CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204683Orig1s000

CHEMISTRY REVIEW(S)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

TO: CMC MEMO-TO-FILE

FROM: P. Shiromani, Ph.D

SUBJECT: NDA 204683 – Desvenlafaxine ER Tablets, 50 mg and 100 mg

DATE: 24-Jun-2013

The attached Summary Report from the Office of Compliance was received on 20-Jun-2013, with an 'Acceptable' overall recommendation. There are no other CMC pending issues. Accordingly, this NDA is recommended for approval from a CMC perspective. The CMC Review was submitted to DARRTS on 13-May-2013.

APPEARS THIS WAY ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

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ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 204683/000
Org. Code: 130
Priority: 5
Stamp Date: 13-SEP-2012
PDUFA Date: 13-JUL-2013
Action Goal:
District Goal: 14-MAY-2013

Sponsor: OSMOTICA PHARM CORP
1205 CULBRETH DR STE 200
WILMINGTON, NC 28405
Brand Name: Khedezla (Desvenlafaxine)
Estab. Name:
Generic Name: Desvenlafaxine Extended Release Tablets,

Product Number; Dosage Form; Ingredient; Strengths

001; TABLET, EXTENDED RELEASE; DESVENLAFAXINE; 50MG
002; TABLET, EXTENDED RELEASE; DESVENLAFAXINE; 100MG

FDA Contacts:			
	S. BHAMIDIPATI	Prod Qual Reviewer	3017962426
	T. BOUIE	Product Quality PM	3017961649
	W. BENDER	Regulatory Project Mgr	3017962145
	C. TELE	Team Leader	3017961762

Overall Recommendation:				
	ACCEPTABLE	on 20-JUN-2013	by C. CAPACCI-DANIEL ()	3017963532
	PENDING	on 10-OCT-2012	by EES_PROD	
	PENDING	on 10-OCT-2012	by EES_PROD	

Establishment: **CFN:** 1049418 **FEI:** 1049418
AAIPHARMA INC
WILMINGTON, , UNITED STATES 28405
DMF No: **AADA:**
Responsibilities: (b) (4)
FINISHED DOSAGE MANUFACTURER
Profile: TABLETS, EXTENDED RELEASE **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 03-JUN-2013
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: (b) (4)
DMF No: **AADA:**
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: (b) (4) **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 16-OCT-2012
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

FDA CDER EES
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FDA CDER EES
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SUMMARY REPORT

Establishment: **CFN:** **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 20-JUN-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: (b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 16-OCT-2012

Decision: ACCEPTABLE

Reason BASED ON PROFILE

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

/s/

PRAFULL K SHIROMANI
06/24/2013

RAMESH K SOOD
06/24/2013

NDA 204683

Tradename
(Desvenlafaxine) ER Tablets
50 and 100 mg

Osmotica Pharmaceuticals, Inc.

Division of Psychiatry Products, HFD 130

Shastri Bhamidipati, Ph.D.
And
Prafull Shiromani, Ph.D.
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 204683

2. REVIEW #: 1

3. REVIEW DATE: 13-May-2013

4. REVIEWERs: Prafull Shiromani Ph.D. and Shastri Bhamidipati Ph.D.

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 204683	13-Sep-2012
Supplement S0009: Applicant's Responses to CMC IR Letter	21-Mar-2013
Applicant's Response to CMC IR Letter	05-Apr-2013
Supplement S0011	24-Apr-2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Osmotica Pharmaceuticals
Address:	1205 Culbreth Drive, Suite 200, Wilmington, NC 28405; Phone: 910-509-0114

Chemistry Review Data Sheet

Representative:	Christopher Smith, CQE, RAC, President, Coastal Pharmaceutical Consultants, Inc., 7950 Old River Road, Burgaw, NC 28425
Telephone:	910-259-8877

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: (b) (4)
b) Non-Proprietary Name (USAN): Desvenlafaxine (base)
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 2
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b) (2)

10. PHARMACOL. CATEGORY: Treatment of major depressive disorder

11. DOSAGE FORM: Extended Release Tablet

12. STRENGTH/POTENCY: 50 mg and 100 mg

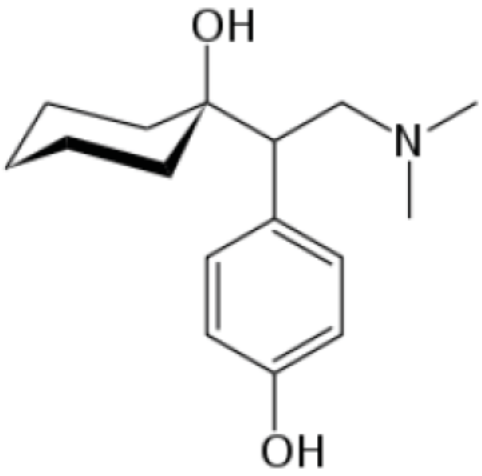
13. ROUTE OF ADMINISTRATION: Oral

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, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



