

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-104

CHEMISTRY REVIEW(S)

Memo to File

NDA 22-104

- The applicant agreed to adopt the interim dissolution specifications proposed by the OCP and outlined in the agency's February 25, 2008 AE Letter. The applicant further agreed to collect dissolution data for 24 tablets on the first 12 batches at release or on all batches at release post approval for 12 months for each strength. The interim dissolution specifications are included below in Table 1.

<u>37.5 mg</u>		<u>75 mg, 150 mg and 225 mg</u>		
4 hour		4 hour		b(4)
12 hour		12 hour		
20 hour	NLT -	20 hour	NLT -	

- The applicant has requested a 24-month shelf life for the drug product. The applicant submitted up to 24 months of long term data and 6 months of accelerated stability data for the drug product in — bottles. The applicant also included 18 months of data for 3 batches (1 batch each of the 37.5, 75 and 225 mg tablets) together with 12 months of data for 8 batches (2 batches of each strength) of the drug product packaged in blisters. The applicant has demonstrated that the drug product can be adequately stored at 25° C/60%RH in the HDPE bottles and blisters. The applicant has provided adequate data to support the 24 month expiry (see CMC review #4 for additional details). b(4)
- There were no changes to the CMC sections of the label or package insert.
- For all other CMC information pertaining to this NDA, please see previous reviews.
- The recommendation from a CMC perspective is APPROVAL. All CMC issues have been adequately addressed and there are no outstanding CMC concerns (see CMC review #4 for additional details).

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/s/

Sherita McLamore
5/7/2008 08:49:12 AM
CHEMIST

Ramesh Sood
5/7/2008 09:33:31 AM
CHEMIST

There were not pending CMC issues in the resubmission.
Therefore, a separate branch chief memorandum will not
be written and this memorandum serves as final
CMC recommendation.

12 hour: —
20 hour: NLT —

12 hour: —
20 hour: NLT —

b(4)

An expiration date of 24 months has been assigned for this product based on the provided drug product stability data. All manufacturing sites have been found acceptable by the Office of Compliance.

Recommended action: The application is recommended as “**Approval**” from CMC perspective.

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/s/

Ramesh Sood
2/28/2008 11:34:56 AM
CHEMIST



NDA 22-104

Venlafaxine Hydrochloride Extended Release Tablets

Osmotica Pharmaceuticals Corporation

Sherita D. McLamore, Ph.D.



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A. Labeling & Package Insert	Error! Bookmark not defined.
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Chemistry Review Data Sheet

1. NDA 22-104
2. REVIEW: #4
3. REVIEW DATE: February 27, 2008
4. REVIEWER: Sherita D. McLamore, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	December 11, 2006
Amendment	January 19, 2007
Amendment	September 9, 2007

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	December 28, 2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Osmotica Pharmaceutical Corporation
Address:	1205 Culbreth Drive Suite 200 Wilmington, NC 28405
Representative:	n/a
Telephone:	910-509-0115

8. DRUG PRODUCT NAME/CODE/TYPE:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

- a) Proprietary Name: Venlafaxine Hydrochloride Extended Release Tablets
- b) Non-Proprietary Name (USAN): venlafaxine hydrochloride
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Major Depressive Disorder and
Social Anxiety Disorder

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 37.5 mg, 75 mg, 150 mg and 225 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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

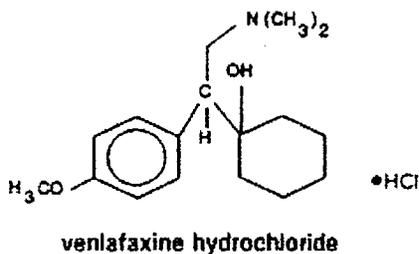
Chemical Name: (±)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol hydrochloride
Molecular Formula: C₁₇H₂₇NO₂·HCl
Molecular Weight: 318.87



CHEMISTRY REVIEW



Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	II			3	adequate		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A

b(4)

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")

Chemistry Review Data Sheet

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-699	Innovator NDA. Effexor XR
IND	71,288	Original IND

