

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204150Orig1s000

CHEMISTRY REVIEW(S)

**NDA 204-150 (Desvenlafaxine Extended-Release
Tablets (50 mg and 100 mg))**

Alembic Pharmaceuticals Limited

Mohan K. Sapru, Ph.D.

*Office of New Drug Quality Assessment
Division I/Branch I*

Reviewed for the Division of Psychiatry Products, HFD-130.

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Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: The application was submitted under Section 505(b)(2) of the Federal Food Drug and Cosmetic Act and 21 CFR §314.54.
10. PHARMACOL. CATEGORY/INDICATION: A serotonin-norepinephrine reuptake inhibitor (SNRI) for the treatment of major depressive disorder (MDD).
11. DOSAGE FORM: Extended-Release Tablets.
12. STRENGTH/POTENCY: 50 mg and 100 mg.
13. ROUTE OF ADMINISTRATION: Oral.
14. Rx/OTC DISPENSED: X Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS Product – Form Completed.
 X Not a SPOTS Product.

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

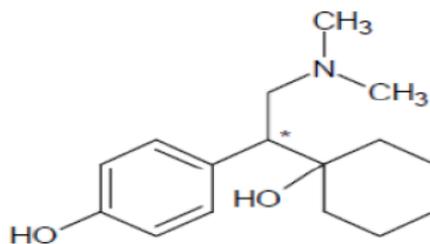
Chemical Name: (\pm)-1-[2-(dimethylamino)-1-(4-phenol)ethyl]-cyclohexanol
or *RS*-4-[2-dimethylamino-1-(1-hydroxycyclohexyl)ethyl]phenol

Molecular Formula: C₁₆H₂₅NO₂

Molecular Weight: 263.38

CAS No.: 93413-62-8

Structure:



* Chiral Centre

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMF(s):

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED
25527	II	Alembic Pharmaceuticals Limited	O-Desmethyl Venlafaxine Drug Substance	1	Adequate	09-Nov-2012
SN-008 Amend ment		Alembic Pharmaceutical s Limited	O-Desmethyl Venlafaxine Drug Substance	1	Adequate	09-Nov-2012

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application; therefore, the DMF did not need to be reviewed).

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	113,100	Treatment of major depressive disorder.

18. STATUS:

Chemistry Review Data Sheet

ONDQA:

CONSULTS/ CMC-RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	ACCEPTABLE	24-Sept-2012	R. Safaai-Jazi
Methods Validation	Not requested. The methods are conventional and don't qualify for internal validation by the FDA laboratories.	20-Aug-2012	Mohan K. Sapru, Ph.D.
Environmental Assessment	Categorical Exclusion	20-Aug-2012	Mohan K. Sapru, Ph.D.
Biopharmaceutics	ACCEPTABLE	25-Nov-2012	John Duan, Ph.D.
Microbiology	N/A	N/A	N/A

Executive Summary Section

The Executive Summary (NDA 204150)**I. Recommendations.****A. Recommendation and Conclusion on Approvability.**

From the chemistry, manufacturing and controls (CMC) perspective, this new drug application (NDA 204-150) for desvenlafaxine extended-release tablets (50 mg and 100 mg) is recommended for approval.

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

Not applicable at this stage.

