the 50 mg strength; one that does not overlap with any of the colors used for Pristiq strength differentiation. This may help to minimize the potential for confusion.

2. Although the two product strengths are outlined in color, they lack adequate differentiation. Consider expanding the color with the use of a color block as a background for the statement of strength in order to increase prominence and improve differentiation between the product strengths. Ensure adequate contrast between the background colors and the text font color to enhance the readability.
3. Ensure the expiration date format is presented in a manner that is clearly understood (e.g., Month/Day/Year).
4. The medication guide statement lacks prominence. Use a bold font for the statement in order to increase its prominence.

D. Blister Labels

See Comments C.1 and C.2, above.

If you have further questions or need clarifications, please contact Sandra Rimmel, Project Manager, at 301-796-2445.

APPENDICES

APPENDIX A: REFERENCES

Miller, Cathy. Pristiq (Desvenlafaxine) Extended-release Tablets (NDA (b) (4) Label and Labeling Review, OSE Review 2011-207, dated April 19, 2011.

APPENDIX B: DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

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Appendix I: ISR numbers of cases discussed in this review

ISR Numbers					
7420575	7418845	8223574	7538724	7706969	7482188
7682194	7482220	8369959	7701882	8557692	8026828
8538384	7738709	8351157	8556888	7670087	7498794
7397688	7596191	7671530	7434140	7718413	8492308
7434356	7532119	7815920	7568896	8011549	7464401
7880197	7582497	8245968	7919462	8196347	7628425
8094262	7547496	7418866	7785349	8488691	7522795
7634112	7691889	7501954	7921245	7496807	7448630
7532114	7610373	8265529	8118043	7676385	7422020
8196377	7864496	8353987	8041278	7681141	7482122
8175908	7894165	8212708	8104856	7936832	8420780
8394701	7958207	8286196	8204323	7755151	8577260
8207267	8011562	7439302	7441620	7966862	8559778
8506637	8355744	7676325	7752163	8157422	7383083
8549161	8226008	7587987	7565887	7547512	
8524473	8196268	7929898	7670081	7645580	
7388077	8170087	7761379	7634157	7956385	
7384527	8448277	7738717	7959516	7946703	
7587964	7441595	8549761	7885369	8094329	
7588042	7461491	7406985	7776240	8140382	
7565899	7505251	7572021	8266970	8329067	
7550073	7670073	8572991	8207237	7427293	
7723480	7617483	7801794	8535039	7460811	
7758408	7950785	7946708	7733013	7410794	
8424913	7780775	7908777	7639026	7597815	
8372789	7785360	7420400	7388066	7403167	
8339107	7794818	7459349	7456062	8423637	
8397173	7729210	8135773	8471154	8369017	
8535666	8306827	7561749	7456093	7682220	
7383071	8445102	8231056	7785345	8320645	

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/s/

LORETTA HOLMES
11/02/2012

SCOTT M DALLAS on behalf of IRENE Z CHAN
11/04/2012

SCOTT M DALLAS
11/04/2012

MEMORANDUM

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

DATE: October 4, 2012

TO: Thomas P. Laughren M.D.
Director,
Division of Psychiatry Products

FROM: Arindam Dasgupta Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

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

and

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIRs Covering NDA 204150, Desvenlafaxine
(Base) Extended-Release 50 mg and 100 mg Tablets
sponsored by ALEMBIC Pharmaceuticals Limited India

At the request of the Division of Psychiatry Products (DPP), the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted inspections of the clinical and analytical portions of the following bioequivalence studies:

Study Number-1: 413-11

Study Title: An open label randomized two-treatment three period three sequence single oral dose, crossover study to evaluate bioequivalence of Desvenlafaxine (base) extended release tablets 100 mg [Reference: PRISTIQ® (Desvenlafaxine) Extended-Release Tablets 100 mg, Wyeth Pharmaceuticals Inc., USA.] under fasting conditions and evaluation of food effect by relative bioavailability of Desvenlafaxine (base)

extended release tablets 100 mg under fasting and fed conditions in healthy adult human subjects

