CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204516Orig1s000

CHEMISTRY REVIEW(S)

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 27, 2013
FROM: Caroline Strasinger, Ph.D., Review Chemist, Branch IV/ONDQA
THROUGH: Moo-Jhong Rhee, Ph.D., Branch Chief, Branch IV/ONDQA
SUBJECT: Addendum to CMC Review #1 for NDA 204516
TO: NDA 204516

The previous CMC Review #1, dated 1-May-13, noted the following two deficiencies, and therefore made a recommendation of not approval of this NDA:

1. This NDA has ***not*** provided sufficient information to assure identity, strength, purity, and quality of the drug product.

2. An overall "Acceptable" recommendation has ***not*** been made by the Office of Compliance.

Regarding the Item #1, the review dated 26-APR-2013 by the biopharmaceutics reviewer stated the specification for the drug product was not adequate due to dissolution acceptance criteria. On 8-MAY-2013 the Applicant responded agreeing to the agency recommendation of acceptance criterion of Q= (b) (4) at 20 minutes and provided an updated specification for the drug product. An addendum to the original biopharmaceutics review was issued 24-MAY-2013, stating that the specification for the drug product is now **adequate**.

Regarding the Item #2, The Office of Compliance issued a "WITHOLD" recommendation for the drug product manufacturing site (b) (4) facility on 25-JUN-2013 based on incomplete or unsuccessful methods validation (See **Appendix 1** for report on the (b) (4) facility). The Applicant removed (b) (4) as a drug product manufacturer on 26-JUN-2013 (See **Appendix 2** for statement of removal and updated Manufacturer's sheet). The sole drug product manufacturer for this application is the Norwich facility which received an acceptable recommendation on 21-JUN-2013.

An overall "**ACCEPTABLE**" recommendation for the updated facilities involved in the manufacture and testing of the drug product was made on 27-JUN-2013 (See **Appendix 3** for the updated EES report).

Conclusion and Recommendation:

The specification for the drug product is now adequate. Additionally, the Office of Compliance has issued an overall "ACCEPTABLE" recommendation for all facilities involved.

From the ONDQA perspective, this Application is now recommended for APPROVAL.

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APPENDIX 3 – Final EES Report

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 204516/000	**Action Goal:**	
Stamp Date:	28-AUG-2012	**District Goal:**	29-APR-2013
Regulatory:	28-JUN-2013		
Applicant:	NOVEN THERAP	**Brand Name:**	PAROXETINE MESYLATE
	11960 SOUTHWEST 144TH ST	**Estab. Name:**	
	MIAMI, FL 33186	**Generic Name:**	PAROXETINE MESYLATE
Priority:	3	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	580	001; CAPSULE; PAROXETINE MESYLATE; 9.69MG	

Application Comment:

FDA Contacts:	C. STRASINGER	Prod Qual Reviewer	(HFD-800)	3017963776
	K. JENNINGS	Product Quality PM		3017962919
	K. SHILEY	Regulatory Project Mgr	(HFD-580)	3017962117
	D. CHRISTNER	Team Leader		3017961341

Overall Recommendation:	ACCEPTABLE	on 27-JUN-2013	by J. WILLIAMS	()	3017964196
	PENDING	on 27-JUN-2013	by EES_PROD		
	PENDING	on 26-JUN-2013	by EES_PROD		
	PENDING	on 25-JUN-2013	by EES_PROD		
	PENDING	on 25-JUN-2013	by EES_PROD		
	ACCEPTABLE	on 21-JUN-2013	by R. SAFAAI-JAZI	()	3017964463
	PENDING	on 21-JUN-2013	by EES_PROD		

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE OTHER TESTER		
Establishment Comment:	(b) (4)		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	10-OCT-2012				JENNINGSK
OC RECOMMENDATION	16-OCT-2012			ACCEPTABLE	STOCKM
				BASED ON PROFILE	