II. Summary of Chemistry Assessments.**A. Description of the Drug Substance (s) and Drug Product (s)**

Drug Substance: The drug substance desvenlafaxine (O-desmethyl venlafaxine) is a white to off-white crystalline powder, and functions as a serotonin-norepinephrine reuptake inhibitor (SNRI). It has one chiral carbon atom in its structure and exists as (+) and (-) enantiomers. Alembic Pharmaceuticals Limited commercially manufactures a racemic mixture of desvenlafaxine (O-desmethyl venlafaxine). (b) (4) which is used to manufacture the drug product. Regarding drug substance specification, identification is appropriately carried out both by HPLC and infrared spectroscopy. The acceptance limits for residual solvents have been appropriately set in compliance with ICH Q3C limits. Heavy metals are appropriately controlled at levels of not-more-than (NMT) (b) (4) ppm. Furthermore, testing for optical rotation is a part of in-house specification, and all the drug substance batches will be routinely analyzed for optical rotation. HPLC-based methods for determination of desvenlafaxine and related substances, and GC assays for residual solvents have been adequately validated, as per ICH recommendations, for specificity, linearity, accuracy, method precision, ruggedness, and stability-indicating characteristics involving forced degradation. Certificates of analysis for 10 batches of drug substance have been provided. The levels of individual impurities i.e., Impurity (b) (4) and Impurity (b) (4) are either below the quantitation limit or \leq (b) (4) in the tested drug substance batches. Furthermore, in all the tested batches, the residual solvents are present at levels which are below the ICH Q3C limits. For CMC details concerning the drug substance characterization, manufacturing process, process controls, controls of critical steps, process validation, manufacturing process development, and impurity profile, container closure system, and stability, the applicant has referred to the DMF # 25527 (Type II DMF), which has been reviewed and found adequate (refer to DMF # 25527 review by Dr. Mohan Sapru, dated 09-November-2012).

Executive Summary Section

Drug Product: The proposed drug product consists of desvenlafaxine (base) extended-release tablets for oral administration. The clinical formulation will be available in 50 mg and 100 mg tablet strengths. Desvenlafaxine (brand name: Pristiq®), also known as O-desmethylvenlafaxine, is an antidepressant of the serotonin-norepinephrine reuptake inhibitor class, which has been originally developed and marketed by Wyeth (now part of Pfizer). Unlike the innovator drug Pristiq®, which uses the salt form of desvenlafaxine i.e., desvenlafaxine succinate, the applicant has proposed to use desvenlafaxine (base) in the clinical formulation. (b) (4)

The inactive ingredients used in the formulation are commonly used excipients, and no interaction amongst these excipients has been reported. Magnesium stearate, which is a widely used excipient in oral solid dosage formulations, (b) (4). The manufacturing process (b) (4)

The applicant has provided master production batch records. The quantity of each excipient used in the proposed drug product is below the maximum approved potency for oral tablets listed in the FDA Inactive Ingredient Guide for Approval Drug Products (IIG Database). Desvenlafaxine (base) extended-release tablets contain iron oxide red (50 mg and 100 mg tablets) and iron oxide black (100 mg tablets). It is noted that total daily amount of elemental iron in drug product taking maximum recommended daily dose i.e., 100 mg is (b) (4) which complies with the requirements of 21 CFR 73.1200. Based on the drug-excipient compatibility studies, no significant incompatibility issue has been identified with the excipients used in the clinical formulation. The proposed extended release formulation of desvenlafaxine base has been designed to achieve similarity in terms of dissolution and bio-equivalence with reference product Pristiq®. The critical process parameters identified by the applicant include (b) (4)

The identified critical process parameters are monitored and controlled by analyzing the stage sample. Testing has been done at all the critical stages to evaluate the process parameters at scale up level. Specifically, different trials have been undertaken to (b) (4)

The manufacturing process parameters listed in these master production records replicate the procedural steps, and process parameters. No overage of desvenlafaxine is used in the commercial formulation. The batch formula accurately reflects the drug product composition. There is no reprocessing and reworking (as defined in 21 CFR 211.115) for the manufacture of the drug product. The specification for desvenlafaxine (base) extended-release tablets includes (b) (4)

Regarding (b) (4) specification for description, (b) (4)

Dissolution assay parameters and limits have been set on the basis of the product development studies and innovator product dissolution profile. The limits for uniformity of