Study Number-2: 455-11

Study Title: An open label balanced two-treatment two period two sequence single dose oral crossover bioequivalence study of Desvenlafaxine (base) Extended Release Tablets 50 mg [Reference: PRISTIQ® (Desvenlafaxine) Extended-Release Tablets 50 mg, Wyeth Pharmaceuticals Inc., USA.] in healthy adult human subjects under fasting conditions

The audit of the clinical and analytical portions of the studies were conducted at [REDACTED] (b) (4)

[REDACTED] by ORA Investigator Daniel Aisen and OSI Scientist Arindam Dasgupta) and Navi Mumbai, India (conducted 09/24-27/2012 by ORA Investigator Daniel Aisen). The audits included a thorough review of study records, examination of facilities, equipment, interviews and discussions with the firms' management and staff.

Following the inspection at the clinical and analytical sites, no objectionable conditions were observed and Form FDA-483s were not issued.

Conclusions:

Following the above inspections, the DBGLPC reviewer recommends that the clinical and bioanalytical portions of studies 413-11 and 415-11 be accepted for further agency review.

Arindam Dasgupta Ph.D.
Bioequivalence Branch, DBGLPC, OSI

Final Classification:

NAI: Clinical Site #1 and Analytical Site

(b) (4)
FEI: (b) (4)

NAI: Clinical Site #2

Lambda Therapeutic Research Ltd., Navi Mumbai, India
FEI: 3006005701

CC:

CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Dejernett
DBGLPC/BEB/Haidar/Dasgupta
OND/ODEI/DPP/Laughren/Ansah
OCP/DCP1/Zhu/Kumi
ORA/SE-FO/NOL-DO/NOL-NB/KNOX-TN/Aisen
Draft: AD 10/04/2012
Edit: SHH 10/04/2012
BE File # 6329; O:\BE\EIRCOVER\204150ale.des.doc
ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/Electronic Archive/BEB
FACTS: 1399693

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

/s/

ARINDAM DASGUPTA
10/09/2012

SAM H HAIDAR
10/09/2012

WILLIAM H TAYLOR
10/09/2012

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

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

Application: NDA 204150

Application Type: New NDA

Name of Drug: Desvenlafaxine (Base) Extended-Release Tablets 50 mg and 100 mg

Applicant: Alembic Pharmaceuticals Limited

Submission Date: 02/29/2012

Receipt Date: 02/29/2012

1.0 Regulatory History and Applicant's Main Proposals

This is a new 505(b)(2) application which provides for 50mg and 100mg strength of Desvenlafaxine (Base) Extended-Release tablets proposed for treatment of Major Depressive Disorder (MDD).

2.0 Review of the Prescribing Information (PI)

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

3.0 Conclusions/Recommendations

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

In addition, the following labeling issues were identified:

1. Sponsor had included a header (capturing their logo etc.) and a footer in their proposed labeling.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by August 6, 1012. The resubmitted PI will be used for further labeling review.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

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

Highlights (HL)

GENERAL FORMAT

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

Comment:

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

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

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *HL must be less than or equal to one-half page. Or request a waiver.*

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

Comment:

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

Comment:

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

Selected Requirements of Prescribing Information (SRPI)

Comment:

YES

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

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

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

Comment:

YES

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

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

Comment:

Highlights Limitation Statement

NO

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

Comment: *The HL limitation statement must be on the line immediately beneath the HL heading.*

Product Title

YES

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

Comment:

Initial U.S. Approval

NO

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

Selected Requirements of Prescribing Information (SRPI)

Comment: *This statement must be placed immediately beneath the product title.*

Boxed Warning

YES

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

Comment:

NO

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

Comment: *Heading needs to be centered.*

NO

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

Comment: *This statement needs to be centered immediately beneath the heading.*

YES

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

Comment:

YES

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

Comment:

Recent Major Changes (RMC)

N/A

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

Comment:

N/A

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

Comment:

