CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204683Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 204683 SUPPL # HFD #

Trade Name Khedezla

Generic Name Desvenlafaxine Extended-Release 50 mg and 100 mg Tablets

Applicant Name Osmotica Pharmaceutical Corporation

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(2)

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

YES ☐ NO ☒

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

The sponsor relied on Pristiq as the RLD and submitted bioequivalence data that compared their product to the innovator’s product to support said approval.

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

d) Did the applicant request exclusivity?

YES ☐ NO ☒

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

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

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

1. Single active ingredient product.

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

YES ☒ NO ☐

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

NDA# 021992 Pristiq

NDA# 204150 Alembic Pharmaceuticals LTD

NDA#

2. Combination product.

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

YES ☐ NO ☒

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☐

If yes, explain:

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

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

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

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

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

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

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

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

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

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

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

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: William Bender, R.Ph., CAPT, USPHS
Title: Senior Regulatory Project Manager
Date:

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

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

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

/s/

WILLIAM H BENDER
07/10/2013

MITCHELL V Mathis
07/11/2013

ACTION PACKAGE CHECKLIS

APPLICATION INFORMATION[1]

NDA # 204683 BLA #	NDA Supplement # 000 BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Khedezla Established/Proper Name: Desvenlafaxine (base) Extended-Release Dosage Form: 50 mg and 100 mg tablets		Applicant: Osmotica Pharmaceutical Corporation Agent for Applicant (if applicable): Carmella Moody
RPM: CAPT William Bender		Division: Division of Psychiatry Products (DPP)

NDAs and NDA Efficacy Supplements:

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

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

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

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

Pristiq (NDA 021992)

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

Different salt.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☒ This application relies on (explain) the RLD, Pristiq (NDA 021992)

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

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

☒ No changes ☐ Updated Date of check:

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

❖ Actions	
• Proposed action • User Fee Goal Date is July 13, 2013	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

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

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

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

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

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

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

Comments:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☒ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[4]	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AP Letter – July 10, 2013
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	July 3, 2013
• Original applicant-proposed labeling	September 13, 2012
• Example of class labeling, if applicable	PRISTIQ Labeling (NDA 021992), Alembic Labeling (NDA 204150)

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

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	See above
• Original applicant-proposed labeling	See above
• Example of class labeling, if applicable	See above
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	July 3, 2013
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	Both review and letter was dated April 24, 2013
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 10/25/2012 ☒ DMEPA 11/13/2012; 04/24/2013;06/25/2013; 07/03/2013 ☒ DMPP/PLT (DRISK) 05/17/2013 ☒ ODPD (DDMAC) 05/07/2013 ☒ SEALD 06/19/2013 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)*	RPM Filing Review- 11/27/2012
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2) 06/10/2013
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☐ Not a (b)(2) 07/08/2013
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC May 29,2013 (Peds Record in DARRTS as Peds entry on May 21, 2013 If PeRC review not necessary, explain: ____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☐ Included

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

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 11/04/2011
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None N/A
Division Director Summary Review *(indicate date for each review)*	☐ None July 10, 2013
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 06/19/2013
PMR/PMC Development Templates *(indicate total number)*	☐ None
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	06/19/2013
• Clinical review(s) *(indicate date for each review)*	06/04/2013
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Please see clinical review on 06/04/2013
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None

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

❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 05/07/2013
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☒ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 05/31/2013; 11/08/2012 (Filing Review)
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None 05/07/2013
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 05/29/2013; 11/08/2012 (Filing Review)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None CMC Primary Review: 06/24/2013; 05/13/2013; 10/01/2012 (Filing Review) OBP Primary Review: 05/09/2013; 11/08/2012 (Filing Review)
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	05/13/2013 and 10/01/2012 (see CMC reviews)
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

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

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

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

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

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

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

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

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

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

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

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/s/

WILLIAM H BENDER
07/10/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 204683

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Osmotica Kereskedelmies Szolgaltato Kft
c/o Coastal Pharmaceutical Consultants, Inc
7950 Old River Road,
Burgaw, NC 28425

ATTENTION: Christopher Smith, CQE, RAC
U.S. Agent and President, Coastal Pharmaceutical Consultants, Inc.