Executive Summary Section

dosage are based on general Pharmacopoeial requirements. The specifications for different excipients are consistent with USP/NF requirements. Certificates of analysis from the excipient manufacturers have been provided, and are acceptable. It is noted that no excipients of human or animal origin are used in the manufacture of the drug product. The bovine spongiform encephalopathy/transmissible spongiform encephalopathy (BSE/TSE)-free certification for the excipients used in the clinical formulation has been provided. Regarding batch analysis data, all the tested batches have complied with the relevant release specification at the time of testing and release for use. Twenty-four certificates of analysis each for the 50 mg tablets and 100 mg tablets have been provided. The levels of individual impurities i.e., Impurity^{(b) (4)} and Impurity^{(b) (4)} have been found at below the quantitation limit or at levels of \leq ^{(b) (4)} % in the tested drug product batches (50 mg and 100 mg tablets). There are no impurities that are unique to the drug product. The applicant has stated that Alembic Pharmaceuticals will use same type of primary packing material (HDPE bottle, closure, aluminum foil and ^{(b) (4)}) for future commercial batches as used in the submission batches. The drug product stability studies are ongoing. Results of 6-month accelerated stability study and 12-month long-term stability study have been provided in the submission. The drug product attributes monitored include description, assay, water content, *in-vitro* dissolution, and levels of impurities. Analysis of stability data demonstrates that the proposed drug product is stable under long-term and accelerated conditions when packaged in HDPE bottles (i.e., 14's, 30's, 90's, 100's, 1000's pack) or blister packs (i.e., 10's ^{(b) (4)} blister packs). Specifically, all tested attributes have remained within specification up to 12 months and 6 months under ICH long-term (25°C/60% RH) and accelerated conditions (40°C/75% RH), respectively. The results from hold studies support applicant's proposed hold time of ^{(b) (4)}

The applicant has committed that hold time shall be reevaluated whenever there is major change in manufacturing formula or any critical manufacturing process parameter of desvenlafaxine (base) extended-release tablets. Based on the stability data, the applicant has appropriately proposed an expiry period of 24 months for the drug product (packaged in the proposed container closure system i.e., HDPE bottles or blister packs) with excursions permitted to 15° to 30°C (59° to 86°F). ^{(b) (4)}

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

The proposed drug product, desvenlafaxine extended-release tablets (50 mg and 100 mg), is to be used for the treatment of major depressive disorder (MDD) in adults. The 50 mg tablets will be light pink colored, diamond shaped, biconvex tablets, debossed with 'L189' on one side and plain on other side. The 100 mg tablets will be dark brown colored, diamond shaped, biconvex tablets, debossed with 'L190' on one side and plain on other side. Desvenlafaxine extended-

Executive Summary Section

release tablets 50 mg and 100 mg tablets will be packaged in the following configurations:

- 14 and 30 Tablets Bottle Packs: 14 or 30 tablets in white opaque HDPE bottle (40 cc) sealed with induction seal with (b) (4) cap.
- 90 and 100 Tablets in HDPE Bottle Pack: 90 or 100 tablets in white opaque HDPE bottle (60 cc) sealed with induction seal with (b) (4) cap.
- 1000 Tablets in HDPE bottle Pack: 1000 tablets in white opaque HDPE bottle (750 cc) sealed with induction seal with (b) (4) cap.
- 10 Tablets Blister Pack (Alu (b) (4) 10 tablets blister of plain aluminum foil and transparent (b) (4) film.

C. Basis for Approvability or Not-Approval Recommendation.

During the review process for this NDA, several deficiencies concerning the drug substance and the drug product were identified and communicated to the Type II DMF holder and the applicant, respectively. All the identified deficiencies have been satisfactorily resolved by the DMF holder and the applicant. Specifically, based on Agency recommendation, the DMF holder has agreed to change the designation of starting material (b) (4). In addition, in response to Agency recommendations, the acceptance limit for the Impurity (b) (4) as been tightened from NMT (b) (4) to NMT (b) (4) and testing for (b) (4) has been included in the revised drug substance specification. Regarding drug product specification, the applicant in compliance with Agency recommendations, has tightened the acceptance limit for the Impurity (b) (4) from NMT (b) (4) to NMT (b) (4). Furthermore, as recommended by the Agency, Alembic Pharmaceutical has included microbiological testing in revised drug product specification. Thus, the revised drug substance and drug product specifications are adequate. Furthermore, in response to Agency recommendations, the applicant has revised the post-approval stability commitment. Specifically, the applicant has committed to perform stability studies on the first three commercial lots of desvenlafaxine extended release tablets (50 mg and 100 mg) under both long-term storage conditions as well as accelerated storage conditions. From the CMC perspective, there are no outstanding labeling-related issues. Lastly, all the listed drug substance and drug product manufacturing facilities have been deemed to be “acceptable” based on recommendation from the office of compliance (refer to the Establishment Inspection Report section on pages 101-102 of this review). The Biopharmaceutical aspects of this NDA have been reviewed and found adequate by the Biopharmaceutics review team (refer to the Biopharmaceutics review by Dr. John Duan).