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	9/6/07	S. Ferguson
Pharm/Tox	N/A	N/A	Linda Fossom, Ph.D.
Biopharm	Acceptable-interim specifications accepted	02/25/08	Kofi Kumi Ph.D.
LNC	N/A	N/A	N/A
Methods Validation	Validation from FDA labs not required	N/A	Sherita McLamore, Ph.D.
OPDRA	N/A	N/A	N/A
EA	Categorical Exclusion Acceptable		Sherita McLamore, Ph.D.
Microbiology	N/A	N/A	N/A

APPEARS THIS WAY ON ORIGINAL

CHEMISTRY REVIEW

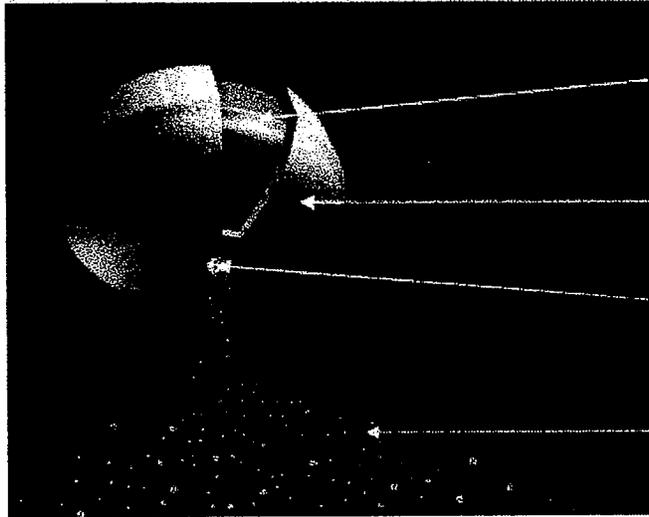
Executive Summary Section

The osmotic technology used includes manufacturing

Next, a single hole is drilled into one side of the tablet using a laser. As tablet passes through the gastrointestinal tract, water pressure from the intestinal fluids causes pressure to build up in the tablet core and the core content is forced out of the tablet through the laser drilled hole.

b(4)

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Tablet core (extended release of the active ingredient)

Semi-permeable membrane

Laser drilled orifice

Drug available for absorption

The drug product composition includes compendial grade mannitol, Povidone, Microcrystalline Cellulose, Polyethylene Glycol (PEG), Colloidal Silicon Dioxide, Magnesium Stearate, Cellulose Acetate

b(4)

The formulation also includes

The drug product will be manufactured and packaged by

The drug product is available in four different strengths, 37.5 mg, 75 mg, 150 mg and 225 mg. All tablets contain the same components.

b(4)



The Chemistry Review for NDA 22-104

The Executive Summary

A. Recommendation and Conclusion on Approvability

1. The recommendation from a Chemistry, Manufacturing, and Controls (CMC) perspective is APPROVAL. All CMC issues have been adequately addressed. There are no outstanding CMC concerns.

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)

Venlafaxine hydrochloride is a neuronal serotonin and norepinephrine reuptake inhibitor currently approved for the treatment of depression and general anxiety disorder. Venlafaxine hydrochloride was investigated under IND 71,288 and was approved for use under NDA 20-699.

The drug product, Venlafaxine Extended Release Tablet is a once a day treatment for major depressive disorder (MDD) and social anxiety disorder (SAD). The drug product is an osmotic tablet

_____ This technology has been employed successfully in other FDA approved products such as Allegra D 24, Nifedipine Extended-release tablets and Oxybutynin Chloride Extended-release tablets.

The osmotic technology used includes manufacturing _____

_____ Next, a single hole is drilled into one side of the tablet using a laser. _____ As tablet passes through the gastrointestinal tract, water pressure from the intestinal fluids causes pressure to build up in the tablet core and the core content is forced out of the tablet through the laser drilled hole.

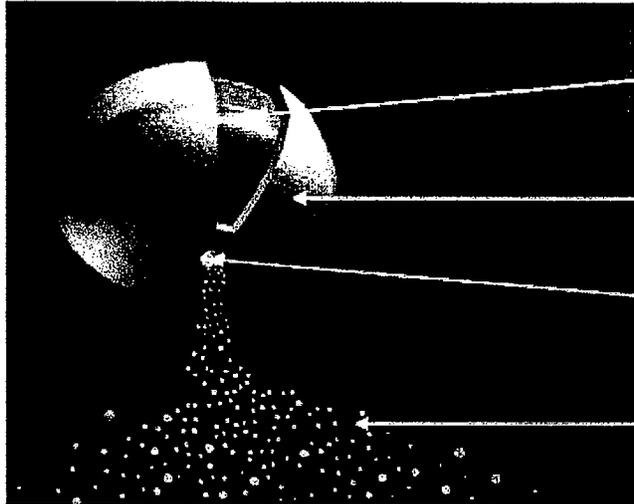
b(4)

b(4)