The chemical nomenclature for desvenlafaxine is 4-[2-dimethylamino-1-(1-hydroxycyclohexyl) ethyl]phenol with a chemical formula of C16H25NO2 and a molecular mass of 263.375 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS LOA
(b) (4)	II		(b) (4)	1	Adequate	10-May-2013	26-Aug-2012
				4			12-Oct-2005
	III			4			04-Feb-2012
				4			24-Feb-2011
				4			05-Apr-2011
	III			4			08-Jun-2012

Chemistry Review Data Sheet

		(b) (4)				
(b) (4)		(b) (4)	4			25-May-2012
			4			04-Apr-2011
						13-Jun-2012
			4			12-May-2012
	III		4			06-Oct-2011
	III		4			04-Apr-2011
			4			04-Apr-2011
			4			05-Oct-2011
	III		4			22-Feb-2011
			4			04-Apr-2011
			4			13-May-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: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox			
Biopharm	Recommended for approval	09-May-2013	E. Chikale
LNC			
Methods Validation	Samples of the DS, DP and reference compounds are available		Validation is not required since the analytical methods are conventional
OPDRA			
EA	Their claim for categorical exclusion is acceptable.	30-Apr-2013	P. Shiromani
Microbiology	N/A		

The application submission(s) covered by this review was taken in the date order of receipt. __x__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 204683

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant has provided adequate responses to the FDA CMC IR letters. Additionally, their latest supplement, S0011, of 24-Apr-2013 was reviewed to be acceptable. The ONDQA Biopharm review has been satisfactorily completed and submitted into DARRTS. There are no CMC pending issues. However, OC's overall acceptable recommendation based on site inspection is pending and when received will be entered into DARRTS as a Memo-to-File. Once this acceptable recommendation is received the NDA will be recommended for approval from a CMC perspective.

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

II. Summary of Chemistry Assessments

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

DRUG SUBSTANCE

Desvenlafaxine 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 is a white off-white powder with one chiral center (b) (4) The solubility of Desvenlafaxine base is pH dependent with maximum solubility of 13 mg/mL at pH 4. The sponsor referred to Type II DMF (b) (4) for all chemistry, manufacturing and controls information of Desvenlafaxine base through a letter of authorization from the DMF holder, (b) (4) The DMF has been reviewed and deemed adequate to support this NDA. Desvenlafaxine base as employed in manufacturing the drug product in this NDA has been established to be the stable (b) (4) and characterized by

XPRD analysis. The drug substance has been analyzed at the drug product manufacturing site for identification, assay, related impurities, bulk and tapped densities, and particle size ascertaining its suitability for use. The stability of the drug substance was stated to have been adequately established by the DMF holder with a retest date of (b) (4) from the time of manufacturing.

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 pink colored round tablets, debossed with "OS" on one side and "231" on other side. The 100 mg tablets will be brown colored round tablets, debossed with "OS" on one side and "232" on other side. They are supplied in HDPE bottles of 30, 90, (b) (4) (b) (4). Upon confirmation of identity by UV and HPLC, the bulk tablets will be packaged into the proposed container/closure system at AAI Pharma, Wilmington, NC.

Inactive ingredients for the 50 mg and 100 mg tablets consist of citric acid monohydrate (b) (4) (USP), hypromellose (b) (4) (USP), microcrystalline cellulose and colloidal silicon (b) (4) (USP), (b) (4) (USP), talc (USP), magnesium stearate (b) (4) and (b) (4) film coating. All excipients are commonly used in the solid dosage forms (no novel excipients). None of the excipients are of human or animal origin. (b) (4) The applicant provided extensive formulation, pharmaceutical, and manufacturing process development studies.

Desvenlafaxine (base) extended release oral tablets are manufactured using (b) (4) process. The commercial drug product will be manufactured at AAI Pharma, Wilmington, NC. The proposed regulatory specifications for desvenlafaxine tablets involve straight forward analytical procedures. Validated analytical methods are provided for the determination of assay, related substances, identification, content uniformity, blend homogeneity and dissolution. The applicant provided summary of the operational process parameters and in-process controls (testing/monitoring) recommended for manufacturing this product based on the process development and registration lots. Risk assessment data of unit manufacturing process has been provided for the robust manufacture of the drug product.

Stability batches of Desvenlafaxine (Base) Extended-Release Tablets 50 mg and 100 mg are packaged in HDPE bottles of 30's, 90's, [redacted] (b) (4)). Six months accelerated and updated twelve months long term stability data are provided for both strengths. Based on the satisfactory stability data and its statistical analysis, the applicant's proposal of a 24-month shelf-life for the product is acceptable, in conformance to ICH Q1E 2.4.1.1.