In conclusion, since the applicant has satisfactorily addressed all the identified CMC deficiencies, from the CMC perspective, this NDA for desvenlafaxine extended-release tablets (50 mg and 100 mg) is recommended for approval.

III. Administrative.

A. Reviewer's Signature

Mohan Sapru

Executive Summary Section

B. Endorsement Block

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

Chemistry Team Leader: Ramesh Sood, Ph.D.

C. CC Block

Project Manager: Kofi Ansah

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/s/

MOHAN K SAPRU
11/26/2012

RAMESH K SOOD
11/26/2012

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

Initial Quality Assessment

NDA: 204-150

OND Division:	Division of Psychiatry Products
Applicant:	Alembic Pharmaceuticals Limited
NDA Filing Category:	505(b)(2)
Letter Date:	29-FEB-12
Stamp Date:	29-FEB-12
PDUFA Date:	29-DEC-12
Proposed Trade Name:	Tradename has not been proposed
Established Name:	Desvenlafaxine (base) Extended-Release Tablets
Dosage Form:	Tablet (Extended-Release)
Strengths:	50 mg and 100 mg
Route of Administration:	Oral
Indication:	Treatment of major depressive disorder [MDD]
Assessor:	Chhagan G. Tele, Ph.D.
ONDQA Fileability:	Yes

Background

Desvenlafaxine (base) is a selective inhibitor of the human serotonin (5-HT) and norepinephrine (NE) monoamine transporters and is commonly referred to as a serotonin-norepinephrine reuptake inhibitor (SNRI) for oral administration. Desvenlafaxine (base) Extended-Release tablet (50 mg and 100 mg strengths) was developed for the treatment of major depressive disorder in adults under IND 113,100 (allowed 13-DEC-11 for MDD). Applicant has developed an extended-release tablet formulation that contains desvenlafaxine (Base) as the active ingredient as opposed to desvenlafaxine succinate salt (Pristiq®, Wyeth's US NDA 21-992) which is a currently approved (approved 29-FEB-08) product in the United States for the treatment of MDD. The route of administration, dosage form, and strengths of Desvenlafaxine (Base) ER Tablets 50 mg and 100 mg of Alembic Pharmaceuticals Limited are same as that of the Reference Listed Drug, PRISTIQ® (desvenlafaxine) ER Tablets 50 mg and 100 mg. Applicant relies on the existing data approved for the listed US NDA 21-992, Pristiq® Tablets of Wyeth to pursue this 505(b)(2) application. The Agency's previous findings of safety and effectiveness for the innovator Desvenlafaxine Succinate product (Pristiq®) should be bridged by the bioequivalence to the applicant's Desvenlafaxine 50 mg and 100 mg Tablets strengths. According to the information published in Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) for the Reference Listed Drug PRISTIQ® (desvenlafaxine) ER Tablets, there are unexpired patents and exclusivity remaining under 505 (j)(4)(D) of the Food, Drug and Cosmetic Act. Electronic submission is provided for the CMC information for the review. The applicant provided Quality Overall Summary in the submission. The applicant had a Pre-IND meeting (Type B, 05-OCT-2011) with the clinical division to discuss the following:

- A proposal to submit marketing applications pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act to obtain approval of Desvenlafaxine Extended Release Tablets, 50 and 100 mg for the same indications as those approved for Pristiq®;
- Acceptability of reliance on the FDA's previous findings of safety of Pristiq® to fulfill requirements for toxicological and clinical safety data;
- Acceptability of establishing therapeutic equivalence of the proposed drug product by performing bioequivalence studies to demonstrate that the proposed formulation of the drug product achieve C_{max} and AUC values within 80% to 125% of those of the reference listed drug product, Pristiq®

Minutes of this meeting can be found in DARRTS and should be read by the reviewers (CMC and Biopharmaceutics). No CMC specific meetings have been held with the sponsor; however the reviewers need to bridge any changes and agreements evolved from this meeting, amendments, and annual reports submitted during the drug development.