Executive Summary Section

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Tablet core (extended release of the active ingredient)

Semi-permeable membrane

Laser drilled orifice

Drug available for absorption

The drug product composition includes compendial grade mannitol, Povidone Microcrystalline Cellulose, Polyethylene Glycol (PEG) — Colloidal Silicon Dioxide, Magnesium Stearate, Cellulose Acetate

b(4)

The formulation also includes

The drug product will be manufactured and packaged by

The drug product is available in four different strengths, 37.5 mg, 75 mg, 150 mg and 225 mg. All tablets contain the same components.

b(4)

The drug substance will be manufactured and packaged by

b(4)

The applicant referenced DMF — for all information pertaining to the drug substance. DMF was reviewed and was found to contain adequate information to support this NDA. The drug substance is described as a non-hygroscopic, white to off-white crystalline powder with a melting point of 210-218°C. The molecular formula for the drug substance is C₁₇H₂₇NO₂·HCl and the molecular weight is 318.87.

Executive Summary Section

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

The drug product is being developed as an extended release formulation venlafaxine hydrochloride. The applicant used the innovator drug Effexor as a comparator. The drug product has maximum daily dose of 225 mg and is being developed for the treatment of MDD and SAD.

b(4)

The applicant has requested a 24-month shelf life for the drug product. The applicant submitted up to 24 months of long term data and 6 months of accelerated stability data for the drug product in — bottles. The applicant also included 18 months of data for 3 batches (1 batch each of the 37.5, 75 and 225 mg tablets) together with 12 months of data for 8 batches (2 batches of each strength) of the drug product packaged in blisters. The applicant has demonstrated that the drug product can be adequately stored at 25° C/60%RH in the — bottles and blisters. At the time tested, the related substances were below the level of qualification and there were virtually no deviations in the assay or weight. The applicant has provided adequate data to support the 24 month expiry. Accordingly, the recommendation from a CMC perspective for NDA 22-104 is Approval.

b(4)

All sites were submitted to the Office of Compliance in January of 2007. The final recommendation from the Office of Compliance for this application is Acceptable.

C. Basis for Approvability or Not-Approval Recommendation

Two comments were conveyed to the applicant in the agency's October 04, 2007 Approvable Letter. The responses to the comments are summarized in this review. In the response, the applicant adequately addressed the CMC concerns. In the previous review, it was concluded that the applicants proposed dissolution specification were not acceptable. At that time, OCP proposed dissolution specification for the drug product. In this response, the applicant proposed a new set of dissolution specifications for the drug product. The new dissolution specification included one set of acceptance criterion for the 37.5 mg table and another set of acceptance criterion for the 75, 150 and 225 mg tablets. Initially, it was concluded that the applicant's proposal to have two different sets of dissolution specifications for the drug product was not acceptable as there was no precedent. In a meeting with the clinical division, it was concluded that the applicant could not manufacture product to meet the acceptance criteria proposed by OCP. Accordingly, the OCP proposed that the applicant adopt the dual specifications proposed in this submission as interim dissolution specification. As a condition of the interim specification, the OCP indicated following:

The sponsor should collect dissolution data for 24 tablets (up to L3 stage of testing) on the first 12 batches at release or on all batches at release post



Executive Summary Section

approval for a period of 12 months, for each strength, which ever comes first. The sponsor should submit this information to the Agency by 14 months from the date of approval so that a 'final' specification can be set for the product... the sponsor should provide justification, based on the data available after the requested testing period, why a single dissolution specification, such as the one proposed by the Agency provided below, could not be adopted for Venlafaxine ER... The sponsor should submit the data requested for the IVIVC as agreed to by the sponsor as this could also facilitate the setting of a 'final' dissolution specification for this product.