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

(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Establishment Comment: (b) (4)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	10-OCT-2012				JENNINGSK
OC RECOMMENDATION	16-OCT-2012			ACCEPTABLE	STOCKM
				BASED ON PROFILE	

(b) (4)

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

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment Comment: (b) (4)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	10-OCT-2012				JENNINGSK
SUBMITTED TO DO	15-OCT-2012	10-Day Letter			SAFAAIJAZIR
DO RECOMMENDATION	24-OCT-2012			WITHHOLD	PHILPYE
WL ISSUED				PENDING REGULATORY ACTION WITH	
SUBMITTED TO DO	17-MAY-2013	10-Day Letter			SAFAAIJAZIR
PDUFA 26-JUN-2013					
DO RECOMMENDATION	23-MAY-2013			ACCEPTABLE	PHILPYE
				BASED ON FILE REVIEW	
OC RECOMMENDATION	24-MAY-2013			ACCEPTABLE	PRABHAKARAR
OTHER TESTER = (b) (4) E				DISTRICT RECOMMENDATION	

Establishment: CFN: 1350044 FEI: 1350044

NORWICH PHARMACEUTICALS INC

6826 STATE HIGHWAY 12
NORWICH, NY 138153335

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment Comment: DRUG PRODUCT MANUFACTURING, PACKAGING (b) (4) BLISTER) LABELING, RELEASE TESTING, AND STABILITY TESTING (on 19-SEP-2012 by K. JENNINGS () 3017962919)

Profile: CAPSULES, PROMPT RELEASE **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	10-OCT-2012				JENNINGSK
SUBMITTED TO DO	16-OCT-2012	GMP Inspection			STOCKM
PLEASE NOTE THAT PDUFA GOAL DATE IS NOT UNTIL JUNE 2013; SITE WILL BE DUE FOR INSPECTION BEFORE THAT TIME					
DO RECOMMENDATION	31-OCT-2012			ACCEPTABLE	KGONZALE
LAST EI COVERED PROFILE CLASS CHG AND WAS NAI.				BASED ON FILE REVIEW	
OC RECOMMENDATION	01-NOV-2012			ACCEPTABLE	SAFAAIJAZIR
				DISTRICT RECOMMENDATION	
SUBMITTED TO DO	21-JUN-2013	10-Day Letter			SAFAAIJAZIR
PDUFA JUNE 28 2013					
DO RECOMMENDATION	21-JUN-2013			ACCEPTABLE	KGONZALE
NO OUTSTANDING COMPLIANCE ISSUES. AN INSPECTION OF THE FACILITY IS SCHEDULE TO START THE WEEK OF JULY 08, 2013.				BASED ON FILE REVIEW	
OC RECOMMENDATION	21-JUN-2013			ACCEPTABLE	SAFAAIJAZIR
				DISTRICT RECOMMENDATION	

Establishment: CFN: 2530802 FEI: 1000522077

PACKAGING COORDINATORS, INC. (FRMLY CATALENT PHARMA SOLUTIONS LLC)

3001 RED LION RD
PHILADELPHIA, PA 19114

DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Establishment Comment: BLISTER PACKAGING, SECONDARY PACAKGING, AND LABELING FOR DRUG PRODUCT (on 19-SEP-2012 by K. JENNINGS () 3017962919)

Profile: CAPSULES, PROMPT RELEASE **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	10-OCT-2012				JENNINGSK
OC RECOMMENDATION	16-OCT-2012			ACCEPTABLE	STOCKM
PACKAGING ONLY				BASED ON PROFILE	

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

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

FINISHED DOSAGE OTHER TESTER

Establishment Comment: (b) (4)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	10-OCT-2012				JENNINGSK
SUBMITTED TO DO	10-OCT-2012	GMP Inspection			SAFAAIJAZIR
PDUFA GOAL DATE: 28-JUN-2013					
ASSIGNED INSPECTION TO IB	13-OCT-2012	GMP Inspection			PHILPYE
DO RECOMMENDATION	01-MAR-2013			ACCEPTABLE	PHILPYE
				BASED ON FILE REVIEW	
OC RECOMMENDATION	04-MAR-2013			ACCEPTABLE	STOCKM
				DISTRICT RECOMMENDATION	