Drug Substance

The drug substance will be manufactured commercially by Alembic Pharmaceuticals Ltd. in Panelav (Gujarat, India) and used as racemic mixture of two stereoisomers. Desvenlafaxine (base) information is cross-referenced to DMF #25527 [Alembic Pharmaceuticals Ltd. in Panelav, Gujarat, India] regarding chemistry, manufacture, control, reference standards, stability, and packaging. The applicant provided a LoA dated 27-FEB-12 to refer DMF #25527 for the drug substance CMC information. DMF #25527 will need to be found adequate to support NDA. In NDA submission, the applicant provided Desvenlafaxine (base) release specification, release data of the drug substance batches used in manufacture of drug product batches for NDA submission batches, and summary of the analytical method verification reports. Desvenlafaxine (base) supplied by Alembic Pharmaceuticals Ltd. is a white to off-white crystalline powder. The melting point of the racemic mixture is approximately (b) (4). Desvenlafaxine manufactured by Alembic Pharmaceuticals Limited is (b) (4). (b) (4) reviewer need to evaluate this information to be sure that there is no change in (b) (4) during stability studies.

Drug Product

Desvenlafaxine (base) extended release oral tablets will be available in 50 mg and 100 mg tablet strengths. The 50 mg tablets will be light pink colored, diamond shaped, biconvex tablets, debossed with 'L189' on one side and plain on other side. The 100 mg tablets will be dark brown colored, diamond shaped, biconvex tablets, debossed with 'L190' on one side and plain on other side. They are supplied in bottles of 14, 30, 90, 100, 1000 HDPE tablets, and blister strips of 10 tablets. Upon confirmation of identity by UV and HPLC, the bulk tablets will be packaged into the proposed container/closure system at Alembic.

Inactive ingredients for the 50 mg and 100 mg tablets consist of alginic acid (NF), citric acid monohydrate powder (USP), hypromellose (USP), microcrystalline cellulose (NF), povidone (USP), talc (NF), magnesium stearate (NF) and film coating, which consist of hypromellose, titanium dioxide, polyethylene glycol, talc, iron oxide red (50 mg and 100 mg tablets), and iron oxide black (100 mg tablets). According to 21 CFR 73.1200, the total daily amount of elemental iron should not exceed 5 mg. Calculations of the daily amount of elemental iron in Desvenlafaxine (Base) Extended-Release Tablets taking the maximum recommended daily dose (b) (4) (50 mg strength) (b) (4) (100 mg strength). All excipients are commonly used in the solid dosage forms (no novel excipients). None of the excipients are of human or animal origin.

The applicant provided pharmaceutical and manufacturing process development studies (b) (4) (b) (4) to achieve required scale up, dissolution profile, and content uniformity. The assigned reviewer will need to review in detail about these studies for the compatibility and robust manufacturability of the drug product.

Desvenlafaxine (base) extended release oral tablets are manufactured using (b) (4). No overage of desvenlafaxine is used in the commercial formulation. The commercial drug product will be manufactured at Alembic Pharmaceuticals Ltd. in Panelav, Gujarat, India. The proposed regulatory specifications for desvenlafaxine tablets involve straight forward analytical procedures. Validated analytical methods are provided for the determination of assay, related substances, and dissolution. The reviewer needs to look for the adequacy of the validation parameters. Several in-process controls were provided by the applicant (b) (4) (b) (4) from the knowledge of the batches that have been manufactured so far. The reviewer needs to evaluate these parameters in development of robust process.

Hold time study for (b) (4) is provided (Module 3, section 3.2.P.8.1). Based on the data following holding period has been proposed.

(b) (4)

The reviewer needs to evaluate these hold times in development of robust process.

Alembic has manufactured exhibit batches as per the manufacturing procedure provided in section 3.2.P.3 of the submission. Drug product batches of each strength (batch size (b) (4) tablets) are manufactured and packaged in commercial container/closure system are analyzed and packed at Alembic Pharmaceuticals Limited (Formulation Division), Panelav.