N/A

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

Comment:

N/A

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

Comment:

Indications and Usage

YES

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

Comment:

Selected Requirements of Prescribing Information (SRPI)

Dosage Forms and Strengths

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

Comment:

Contraindications

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

Comment:

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

Comment:

Adverse Reactions

- NO** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: *Statement is missing sponsor's portion (i.e., manufacturer's name and US phone #).*

Patient Counseling Information Statement

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

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

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

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

Comment: *Use the following; "See 17 for PATIENT COUNSELING INFORMATION and Medication Guide" without the quotation marks.*

Revision Date

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

Comment: *Please insert a place holder date presented as MM/YYYY or Month/Year to be replaced by the month/year of the the application approval.*

Contents: Table of Contents (TOC)

GENERAL FORMAT

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

Comment:

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

Selected Requirements of Prescribing Information (SRPI)

Comment:

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

Comment:

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

Comment:

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

Comment:

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

Comment:

- NO** 34. When a section or subsection is omitted, the numbering does not change.

Comment: See FPI below regarding Section 12

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

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

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

Comment:

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

Comment:

- NO** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

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

Selected Requirements of Prescribing Information (SRPI)

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

Comment: Note for e.g., 12.4 and 12.5 should be Microbiology and Pharmacogenomics, respectively, by guidance. If omitted the numbering does not change.

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

Comment:

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

Comment:

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

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

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

Comment:

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

Comment:

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

Comment:

Selected Requirements of Prescribing Information (SRPI)

Contraindications

- YES** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

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

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

Comment:

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

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

Comment:

Patient Counseling Information

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

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

Comment: *Include the following statement at the beginning of Section 17; “See FDA-approved patient labeling (Medication Guide)”.*

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

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
07/17/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 204150 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: Desvenlafaxine (Base) Extended-Release Dosage Form: Tablets Strengths: 50 mg and 100 mg		
Applicant: Alembic Pharmaceuticals Limited Agent for Applicant (if applicable): Hari Nagaradona, Ph.D. , Director, Regulatory Affairs; INC Research, LLC , 7361 Calhoun Place, Suite 500, Rockville, MD 20855		
Date of Application: February 29, 2012 Date of Receipt: February 29, 2012 Date clock started after UN:		
PDUFA Goal Date: December 29, 2012	Action Goal Date (if different): December 28, 2012	
Filing Date: April 29, 2012	Date of Filing Meeting: April 23, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 2		
Proposed indication(s)/Proposed change(s): Major Depressive Disorder (MDD)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): IND 113100				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	✓			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	✓			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	✓			“This is a 505(b)(2) application” has been added in DARRTS under application comments.
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		✓		AIP list checked on 04/23/12.
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	✓			A 2 nd form was received on 3/12/12 for the residual \$40.

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>✓</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>✓</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>✓</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td>NDA 021992</td> <td>PRISTIQ</td> <td>NCE</td> <td>03/01/13</td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	NDA 021992	PRISTIQ	NCE	03/01/13									<p>✓</p>			<p>New Chemical Entity (exclusivity expires March 1, 2013)</p>
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
NDA 021992	PRISTIQ	NCE	03/01/13																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the <i>Orphan Drug Designations and Approvals</i> list at: http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>✓</p>																		

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

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

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	✓			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	✓			Annexure I & II with establishment info attached.
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?		✓		Form FDA 3542a was not used but collated info from orange book site was provided.
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	✓			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	✓			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment

<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>		✓		
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			✓	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>		✓		
Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	✓			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?		✓		
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>		✓		
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>			✓	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		✓		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>			✓	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>		✓		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	✓			
Is the PI submitted in PLR format? ⁴	✓			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?		✓		Consult drafted to be sent asap.
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)		✓		Consult drafted to be sent asap.
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?		✓		Consult drafted to be sent asap.
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	✓			
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	✓			
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	✓			
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			✓	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>			✓	
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):		✓		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>		✓		
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		✓		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 04/29/12

NDA #: 204150

PROPRIETARY NAME:

ESTABLISHED/PROPER NAME: Desvenlafaxine (Base) Extended-Release

DOSAGE FORM/STRENGTH: 50mg and 100mg Tablets

APPLICANT: Alembic Pharmaceuticals Limited

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

BACKGROUND: Filing meeting for this new 505(b)(2) NDA for Desvenlafaxine (Base) Extended-R proposed for treatment of MDD. The RLD is PRISTIQ (i.e., NDA 021992) and the submission also references IND 113100.