Dear Mr. Smith:

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

We also refer to your correspondence dated January 24, 2013, received January 25, 2012, requesting review of your proposed proprietary name, Khedezla. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Khedezla, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your January 24, 2012, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sandra Rimmel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, William Bender, at (301) 796-2145.

Sincerely,
{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
04/24/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204683

FILING COMMUNICATION

Osmotica Pharmaceutical
Attention: Carmella S. Moody, Ph.D.
Director, Regulatory Affairs
1205 Culbreth Drive, Suite 200
Wilmington, NC 28405

Dear Dr. Moody:

Please refer to your New Drug Application (NDA) dated 9/13/2012, received 9/13/2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for (b) (4) (desvenlafaxine) extended-release tablets 50 mg and 100 mg.

We also refer to your amendments(s) dated 10/04/2012 and 10/10/2012.

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

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 12, 2013.

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

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

Full Prescribing Information (FPI)

GENERAL FORMAT

1. 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: *This statement is present but not at the beginning of the clinical trails experience section. Additionally, the sponsor needs to change this section to clinical trials, not clinical studies.*

We request that you resubmit labeling that addresses these issues by December 5, 2012. The resubmitted labeling will be used for further labeling discussions.

Biopharmaceutics information request:

- Provide solubility data for desvenlaxavine (b) (4) across the physiological pH range.
- Provide the complete dissolution data for the testing conducted to demonstrate the discriminating capability of the proposed dissolution method.
- Provide a proposed drug release mechanism for your drug product with supporting data if available.

CMC stability information request

- Provide three months additional stability, for a total of 12 months stability data, at the long-term stability storage condition for both potencies in all packages.

Additionally, under 21 CFR 314.54(a)(1)(vi), a 505(b)(2) application must contain a patent certification or statement with respect to any relevant patents that claim the listed drug or that claim any other drugs on which the investigations relied on for approval of the application were conducted, or that claim a use for the listed or other drug. Your 505(b)(2) application relies upon the Agency's finding of safety and effectiveness for NDA 21992 for Pristiq (dexvenlafaxine succinate) Extended Release Tablets, but does not contain a patent certification or statement with respect to each patent listed in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book) for the listed drug upon which you rely. After you submitted your 505(b)(2) application, the NDA holder for Pristiq (desvenlafaxine succinate) Extended Release Tablets timely filed information on U.S. Patent No. 8,269,040 ('040' patent) for listing in the Orange Book. In accordance with section 505(b)(2) of the FDCA and 21 CFR 314.50(i), you must submit an appropriate patent certification or statement with respect to the '040' patent.

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied. We also acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied

If you have any questions, please call CAPT William Bender, Senior Regulatory Project Manager, at (301) 796-2145.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

THOMAS P LAUGHREN
11/14/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 111073

MEETING MINUTES

Osmotica Pharmaceutical
Attention: Carmella S. Moody, Ph.D.
Director, Regulatory Affairs
1205 Culbreth Drive, Suite 200
Wilmington, NC 28405

Dear Dr. Moody:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Desvenlafaxine Extended Release Tablets, 50 mg and 100 mg.

We also refer to the telecon between representatives of your firm and the FDA on November 1, 2011. The purpose of the meeting was to discuss your planned development program for a 505(b)(2) submission.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call CDR William Bender, Regulatory Project Manager at (301) 796-2145.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	November 1, 2011
TIME:	4:00pm to 5:00pm
LOCATION:	CDER WO 4201 (teleconference)
APPLICATION:	IND 111073
DRUG NAME:	Desvenlafaxine ER Tablets, 50 mg and 100 mg
TYPE OF MEETING:	Type B End of Phase 2/ Pre-NDA teleconference
MEETING CHAIR:	Thomas Laughren, M.D., Division Director
MEETING RECORDER:	CDR William Bender, Regulatory Project Manager

FDA ATTENDEES

Thomas Laughren, M.D., Division Director, Division of Psychiatry Products
Mitchell Mathis, M.D., Deputy Division Director
Robert Levin, M.D., Clinical Team Leader
Christina Burkhart, M.D., Clinical Reviewer
Chhagan Tele, Ph.D., Pharmaceutical Assessment Lead
Thomas Wong, Pharmaceutical Assessment Reviewer
John Duan, Ph.D., ONDQA Biopharmaceutics Reviewer
Andre Jackson, Ph.D., OCPB Reviewer
Bill Bender, R.Ph., Project Manager