There are no additional concerns to be addressed from a CMC point of view. Accordingly, the recommendation from a CMC perspective is **APPROVAL**.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

SMcLamore/Date
RSood

C. CC Block

Orig. NDA 22-104
Division File
TOliver

11 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Sherita McLamore
2/28/2008 09:59:04 AM
CHEMIST

Ramesh Sood
2/28/2008 11:31:47 AM
CHEMIST

NDA 22-104

Venlafaxine Hydrochloride Extended Release Tablets

Osmotica Pharmaceuticals Corporation

Sherita D. McLamore, Ph.D.



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Chemistry Review Data Sheet

1. NDA 22-104
2. REVIEW: #2
3. REVIEW DATE: September 20, 2007
4. REVIEWER: Sherita D. McLamore, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents
Original Submission
Amendment

Document Date
December 11, 2006
January 19, 2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed
Amendment

Document Date
September 9, 2007

7. NAME & ADDRESS OF APPLICANT:

Name: Osmotica Pharmaceutical Corporation
Address: 1205 Culbreth Drive
Suite 200
Wilmington, NC 28405
Representative: n/a
Telephone: 910-509-0115

8. DRUG PRODUCT NAME/CODE/TYPE:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

- a) Proprietary Name: Venlafaxine Hydrochloride Extended Release Tablets
- b) Non-Proprietary Name (USAN): venlafaxine hydrochloride
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Major Depressive Disorder and
Social Anxiety Disorder

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 37.5 mg, 75 mg, 150 mg and 225 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

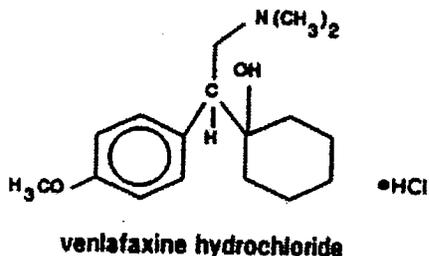
Not a SPOTS product

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

Chemical Name: (±)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol hydrochloride
Molecular Formula: $C_{17}H_{27}NO_2 \cdot HCl$
Molecular Weight: 318.87

CHEMISTRY REVIEW

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	II			3	adequate		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A

b(4)

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")



CHEMISTRY REVIEW



Chemistry Review Data Sheet

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-699	Innovator NDA. Effexor XR
IND	71,288	Original IND

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	9/6/07	S. Ferguson
Pharm/Tox	N/A	N/A	Linda Fosson, Ph.D.
Biopharm	Acceptable-changed dissolution specifications	9/20/07	Kofi Kumi Ph.D.
LNC	N/A	N/A	N/A
Methods Validation	Validation from FDA labs not required	N/A	Sherita McLamore, Ph.D.
OPDRA	N/A	N/A	N/A
EA	Categorical Exclusion Acceptable		Sherita McLamore, Ph.D.
Microbiology	N/A	N/A	N/A

APPEARS THIS WAY ON ORIGINAL

The Chemistry Review for NDA 22-104

The Executive Summary

A. Recommendation and Conclusion on Approvability

The Chemistry, Manufacturing, and Controls (CMC) section of NDA 22-104 is Approvable. See section II.C of the executive summary for the pending issue related to the expiration date assignment. The following comments will be conveyed to the applicant the forthcoming Action letter.

1. *Your revised label includes the term "equivalent to" the label strength in terms of Venlafaxine. This is not acceptable. Please revise your label to include the product strength as follows:*

*Venlafaxine
Extended Release Tablets
37.5 mg**

**present as Venlafaxine Hydrochloride*

2. *Please submit updated stability data and re-evaluate your dissolution data with regards to the dissolution specifications proposed above.*

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)

Venlafaxine hydrochloride is a neuronal serotonin and norepinephrine reuptake inhibitor currently approved for the treatment of depression and general anxiety disorder. Venlafaxine hydrochloride was investigated under IND 71,288 and was approved for use under NDA 20-699.