REVIEW TEAM:

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

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

Bioresearch Monitoring (OSI)	Reviewer:	Sripal Mada, M.D.	Y
	TL:	Sam Haidar, M.D.	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees	Mitchell Mathis, M.D. (DDD for DPP)		Y
	Thomas Laughren, M.D. (DD for DPP)		Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: <i>eCTD format.</i></p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: <i>Clinical Pharm (Bio-equivalence) study sites inspections requested through OSI.</i></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p>If no, for an original NME or BLA application, include the reason. For example:</p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments: <i>BE study sites inspections requested.</i></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments: <i>Relies on RLD with no new PT information provided; involvement will depend on CMC.</i></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments: Categorical Exclusion requested per CMC initial assessment dated 03/07/12.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Thomas Laughren, M.D., Division Director, DPP	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
	Receipt Date: 02/29/12 Day 45: 04/14/12 Day 60: 04/29/12 Day 74: 05/13/12 Mid-Cycle: 07/29/12 Month 8: 10/29/12 PDUFA Date: 12/29/12
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <i>But ONDQA/ Biopharmaceutics reviewer's comments and Information Request/ Questions are to be conveyed in 74-day letter.</i> <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by

	Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter (<i>Note: Labeling issues will be sent separately via an Advice Letter</i>)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Kofi Ansah, Pharm.D.

04/19/2012

Regulatory Project Manager

Date

Paul David, R.Ph.

05/10/2012

Chief, Project Management Staff

Date

Appendix A (NDA and NDA Supplements only)

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

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

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

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

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

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

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

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

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

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

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

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
05/11/2012

MEMORANDUM

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

DATE: April 11, 2012

TO: Associate Director
International Operations Drug Group
Division of Foreign Field Investigations

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

SUBJECT: FY 2012, **High Priority CDER User Fee NDA Pre-Approval
Data Validation Inspection**, Bioresearch Monitoring,
Human Drugs, CP 7348.001

RE: NDA 204-150
DRUG: Desvenlafaxine (Base) Extended-Release 50 mg
and 100 mg Tablets
SPONSOR: ALEMBIC Pharmaceuticals, Limited, India

This memo requests inspections of the clinical and analytical portions of the following bioequivalence studies. **Please provide a minimum period of advance notice to the inspected facility. The site and sponsor should not be informed in advance of the application, drug names, the studies to be inspected, or the focus of the inspection. The information will be provided to the sites at the inspection opening meeting. At the request of the Review Division, these inspections should be completed before August 29, 2012.**

Study Number-1: 413-11

Study Title: "An open label randomized two-treatment three period three sequence single oral dose, crossover study to evaluate bioequivalence of Desvenlafaxine (base) extended release tablets 100 mg under fasting conditions and evaluation of food effect by relative bioavailability of Desvenlafaxine (base) extended release tablets 100 mg under fasting and fed conditions in healthy adult human subjects"

Clinical Site: Lambda Therapeutic Research Ltd.
7th Floor, The Great Eastern Summit-A,
Plot No. 56, Sector-15, CBD
Belapur, Navi Mumbai- 400 614, India
TEL: +91-22-27562220/27562224
FAX: +91-22-27562231

Administrative

Contact: Sunil R. Budhkar, Associate VP, QA
Email: budhkar@lambda-cro.com

Study Number-2: 455-11

Study Title: "An open label balanced two-treatment two period
two sequence single dose oral crossover
bioequivalence study of Desvenlafaxine (base)
Extended Release Tablets 50 mg in healthy adult
human subjects under fasting conditions"