The Applicant has provided adequate responses (on 21-Mar-2013, 05-Apr-2013) to the Agency CMC IR letter, one of which is to include a test for microbial purity in the drug product specification. The provided updated specification includes this test.

Their latest supplement, S0011, of 24-Apr-2013 was reviewed to be acceptable.

[redacted] (b) (4)

The ONDQA Biopharm review was completed on 09-May-2013 with a recommendation for approval.

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

INDICATIONS AND USAGE

The drug is a selective serotonin and norepinephrine reuptake inhibitor (SNRI), is indicated for the treatment of major depressive disorder [MDD].

DOSAGE AND ADMINISTRATION

Recommended dose: 50 mg once daily with or without food.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided adequate responses to the FDA CMC IR letters. Additionally, their latest supplement, S0011, of 24-Apr-2013 was reviewed to be acceptable. The ONDQA Biopharm review has been satisfactorily completed and submitted into DARRTS. There are no CMC pending issues. However, OC's overall acceptable recommendation based on site inspection is pending and when received will be entered into DARRTS as a Memo-to-File. Once this acceptable recommendation is received the NDA will be recommended for approval from a CMC perspective.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Prafull Shiromani Ph.D. and Shastri Bhamidipati
ChemistryTeamLeaderName/Date: Ramesh Sood Ph.D.
ProjectManagerName/Date: William Bender

C. CC Block

224 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

PRAFULL K SHIROMANI
05/13/2013

SHASTRI P BHAMIDIPATI
05/13/2013

RAMESH K SOOD
05/13/2013

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

Initial Quality Assessment
NDA: 204683

OND Division:	Division of Psychiatry Products
Applicant:	Osmotica Kereskedelmies Szolgaltato Kft
NDA Filing Category:	505(b)(2)
Letter Date:	13-SEP-12
Stamp Date:	13-SEP-12
PDUFA Date:	13-JUL-13
Proposed Trade Name:	(b) (4)
Established Name:	Desvenlafaxine (base) Extended-Release Tablets
Dosage Form:	Tablet
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 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. The sponsor of this application is Osmotica Kereskedelmies Szolgaltato Kft (Budapest, Hungary). Osmotica Pharmaceutical (Wilmington, NC) is the US Agent. Desvenlafaxine (base) Extended-Release tablet (50 mg and 100 mg strengths) was developed for the treatment of major depressive disorder in adults under IND 111073 (allowed 24-MAR-11 for MDD). Osmotica submitted a 505(b)(2) NDA for (b) (4) (desvenlafaxine base ER tablets, 50 mg and 100 mg strengths) with clinical and preclinical data reference to the Wyeth's US NDA 021992 for Pristiq® (desvenlafaxine succinate salt), a currently 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 Osmotica are same as that of the Reference Listed Drug, Pristiq® ER Tablets 50 mg and 100 mg. (b) (4) (Desvenlafaxine ER Tablets) 50 mg and 100 mg (b) (4) 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 teleconference meeting (Type B, 01-NOV-2011) with the clinical division to discuss a proposal to submit 505(b)(2) marketing application to obtain approval of Desvenlafaxine Extended Release Tablets, 50 and 100 mg for the same indications as those approved for Pristiq® and acceptability of reliance on the FDA's previous findings of safety of Pristiq® to fulfill requirements for toxicological and clinical safety data. In addition, tests and specifications for the desvenlafaxine drug substance and drug product; dose dumping potential in alcohol, (b) (4) desvenlafaxine ER tablets manufacturing process, stability program, and quantity of stability data for submission in the NDA was discussed. 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 ER Tablets strengths. 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

Desvenlafaxine (base) CMC information is cross-referenced to DMF (b) (4) regarding chemistry, manufacture, control, reference standards, stability, and packaging. The drug substance will be manufactured commercially by (b) (4) and an alternate manufacturing site, (b) (4). The reviewer needs to evaluate any changes in the manufacturing processes, control, packaging, and stability among these sites. The solubility of Desvenlafaxine base is pH dependent. The greatest solubility is at pH 4 with a solubility of 13 mg/mL. Desvenlafaxine base (b) (4) The applicant provided a LoA dated 26-AUG-12 to refer DMF (b) (4) for the drug substance CMC information. DMF (b) (4) 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 is a white to off-white powder. Desvenlafaxine manufactured by (b) (4) site is crystalline (b) (4). The 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 pink colored round tablets, debossed with "OS" on one side and "231" on other side. The 100 mg tablets will be brown colored round tablets, debossed with "OS" on one side and "232" on other side. They are supplied in HDPE bottles of 30, 90, (b) (4) (b) (4). Upon confirmation of identity by UV and HPLC, the bulk tablets will be packaged into the proposed container/closure system at AAI Pharma, Wilmington, NC.