Osmotica Participants:
Carmella S. Moody, Ph.D. Director, Regulatory Affairs
Mark S. Aikman, Pharm.D., Vice President Regulatory Affairs and Quality Assurance
Glenn Meyer, Ph.D., Chief Scientific Officer
David Boyd, Pharm. D., Director Clinical
Gustavo Fischbein, Medical Director
Angela Dentiste, Vice President Clinical Operations and Contract Officer
Laurie Tracy, Project Management
Tim Davis, Manager Regulatory Affairs

Background:

Osmotica Pharmaceutical has requested a teleconference with the Agency to discuss the planned development program for a 505(b)(2) NDA submission for Desvenlafaxine Extended Release Tablets, 50 mg and 100 mg. Osmotica requests feedback on CMC, Clinical, and Regulatory components of the proposed development program as outlined in the Questions section of the meeting request.

Desvenlafaxine Extended Release Tablets (OS230) are an (b) (4) tablet containing desvenlafaxine free base. It is under development for the treatment of major depressive disorder (MDD). A once daily dose of 50 mg per tablet is proposed based on the approved range of dosage for PRISTIQ®. In addition, a 100 mg extended release tablet is being developed which is consistent with currently approved strengths of PRISTIQ.

Desvenlafaxine has been shown to be safe and effective for the treatment of MDD. In 2008, it was approved in the succinate salt form for MDD. Desvenlafaxine is the active moiety of desvenlafaxine succinate, and Osmotica Pharmaceutical believes administration of the base compound can be achieved in a bioequivalent manner to PRISTIQ, thus supporting a 505(b)(2) application.

Osmotica Pharmaceutical plans to perform 5 bioavailability studies comparing the PK of the product to that of the commercially available PRISTIQ® 50 and 100 mg. Four of the studies are single-dose studies, and one will be a steady state study. All will be crossover studies. These will include a single-dose, fasted and fed study for each strength (50 mg and 100 mg) and a steady-state study using the 100 mg strength.

The 50 mg and 100 mg strengths of Desvenlafaxine ER Tablets will be compared to the comparable 50 mg and 100 mg strengths of PRISTIQ® in both fasted and fed studies. The 100 mg strengths of both products will be compared in the steady-state study. (b) (4) The number of subjects to be used in each study will be determined based on pilot studies of early formulations of Desvenlafaxine ER Tablets: therefore, the sample sizes may be modified as needed as the program progresses.

The agenda includes a discussion of: 1) tests and specifications for the desvenlafaxine drug substance; 2) information to justify an alternate API manufacturing site; 3) Desvenlafaxine ER Tablets manufacturing process; 4) stability program; 5) data for inclusion in an alternate site justification; 6) quantity of stability data for submission in the NDA; 7) the clinical program; and 8) discussion of regulatory issues for eCTD submission.

Questions:

CMC

Question 1: Does the Agency agree that the proposed tests and specifications for the desvenlafaxine drug substance are acceptable for 505(b)(2) submission?

> ***Preliminary Comments:*** *Your proposed testing appears reasonable at this time. However you must include acceptance criterion for a three-point particle size specification or justify the absence of specification limits based on the impact of particle*

size on product performance and manufacturability. Ultimate acceptability of your specifications (test methods and specification limits) or justification will be determined as part of the NDA review.

Discussion at Meeting: *No further discussion.*

Question 2: Does the Agency agree that the proposed tests and specifications for the Desvenlafaxine ER Tablets are acceptable for 505(b)(2) submission?

Preliminary Comments: *Your proposed identification acceptance criterion for drug product specification is determined using an HPLC method. Identification solely by retention time is not regarded as being specific (refer ICH Q6A: Test procedures and acceptance Criteria for New Drug Substances and Drug Products). Include a specific identification test (e.g., Infrared spectroscopy) as part of the drug product specification. You also need to provide justification for the absence of microbial quality test.*

We do not agree with your dissolution specification. The in vitro dissolution method has not been specified and the proposed dissolution acceptance criteria have not been justified.