Clinical Site: Lambda Therapeutic Research Ltd.
Plot No. 38, Near Silver Oak Club
S.G. Highway, Gota, Ahmedabad - 380 061, India
TEL: +91-79-40202701
FAX: +91-79-40202021

Administrative

Contact: Sunil R. Budhkar, Associate VP, QA
Email: budhkar@lambda-cro.com

Please check the batch numbers of the test and reference formulations used in the studies with the descriptions in documents submitted to the Agency. The sites conducting the above bioequivalence studies are responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided for subject dosing. Please confirm whether reserve samples were retained as required by 21 CFR 320.38 and 320.63. Samples of the test and reference drug formulations should be collected and mailed to the Division of Drug Analysis, St. Louis, MO, for screening. Please obtain a written assurance from the clinical investigator (CI) or the responsible person at the CI's site that the reserve samples are representative of those used in their specific bioequivalence studies, and that they were stored under conditions specified in accompanying records. Document the CI's signed and dated statement (21 CFR 320.38(d, e, g) on the facility's letterhead, or Form FDA 463a,

Affidavit. Include the written statement in Sample Collection Report (CR) as a DOC sample.

Please have the records of all subjects in the study audited. The subject records in the submission should be compared to the original documents at the firm. The protocol and actual study conduct, IRB approval, drug accountability, as well as the source documents and case report forms for dosing, clinical and laboratory evaluations related to the primary endpoint, adverse events, concomitant medications, inclusion/exclusion criteria and number of evaluable subjects should be examined. The SOPs for the various procedures need to be scrutinized. Dosing logs must be checked to confirm that correct drug products were administered to the subjects. Please verify that the subjects were compliant with the trial regimen and confirm the presence of 100% of the signed and dated consent forms, and comment on this informed consent check in the EIR. In addition to the standard investigation involving source documents, the correspondence files should be examined for sponsor-requested changes, if any, to the study data or report. Relevant exhibits should be collected for all findings, including discussion items at closeout, to assess the impact of the findings. Also, please determine if the subjects met the protocol inclusion/exclusion criteria.

Analytical Site:

[REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Analytical Investigator:

[REDACTED] (b) (4)
[REDACTED]

Analytical Method: LC-MS/MS

All pertinent items related to the analytical method for the measurement of desvenlafaxine concentrations should be examined and the sponsor's data should be audited. The analytical data provided in the NDA submission should be compared with the original documents at the firm. The method validation and the actual assay of the subject plasma samples, as well as the variability between and within runs, QC, stability, the number of repeat assays of the subject plasma samples, and the reason

for such repetitions, if any, should be examined. The SOP(s) for repeat assays and other relevant procedures must also be scrutinized. In addition to the standard investigation involving the source documents, the files of communication between the analytical site and the sponsor should be examined for their content.

Following identification of the investigator background material will be forwarded directly. **A scientist from DBGC, OSI with specialized knowledge may participate in the analytical inspection to provide scientific and technical expertise.** Please contact DBGC upon receipt of this assignment to arrange scheduling of the inspection.

Headquarters Contact Person: Sripal R. Mada, Ph.D.
(301) 796-4112

DFFI Contact Person: Arindam Dasgupta, Ph.D.
(301) 796-3326

CC:

CDER OSI PM TRACK

OSI/DBGC/BB/Haidar/Skelly/Mada/Dasgupta/Dejernet

ODE1/DPP/Ansah/Laughren

OCP/DCP1/Zhu/Kumi

HFC-130/ORA HQ DFFI IOB BIMO

Draft: SRM 04/09/2012

Edit: MFS 04/09/2012

DSI: 6329; O:\BE\assigns\bio204150.doc

FACTS: 1399693

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

/s/

SRIPAL R MADA
04/11/2012

MICHAEL F SKELLY
04/11/2012
Skelly signing on behalf of Dr. Haidar