The drug product, Venlafaxine Extended Release Tablet is a once a day treatment for major depressive disorder (MDD) and social anxiety disorder (SAD). The drug product is an osmotic tablet

_____ This technology has been employed successfully in other FDA approved products such as Allegra D 24, Nifedipine Extended-release tablets and Oxybutynin Chloride Extended-release tablets.

b(4)

CHEMISTRY REVIEW

Executive Summary Section

The drug substance will be manufactured and packaged by _____
_____ The applicant referenced DMF _____ for all information pertaining to the drug substance. DMF _____ was reviewed and was found to contain adequate information to support this NDA. The drug substance is described as a non-hygroscopic, white to off-white crystalline powder with a melting point of 210-218°C. The molecular formula for the drug substance is $C_{17}H_{27}NO_2 \cdot HCl$ and the molecular weight is 318.87.

b(4)

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

The drug product is being developed as an extended release formulation venlafaxine hydrochloride. The applicant used the innovator drug Effexor as a comparator. The drug product has maximum daily dose of 225 mg and is being developed for the treatment of MDD and SAD. The drug product will be packaged _____

b(4)

The applicant has requested a 24-month shelf life for the drug product. The applicant submitted up to 18 months of long term data and 6 months of accelerated stability data for the drug product in _____ bottles and blisters. The applicant has demonstrated that the drug product can be adequately stored (i.e. all data within specifications) at 25° C/60%RH in the _____ bottles and blisters. At the time tested, the related substances were below the level of qualification and there were virtually no deviations in the assay or weight. The applicant will be asked to provide updated stability data and re-evaluate the dissolution data according to the new dissolution specifications proposed by OCP. Accordingly, NDA 22-104 is Approvable from a CMC perspective.

b(4)

All sites were submitted to the Office of Compliance in January of 2007. The final recommendation from the Office of Compliance for this application is Acceptable.

C. Basis for Approvability or Not-Approval Recommendation

Nine comments were conveyed to the applicant in the agency's July 23, 2007 Information Request Letters. The responses to the comments are summarized in this review. In the response, the applicant adequately addressed all CMC concerns. All dissolution results remained within the originally proposed acceptance criteria, however, OCP has deemed the propose specification limits unacceptable and proposed new specifications for the dissolution which will be communicated to the applicant in the action letter. Additionally, at this time, we have been advised that the clinical division will be recommending an AE action for this application. Accordingly, the applicant will be asked to submit updated stability data and re-evaluate the dissolution data according to the new dissolution specifications proposed by OCP. For that reason, we will not make a decision on the expiry at this time.



Executive Summary Section

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

SMcLamore/Date

RSood

C. CC Block

Orig. NDA 22-104

Division File

TOliver

12 Page(s) Withheld

X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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

/s/

Sherita McLamore
10/1/2007 11:08:56 AM
CHEMIST

Ramesh Sood
10/2/2007 07:49:52 AM
CHEMIST

NDA 22-104

Venlafaxine Hydrochloride Extended Release Tablets

Osmotica Pharmaceuticals Corporation

Sherita D. McLamore, Ph.D.



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Chemistry Review Data Sheet

1. NDA 22-104
2. REVIEW: #1
3. REVIEW DATE: July 10, 2007
4. REVIEWER: Sherita D. McLamore, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
n/a	

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	December 11, 2006
Amendment	January 19, 2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Osmotica Pharmaceutical Corporation
Address:	1205 Culbreth Drive
	Suite 200
	Wilmington, NC 28405
Representative:	n/a
Telephone:	910-509-0115

8. DRUG PRODUCT NAME/CODE/TYPE:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

- a) Proprietary Name: Venlafaxine Hydrochloride Extended Release Tablets
- b) Non-Proprietary Name (USAN): venlafaxine hydrochloride
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Major Depressive Disorder and
Social Anxiety Disorder

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 37.5 mg, 75 mg, 150 mg and 225 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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

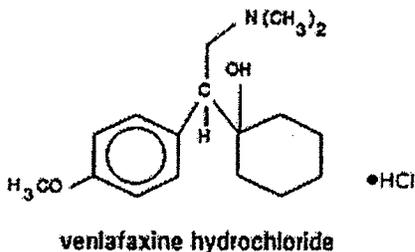
Chemical Name: (±)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol hydrochloride
Molecular Formula: $C_{17}H_{27}NO_2 \cdot HCl$
Molecular Weight: 318.87



CHEMISTRY REVIEW



Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	II			3	adequate		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A

b(4)

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")



CHEMISTRY REVIEW



Chemistry Review Data Sheet

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-699	Innovator NDA. Effexor XR
IND	71,288	Original IND