We recommend that a dissolution method be developed for this specific product and the dissolution method development report be provided, in which the selection of dissolution methodology, including the apparatus, rotation speed, media and temperature should be fully justified to show the discriminating ability for identifying the quality problems if any. All the raw data should be provided in the report, including the individual value, the mean, the standard deviation and the plots under different conditions.

The following points should be considered when setting the dissolution acceptance criteria for your product:

- *Dissolution profile data from the bio-batches (clinical & PK studies) and stability batches should be collected and used for the setting of the dissolution specifications (i.e., specification-sampling time points and specification values).*
- *The in vitro dissolution profile should encompass the timeframe over which at least* (b) (4) *of the drug is dissolved or where the plateau of drug dissolved is reached if incomplete dissolution is occurring.*
- *For extended release products the establishment of at least three specification time-points covering the initial, middle, and terminal phases of the complete dissolution profile data should be set. The acceptance criteria ranges should be based on the overall dissolution data generated at these times.*

In general, the selection of the dissolution specification ranges is based on mean target value ±10% and NLT (b) (4) *% for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an approved In Vitro-In Vivo Correlation (IVIVC) model.*

All other tests are acceptable and the acceptability of the acceptance criteria is a review issue.

Discussion at Meeting: *No further discussion.*

Question 3: Does the Agency agree that the proposed plan for investigating the "dose dumping" potential for the drug product in alcohol is acceptable for 505(b)(2) submission?

Preliminary Comments: *There is not enough information for us to answer this question. The following points should be considered during the evaluation of the in vitro alcohol induced dose dumping of your product:*

- *Dissolution testing should be conducted using the optimal dissolution apparatus and agitation speed. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile.*
- *The following alcohol concentrations for the in vitro dissolution studies are recommended: 0%, 5%, 10%, 20%, and 40%.*
- *In general;*
  - *If the optimal dissolution medium is 0.1N HCl; dissolution profiles in this 0.1 N HCl (pH 1.2) containing the above range of alcohol concentrations would be sufficient.*
  - *If the optimal dissolution medium is NOT 0.1N HCl; dissolution profiles using the above range of alcohol concentrations in 0.1N HCl and in the optimal dissolution medium are recommended.*
  - *If the optimal dissolution medium has not been identified; dissolution profiles using the above range of alcohol concentrations in three physiologically relevant pH media (pH 1.2, 4.5, and 6.8) are recommended.*
  - *If the dissolution of the MR product is pH independent; then dissolution data in 0.1N HCl with the above range of alcohol concentrations is sufficient.*
- *The shape of the dissolution profiles should be compared to determine if the modified release characteristics are maintained, especially in the first 2 hours.*
- *The f2 values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated (using 0% alcohol as the reference).*
- *The report with the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study should be provided to FDA for review and comments.*

Discussion at Meeting: *No further discussion.*

Question 4: Does the Agency agree that the stability protocols provided are acceptable to support a 505(b)(2) submission?

Preliminary Comments: *We are in agreement with your proposed stability protocols for Desvenlafaxine ER Tablets, 50 mg and 100 mg.*

Discussion at Meeting: *No further discussion.*

Question 5: Does the Agency agree that the NDA may be submitted with 9 months of "real-time" stability data on 3 batches of each strength, with an additional 3 months of stability data submitted during the NDA review process, at least 2 months before the PUDUFA action date, is acceptable?

Preliminary Comments: *We recommend that you submit 12 months of long-term and 6 months of accelerated stability data for three primary batches of each strength using the to-be-marketed formulation, manufacturing process, and packaged in the proposed commercial packaging. Two of the three batches of each strength should be at least pilot scale batches and the third one can be smaller, if justified. Where possible, batches of the drug product should be manufactured by using different batches of the drug substance. Additional data received prior to mid cycle (i.e. 5 months for a standard submission) will be reviewed as part of the original application. Data received later may not be reviewed during the same review cycle. Refer to ICH Q1A(R2): Stability Testing of New Drug Substances and Products.*

Discussion at Meeting: *The sponsor clarified that 9 months of "real-time" stability data on 3 batches of each strength will be submitted in the initial NDA filing. Additional stability data will be submitted before the mid cycle (5 months). We responded that this is acceptable. We also mentioned that any data submitted after the mid cycle may not be reviewed.*

Question 6: Does the Agency agree that the proposal for data to support a manufacturing site change, for submission in the 505(b)(2) is acceptable.