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

Exhibit batches of Desvenlafaxine (Base) Extended-Release Tablets 50 mg and 100 mg are packed in HDPE bottles of 14's, 30's, 90's, 100's, 1000's pack and blister pack (i.e. 10's (b) (4) blister pack). 6 months Accelerated and 12 months long term stability data for Desvenlafaxine (Base) Extended-Release Tablets 50 mg and 100 mg are provided.

The sponsor proposed a tentative 24 month expiry for the product based on the stability data.

Critical Issues for Review

- The NDA applicant references DMF #25527 [Alembic Pharmaceuticals Ltd. in Panelav, Gujarat, India] for information on Desvenlafaxine (Base). DMF #25527 will need to be evaluated and found acceptable to support this NDA.
- It is noted in the submission that the (b) (4) is retained with the drug substance during stability (b) (4). The reviewer need to evaluate this information to be sure that there is no change in (b) (4) during stability studies.
- The compatibility of the excipients used in the drug product will need to be evaluated.
- The effect of (b) (4) speed on tablet strength need to be examined closely.
- Need to confirm the adequacy of the critical parameters for the tablets like thickness, length, width, Tablet Hardness and Friability. Tablet hardness and friability needed to be evaluated ((b) (4) debossing process).
- Justification of the exclusion of tests and acceptance criteria for tablet hardness, friability, and microbial limits needs to be requested to evaluate whether the level of process understanding and process controls is adequate.
- Hold time study for (b) (4) is provided. The reviewer needs to evaluate these hold times in development of robust process.
- The applicant has set a dissolution specification: 1 h: 1 Not more than (b) (4), 4 h: Between (b) (4), 8 h: Between (b) (4) and 20 h: Not less than (b) (4). The adequacy of the dissolution method and specification limits will need to be determined in conjunction with the ONDQA biopharm reviewer.
- Stability data (i.e., 6 months accelerated and 12 months long-term data) is provided in the NDA submission for the exhibit batches of each strength manufactured at Alembic packaged in commercial configuration at commercial packaging site Panelav. The

reviewer could request updated stability data by mid cycle before the PDUFA date to confirm the expiry date.

- NDA submission contains no nanoscale materials. However, the reviewer should indicate that no nanoscale materials are present (see MAPP 5015.9 entitled, “Reporting Format for Nanotechnology—Related Information in CMC Review.”)
- The reviewer need to confirm consistency in chemical structure, chemical name, molecular formula, and molecular weight of the drug substance with the current USP dictionary and USAN in the Description section of the labeling. Additionally reviewer need to confirm that all the excipients used in the drug product formulation are included.

Comments and Recommendation:

The NDA is fileable from a CMC perspective. The NDA does not appear to incorporate elements of QbD. NDA submission contains no nanoscale materials. The drug substance is manufactured under DMF #25527. DMF should be reviewed to support this NDA. Assignment of the NDA to a single reviewer is recommended. The dissolution part of the submission should be consulted to the ONDQA biopharm group. Dr. John Duan has been assigned as the biopharm reviewer.

A claim for categorical exclusion under 21 CFR §25.31(b) is provided in Module 1. In accordance with 21 CFR §25.31, (b) (4) claims a categorical exclusion [25.31(a)] from the requirement for an Environmental Assessment or Environmental Impact Statement as approval of the drug product will not increase the use of the active moiety. In addition, the applicant states that to the best of their knowledge, no extraordinary circumstances exist that would preclude this claim for categorical exclusion.

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

**PRODUCT QUALITY: CMC AND BIOPHARMACEUTICS
FILING REVIEW FOR NDA**

NDA Number: 204,150	Applicant: Alembic Pharmaceuticals Ltd.	Stamp Date: 29-FEB-12
Drug Name: Desvenlafexine (Base) ER Tablets	NDA Type: Standard	Filing:

CMC Reviewer: Mohan Sapru, Ph. D.
Biopharmaceuticals Reviewer: John Duan, Ph.D.

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

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

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

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

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

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

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

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

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

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

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

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

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

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

Chhagan Tele

07-MAR-12

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

Date

Ramesh Sood

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

Date

APPEARS THIS WAY ON ORIGINAL

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

/s/

CHHAGAN G TELE
03/08/2012
IQA

RAMESH K SOOD
03/08/2012