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Pending	Pending	Pending
Pharm/Tox	Pending	Pending	Linda Fosson, Ph.D.
Biopharm	Pending	Pending	Ronald Kavanaugh Ph.D.
LNC	N/A	N/A	N/A
Methods Validation	N/A	N/A	Sherita McLamore, Ph.D.
OPDRA	N/A	N/A	N/A
EA	Categorical Exclusion Acceptable		Sherita McLamore, Ph.D.
Microbiology	N/A	N/A	N/A

APPEARS THIS WAY ON ORIGINAL



The Chemistry Review for NDA 21-713

The Executive Summary

A. Recommendation and Conclusion on Approvability

The Chemistry, Manufacturing, and Controls (CMC) section of NDA [redacted] is [redacted] is approvable. The approval from a CMC standpoint is contingent on an adequate response to the CMC deficiencies.

b(4)

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)

Venlafaxine hydrochloride is a neuronal serotonin and norepinephrine reuptake inhibitor currently approved for the treatment of depression and general anxiety disorder. Venlafaxine hydrochloride was investigated under IND 71,288 and was approved for use under NDA 20-699.

The drug product, Venlafaxine Extended Release Tablet is a once a day treatment for major depressive disorder (MDD) and social anxiety disorder (SAD). The drug product is an osmotic tablet

b(4)

[redacted] This technology has been employed successfully in other FDA approved products such as Allegra D 24, Nifedipine Extended-release tablets and Oxybutynin Chloride Extended-release tablets.

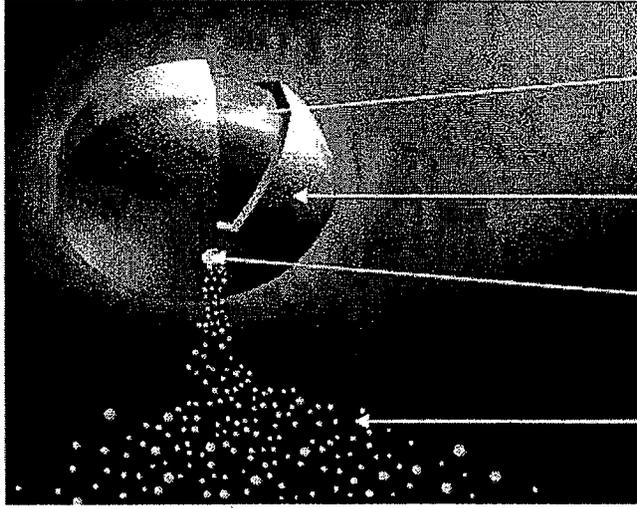
The osmotic technology used includes manufacturing [redacted]

b(4)

[redacted] Next, a single hole is drilled into one side of the tablet using a [redacted] As tablet passes through the gastrointestinal tract, water pressure from the intestinal fluids causes pressure to build up in the tablet core and the core content is forced out of the tablet through the laser drilled hole.

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Executive Summary Section



Tablet core (extended release of the active ingredient)

Semi-permeable membrane

Laser drilled orifice

Drug available for absorption

The drug product composition includes compendial grade mannitol, Povidone, Microcrystalline Cellulose, Polyethylene Glycol (PEG), Colloidal Silicon Dioxide, Magnesium Stearate, Cellulose Acetate

The formulation also includes

The drug product will be manufactured and packaged

b(4)

The drug product is available in four different strengths, 37.5 mg, 75 mg, 150 mg and 225 mg. All tablets contain the same components.

All tablets will be packaged in

b(4)

The drug substance will be manufactured and packaged by

The applicant referenced DMF for all information pertaining to the drug substance. DMF was reviewed and was found to contain adequate information to support this NDA. The drug substance is described as a non-hygroscopic, white to off-white crystalline powder with a melting point of 210-218°C. The molecular formula for the drug substance is C₁₇H₂₇NO₂·HCl and the molecular weight is 318.87.

b(4)



CHEMISTRY REVIEW



Executive Summary Section

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

The drug product is being developed as an extended release formulation venlafaxine hydrochloride. The applicant used the innovator drug Effexor as a comparator. The drug product has maximum daily dose of 225 mg and is being developed for the treatment of MDD and SAD. The drug product will be packaged _____

b(4)