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/s/

CAROLINE STRASINGER
06/27/2013

MOO JHONG RHEE
06/27/2013
Chief, Branch IV

NDA 204516

Brisdelle
(Paroxetine)
7.5mg

Noven Therapeutics

Caroline Strasinger, Ph.D.
Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch IV

CMC Review of NDA 204516
For the Division of Reproductive and Urological Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 204516

2. REVIEW #: #1

3. REVIEW DATE: 28-APR-2013

4. REVIEWER: Caroline Strasinger, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	28-AUG-2012
Amendment 0003	3-OCT-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Noven Therapeutics
Address:	11960 SW 144th Street Miami, FL 33186
Representative:	Snehal Shah, Pharm D, Director, Regulatory Affairs
Telephone:	212-287-0971

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Brisdelle
b) Non-Proprietary Name (USAN): paroxetine
c) Code Name/#: LDMP or MESAFEM
d) Chem. Type/Submission Priority:
- Chem. Type: 3
- Submission Priority: Standard

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

10. PHARMACOL. CATEGORY: treatment of moderate to severe vasomotor symptoms associated with menopause

11. DOSAGE FORM: capsule

12. STRENGTH/POTENCY: 7.5 paroxetine (9.69 mg paroxetine mesylate)

13. ROUTE OF ADMINISTRATION: Oral

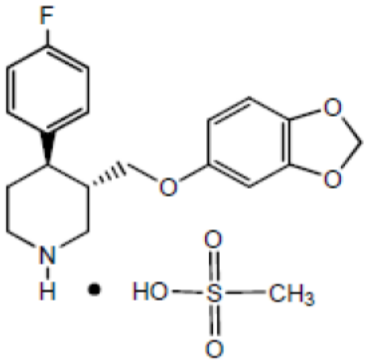
14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

Paroxetine Mesylate:
(-)-trans -4R- (4'-fluorophenyl) - 3S - [(3', 4'-methylenedioxyphenoxy) methyl] piperidine mesylate
$C_{19}H_{20}FNO_3 \cdot CH_3SO_3H$
MW = 425.46



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4	N/A	N/A	N/A
	III			4	N/A	N/A	N/A
	III			4	N/A	N/A	N/A
	III			4	N/A	N/A	N/A
	III			4	N/A	N/A	N/A
	III			4	N/A	N/A	N/A
	III			4	N/A	N/A	N/A
	III			4	N/A	N/A	N/A
	III			4	N/A	N/A	N/A
	IV			4	N/A	N/A	N/A
	III			4	N/A	N/A	N/A
	III			4	N/A	N/A	N/A
	IV			4	N/A	N/A	N/A

(b) (4)	III	(b) (4)	4	N/A	N/A	N/A
	III		4	N/A	N/A	N/A
	III		4	N/A	N/A	N/A
	III		4	N/A	N/A	N/A

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-299	PEXEVA tablets
IND	76636	Paroxetine Mesylate Capsule

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	PENDING	23-Apr-13	Office of Compliance
Pharm/Tox	N/A		
Biopharm	PENDING	26-Apr-13	Deepika Arora Lakhani
LNC	N/A		
Methods Validation	To be done per ONDQA's policy		
DMEPA	N/A		
EA	Claim for categorical exclusion is granted	30-Jan-13	Dr. Caroline Strasinger

Microbiology	N/A		

The Chemistry Review for NDA 204516

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has ***not*** provided sufficient information to assure identity, strength, purity, and quality of the drug product.

An overall "Acceptable" recommendation has ***not*** been made by the Office of Compliance.

Labels and labeling (Description and How Supplied sections) are adequate.

Therefore, from the ONDQA perspective, this NDA is not ready for approval in its present form per 21 CFR 314.125(b)(1) and 21 CFR 314.125(b)(13).