Inactive ingredients for the 50 mg and 100 mg tablets consist of citric acid monohydrate (b) (4) (USP), hypromellose (b) (4) (USP), microcrystalline cellulose and colloidal silicon (b) (4) (USP), (b) (4) talc (USP), magnesium stearate (b) (4) and (b) (4) film coating. All excipients are commonly used in the solid dosage forms (no novel excipients). None of the excipients are of human or animal origin. (b) (4) he applicant provided extensive formulation, pharmaceutical, and manufacturing process development studies. 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). Information about (b) (4) of desvenlafaxine in the commercial formulation is not provided. The reviewer needs to request this information from the applicant. The commercial drug product will be manufactured at AAI Pharma, Wilmington, NC. The proposed regulatory specifications for desvenlafaxine tablets involve straight forward analytical procedures. Validated analytical methods are provided for the determination of assay, related substances, Identification by Retention Time and Identification by UV-Spectrum (PDA detector), Content Uniformity, Blend Homogeneity and dissolution. The reviewer needs to look for the adequacy of the validation parameters. The reviewer needs to evaluate these parameters in development of robust process. The applicant provided summary of the operational process parameters and in-process controls (testing/monitoring) recommended for manufacturing this product based on the process development and registration lots. Risk assessment data of unit manufacturing process has been provided for the robust manufacture of the drug product. The reviewer needs to evaluate this data.

(b) (4)
The reviewer needs to request information about the hold times and evaluate those hold times for the robustness of the process.

AAI Pharma 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) kg) are manufactured and packaged in commercial container/closure system are analyzed and packaged at AAI Pharma, Wilmington, NC.

The batch analyses of the NDA exhibit batches of drug product (three batches of each strength 50 mg and 100 mg) are provided. The dissolution test method (UV) is performed in accordance with USP <711> using the USP Apparatus 1 (Basket) at (b) (4) 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 packaged in HDPE bottles of 30's, 90's (b) (4) . Six months accelerated and nine 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.

(b) (4)

Critical Issues for Review

- The NDA applicant references DMF (b) (4) [AAI Pharma, Wilmington, NC] for information on Desvenlafaxine (Base). DMF (b) (4) 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 drug substance will be manufactured commercially by the facilities in (b) (4) The reviewer needs to evaluate any changes in the manufacturing processes, specifications including analytical methods andvalidation data, and stability data.
- The compatibility of the excipients used in the drug product will need to be evaluated.
- The effect of (b) (4) on tablet strength need to be examined closely.
- Information about (b) (4) of desvenlafaxine in the commercial formulation is not provided. The reviewer needs to request this information from the applicant.
- 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.

- Risk assessment data of unit manufacturing process has been provided for the robust manufacture of the drug product. The reviewer needs to evaluate this data.
- Hold time study for [redacted] is not provided. The reviewer needs to request information about the hold times and evaluate those hold times for the robustness of the process.
- The applicant has set a dissolution specification: 2 h: range [redacted]%, 8 h: Between [redacted]% and [redacted]%, and [redacted] Not less than [redacted]%. 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 9 months long-term data) is provided in the NDA submission for the exhibit batches of each strength manufactured at AAI Pharma packaged in commercial configuration at commercial packaging site. The reviewer could request updated stability data by mid cycle before the PDUFA date to confirm the expiry date.
- The reviewer need to evaluate the comparability protocol so that the transfer of the manufacturing process to [redacted] is equivalent to the current manufacturing process at AAI Pharma Services and ensure the proposed alternate manufacturing facility has the necessary capabilities to manufacture and test Desvenlafaxine ER Tablets 50 mg and 100 mg.
- 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 [redacted]. 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. Elsbeth Chikhale 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, [redacted] 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 will submit all testing, packaging, and manufacturing sites into EES. The reviewer will need to confirm that these sites are correct and that there are no additional sites that need to be entered.

PRODUCT QUALITY: CMC AND BIOPHARMACEUTICS
FILING REVIEW FOR NDA

NDA Number: 204683	**Applicant:** Osmotica Kereskedelmies Szolgaltato Kft	**Stamp Date:** 13-SEP-12
Drug Name: Desvenlafexine (Base) ER Tablets	**NDA Type:** Standard	**Filing:**

CMC Reviewer: Prafull Shiromani, Ph. D.
Biopharmaceuticals Reviewer: Elsbeth Chikhale, 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.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

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

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

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

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

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

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

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

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

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

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

Chhagan Tele 28-SEP-12

Name of Pharmaceutical Assessment Lead or CMC Lead/CMC Reviewer Date
Division of Pre-Marketing Assessment #1
Office of New Drug Quality Assessment

Ramesh Sood

Name of Branch Chief Date
Division of Pre-Marketing Assessment #1
Office of New Drug Quality Assessment

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
09/30/2012
IQA Memo.

RAMESH K SOOD
10/01/2012