The applicant has requested a 24-month shelf life for the drug product. The applicant submitted 9 months of long term and 6 months of accelerated stability data for the drug product in _____ bottles and 3 months of long term and accelerated stability data in blisters. The applicant has demonstrated that the drug product can be adequately stored (i.e. all data within specifications) at 25° C/60%RH for 9 months in the _____ bottles. The applicant only provided 3 months of long term and accelerated stability data for the drug product when stored in the blisters. At the time tested, the related substances were below the level of qualification and there were virtually no deviations in the assay or weight. The While the dissolution results remained within specification, however, there were at least two results at 3 months under 40°/75% RH that were very close to the specification limit. The applicant has not provided adequate data to support a 24-month expiry.

b(4)

All sites were submitted to the Office of Compliance in January of 2007. At this time, all sites with the exception of _____, the drug product packager and labeler, have been found acceptable. The final recommendation from the Office of Compliance is pending.

b(4)

C. Basis for Approvability or Not-Approval Recommendation

Approvability of NDA 22-104 from a Chemistry standpoint is contingent upon an adequate response to the chemistry, manufacturing and controls concerns outlined in this review and on an acceptable recommendation from the Office of Compliance.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

SMcLamore/Date
RSood

C. CC Block

Orig. NDA 22-104
Division File
TOliver

76 Page(s) Withheld

X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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

/s/

Sherita McLamore
8/3/2007 11:10:57 AM
CHEMIST

Ramesh Sood
8/20/2007 04:17:51 PM
CHEMIST

Initial Quality Assessment Branch I

OND Division: Division of Psychiatry Products
NDA: 22-104
Applicant: Osmotica Corp.
Letter Date: 11-DEC -06
Stamp Date: 12-DEC-06
PDUFA Date: 12-OCT-07
Trademark: Not specified
Established Name: venlafaxine hydrochloride
Dosage Form: 37.5, 75, 150, 225 mg Extended-Release Tablets
Route of Administration: Oral
Indication: Major Depressive Disorder/ SAD/ _____
Assessed by: Thomas F. Oliver, Ph.D.

b(4)

Summary

Venlafaxine hydrochloride is an approved drug [Effexor tablets (NDA 20-151, AP 28-DEC-93), Effexor ER Capsules (NDA 20-699, AP 20-OCT-97)] for Major Depressive Disorder, Social Anxiety Disorder, and Panic Disorder. Venlafaxine hydrochloride extended-release tablets were developed for the treatment of Major Depressive Disorder, Social Anxiety Disorder _____ . The sponsor did not have either an EOP2 or a pre-NDA meeting with the agency (IND 71,288). The clinical division did provide input (06-JUL-06) on the sponsor's clinical design (i.e., 4-way crossover studies).

b(4)

Drug Substance

Venlafaxine hydrochloride is a white to off-white crystalline powder. Venlafaxine hydrochloride contains one chiral center, but is being developed as the racemate. The drug substance will be manufactured commercially by _____

b(4)

_____ The NDA applicant references DMF _____ for information on venlafaxine hydrochloride (LoA dated 26-APR-06). DMF _____ was found adequate (see reviews by Mr. David Skanchy, OGD, June 14, 2006, Mr. David Skanchy, OGD, September 28, 2005, Ms. Barbara Scott, OGD, August 24, 2005, Mr. David Skanchy, OGD, August 19, 2004, Ms. T. Wang, OGD, May 22, 2003). The NDA applicant has included a Comparability Protocol for an Alternate API Manufacturer.

Drug Product

Venlafaxine hydrochloride extended-release tablets will be available in four strengths: 37.5 mg, 75 mg, 150 mg, and 225 mg for the treatment of Major Depressive Disorder, Social Anxiety Disorder, _____ . For most patients, the recommended starting dose for Venlafaxine Hydrochloride Extended-Release Tablets is 75 mg/day in a single dose with food (either in morning or evening). The proposed drug product is an osmotic tablet _____

b(4)

All excipients are USP/NF technical grade except the dyes/inks used for coloring and printing. _____

_____ The tablet

core is composed of

b(4)

All tablet strengths are round, biconvex, white coated tablets imprinted in black. The largest intended commercial batch sizes are

_____ for the 37.5 mg, 75 mg, 150 mg and 225 mg, respectively. The venlafaxine hydrochloride extended-release tablets will be manufactured by _____

_____ . The tablets are packaged in _____ bottles.

b(4)

_____ The NDA applicant has included a Comparability Protocol Manufacturing Site Change for changing the drug product manufacturing site.