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

None

II. Summary of Chemistry Assessments

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

Drug product:
BRISDELLE (paroxetine) is an immediate-release, solid oral dosage containing 9.69 mg of paroxetine mesylate (equivalent to 7.5 mg of paroxetine base) in a Size 3 opaque pink/pink body and cap, hard gelatin capsule with "Noven" printed radially in black on the cap and (b) (4) 7.5 mg" (stacked) printed radially in black on the body of the capsule. The drug product is manufactured at two sites; **Norwich Pharmaceuticals in North Norwich, NY** and (b) (4) Several additional companies have been listed as excipient testing and packaging facilities.

Paroxetine mesylate was previously approved as 10, 20, 30, and 40 mg paroxetine mesylate tablets; PEXEVA® (paroxetine mesylate) tablets under NDA 21299. Noven Pharmaceuticals is the Applicant for both this NDA and NDA 21299. (b) (4)

The quality of the drug product is controlled by tests for description, paroxetine identity (HPLC and UV), mesylate identity, assay, related substances, content uniformity, dissolution and microbial purity.

The commercial container closure systems are the same or very similar for both manufacturing facilities (b) (4) and (b) (4) blister packs. (b) (4) Commercial packaging configurations include (b) (4) 30 capsules for blister packs. The Applicant is requesting 36 months of expiration dating; it is granted given the 18 months of registration stability data, 36 months of supportive stability data provided, and the similarity in formulation of the approved PEXEVA product.

Drug substance:
General information for the drug substance, paroxetine mesylate, has been provided in this NDA for reviewer convenience. The drug substance used to manufacture the drug product is the same drug substance as that used to manufacture commercial PEXEVA® tablets (NDA 21299). Therefore, the manufacturer, method of manufacture, and specification for paroxetine mesylate drug substance for the paroxetine capsule are the same as those used for commercial PEXEVA tablets (b) (4) Complete information regarding the CMC of paroxetine mesylate drug substance is provided in NDA 21299. No letter of authorization is necessary to reference the information as Noven is the Applicant for both NDA 204516 and NDA 21299. NDA 21299 was most recently reviewed for drug substance information on 21-NOV-2012 and was found adequate.

Paroxetine mesylate drug substance is manufactured by (b) (4) For the commercial product, all paroxetine mesylate drug substance will be sourced from the (b) (4) Stability data indicates there is no difference between (b) (4) drug substance. Annual reports for NDA 21299 indicate that the drug substance is stable for (b) (4) and a retest date of (b) (4) is proposed.

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

BRISDELLE (paroxetine), 7.5 mg is an orally administered capsule for the treatment of moderate to severe vasomotor symptoms associated with menopause. Systemic hormone therapy is the only FDA approved treatment for VMS. Brisdelle is a nonhormonal therapy. Brisdelle should be taken once daily, at bedtime, with or without food. Brisdelle was specifically developed with a lower dose of paroxetine than the doses used to treat depression, obsessive compulsive disorder, panic disorder, generalized anxiety disorder, social anxiety disorder, and post-traumatic stress disorder. The product should be stored at room temperature and protected from light and humidity.

C. Basis for Not-Approvability Recommendation

21 CFR 314.125(b)(1)

- The specification for the drug product is not deemed adequate due to the dissolution acceptance criterion for the drug product, which has not been resolved yet per the Biopharmaceutics Review dated 26-APR-2013, therefore quality of the drug product can not be assured.

21 CFR 324.125(b)(13)

- An "Acceptable" site recommendation from the Office of Compliance has ***not*** been made. (see the **Appendix 1** on P. 65)

(See the **List of Deficiencies** on p. 64 for all pending issues)

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Caroline Strasinger, PhD	28-APR-2013
ChemistryTeamLeaderName/Date: Donna Christner, PhD	28-APR-2013
ProjectManagerName/Date: Kerri Ann Jennings	28-APR-2013

C. CC Block

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