Preliminary Comments: (b) (4) *Manufacturing site change is considered as Level 3 change according to the SUPAC-MR Guidance. You need to provide data of three batches of each strength of Desvenlafaxine ER Tablets manufactured at the proposed commercial manufacturing site with three months accelerated stability data in the NDA submission in order to support the proposed commercial manufacturing site as per principles described in the SUPAC-MR Guidance.*

From the Biopharmaceutics perspective, a successful bioequivalence study will support a manufacturing site change.

Discussion at Meeting: *No further discussion.*

CLINICAL

In accordance with 21 CFR 320.25(f), Osmotica is proposing to perform 5 bioavailability studies, a single dose, fasted for each strength, a single dose, fed for each strength and a steady state study of the 100 mg strength. The reference product in each study will be the commercially marketed product PRISTIQ®. (b) (4) Synopses of these studies will be provided in the briefing package.

Question 7: Does the Agency agree that the program of pharmacokinetic clinical studies proposed for both strengths of Desvenlafaxine ER Tablets covers the studies needed to support a 505(b)(2) submission?

Preliminary Comments: (b) (4)

(b) (4)

Fed bioequivalence studies are not necessary, however, the effect of food on the Osmotica ER tablet should be evaluated. The sponsor should assess the effect of food on the highest strength of Osmotica Desvenlafaxine (100 mg) extended release tablets.

It is recommended that the assessment of the effect of food be incorporated into the single dose fasting bioequivalence study on the highest strength. (b) (4)

The regulatory assessment of bioequivalence is based on AUC and Cmax meeting the regulatory criteria for bioequivalence, i.e. the 90% confidence interval (CI), using the log transformed data, should be contained within 80% to 125%. In addition, as per our usual assessment for bioequivalence, similarity of Tmax of the two products would also be examined.

(b) (4) *an additional single dose fasting bioequivalence study comparing the 50 mg strength to Pristiq would be necessary.*

The proposed single dose fed study of the test product versus RLD for the 100 mg tablet is not required but would be acceptable in lieu of a food effect study.

Discussion at Meeting: *We affirmed to the sponsor that no steady state studies are required.*

REGULATORY

The reference drug for Desvenlafaxine ER Tablets is the marketed product, Pristiq. The labeling for Pristiq indicates the drug is not to be used in the pediatric population. A (b) (4)

Question 8: Does the Agency agree that pediatric studies for desvenlafaxine ER tablets 50 and 100 mg (b) (4)?

Preliminary Comments: (b) (4)

Discussion at Meeting: (b) (4) *We also let them know that they could request a deferral/waiver in conjunction with their pediatric plan at the time of submission.*

Osmotica plans to submit the 505(b)(2) application as an eCTD with appropriate Module 2 summary sections. It is our plan to address any safety issues in an integrated manner in the Clinical summary and not submit a separate Integrated Summary of Safety.

Question 9: Does the Agency agree that it is acceptable to address safety issues in the summary sections of the eCTD and not combine the safety data into an integrated dataset.

Preliminary Comments: *This is acceptable.*

Discussion at Meeting: *No further discussion.*

Question 10: Does the Agency require a define.pdf file in the 505(b)(2) submission?

Preliminary Comments: *Yes, we request that you provide a define.pdf file.*

Discussion at Meeting: *No further discussion.*

Question 11: Does the Agency require the analysis datasets in ADaM format?

Preliminary Comments: *This is not a requirement; however, we would prefer that you submit the datasets in the ADaM format. We can discuss this further at the meeting.*

Discussion at Meeting: *The sponsor indicated that they will submit the datasets in the ADaM format.*

Question 12: Are there other issues or comments that the Agency considers helpful for the development program?

Preliminary Comments: *Not at this time.*

Discussion at Meeting: *No further discussion.*

Additional Discussion item: *The sponsor asked if the bioequivalence studies could be conducted in India. We told them that we have no objections as long as we had the ability to inspect the sites. We also informed them to maintain the high fat diet as prescribed in the US standards.*

PRESCRIBING INFORMATION

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

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

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page

that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

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

/s/

THOMAS P LAUGHREN
11/04/2011