Critical Issues for Review

- The adequacy of the polymorph and particle size controls will need to be evaluated.
- The NDA applicant has included a Comparability Protocol for an Alternate API Manufacturer. _____ was chosen as an example since the process and specifications are similar. In the event that another manufacturer is chosen the applicant expects that the same protocol would apply as long as the specifications in the original NDA were met and the site had a satisfactory GMP status. The applicant has not previously discussed their protocol with the agency. The adequacy of this comparability protocol will need to be determined.
- The compatibility of the excipients used in the drug product will need to be evaluated. In addition, the acceptability of the dyes/inks used for coloring and printing of the commercial product will need to be evaluated.
- The NDA applicant has not clearly delineated the physical appearance of each tablet strength. As per 21 CFR 206, each tablet strength needs to be uniquely identified. The physical appearance specification limits and the respective labeling will need to be evaluated to determine if each strength is uniquely identified.
- The NDA applicant has included a Comparability Protocol Manufacturing Site Change for changing the drug product manufacturing site. The protocol describes a change in the manufacturing site from _____ . The applicant has identified _____ as the primary choice for the site change. In the event that another facility is chosen the applicant expects that the same protocol would apply as long as the equipment remains in the same sub-classes and the site had a satisfactory GMP status. The applicant has not previously discussed their protocol with the agency. The adequacy of this comparability protocol will need to be determined.

b(4)

b(4)

• The applicant provided the drug product in-process controls for critical steps _____ The adequacy of these in-process controls will need to be evaluated.

b(4)

• The sponsor has set a dissolution specification of 4 hours: _____, 12 hours: _____ and 20 hours: _____. The adequacy of the dissolution method and specification limit will need to be determined in conjunction with OCP. The dissolution data will need to be closely scrutinized across the pivotal clinical batches, the stability batches, and the commercial batches for any inconsistencies.

b(4)

• The role of particle size on product performance will need to be evaluated, and if needed, adequate controls need to be in place to ensure consistent product performance. The sponsor will need to demonstrate that particle size has no clinical ramifications or that particle size (e.g., shape under the curve) as measured in clinical, stability, and commercial batches is rationally controlled to ensure product performance (as outlined in labeling).

• The adequacy of each of the _____ coatings (e.g., thickness) and the respective controls in place for batch to batch consistency will be important, especially for the semi-permeable membrane coat.

b(4)

• The control of orifice (number, size, and location) is critical. How the applicant monitors for the presence of the # of orifices (zero or two versus one), the location of the orifice, and the size of the orifice from tablet to tablet (within a batch) should be evaluated. The effect of how deviations in these areas affect drug performance will be important.

• The applicant utilizes _____ bottle. The adequacy of this _____ will need to be determined.

b(4)

• _____ venlafaxine hydrochloride is listed on the label (e.g., the 37.5 mg bottle label lists venlafaxine hydrochloride, _____ 37.5 mg venlafaxine). The reviewer will need to follow-up on this issue.

b(4)

• The applicant submitted stability data from three representative batches of each strength in each packaging configuration (9 months of long term _____ bottles and 3 months of long term _____ blisters). The sponsor has proposed an expiry of 24 months. Any differences between strengths and packaging configurations will need to be evaluated and an expiry assigned.

b(4)

Comments and Recommendation:

The NDA appears to be fileable from a CMC perspective. My recommendation would be for a single reviewer to be assigned to the NDA. Five sites were submitted into EES (16-JAN-07), however, the reviewer will need to confirm these are the only sites (especially drug substance). In accordance with 21 CFR §25.31, Osmotica Pharmaceutical claims a categorical exclusion from the requirement for an Environmental Assessment or Environmental Impact Statement as approval of the drug product will not result in the drug being administered at a higher dosage, for longer durations, or for different indications presently in effect in the marketplace.

74-day letter issue

_____ venlafaxine hydrochloride is listed on the label [e.g., the 37.5 mg bottle label lists venlafaxine hydrochloride, _____ (37.5 mg venlafaxine)]. The strength will need to correspond to the label claim. The reviewer and PM should include this issue as part of the 74 day letter.

b(4)

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this page is the manifestation of the electronic signature.**

/s/

Thomas Oliver
1/16/2007 03:20:02 PM
CHEMIST

Ramesh Sood
1/16/2007 04:25:10 PM
CHEMIST