CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204516Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 204516	NDA Supplement #: S- n/a	Efficacy Supplement Type SE- n/a
Proprietary Name: Brisdelle Established/Proper Name: paroxetine Dosage Form: capsules Strengths: 7.5mg		
Applicant: Noven Therapeutics		
Date of Receipt: August 28, 2012		
PDUFA Goal Date: June 28, 2013	Action Goal Date (if different):	
RPM: Kim Shiley		
Proposed Indication(s): treatment of moderate to severe vasomotor symptoms associated with menopause		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 020031, Paxil® (paroxetine hydrochloride) 10mg, 20mg, 30mg, 40mg tablets	Animal Findings; Use in Pregnancy, Carcinogenesis, Mutagenesis, Impairment of Fertility

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

paroxetine capsules have a lower systemic exposure than Paxil Tablets as observed from data obtained from the paroxetine capsules PK study and the BE study 982413 from the Pexeva Capsules

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
PAXIL® (paroxetine hydrochloride)	020031	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a new indication and new dosage form.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐
*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☒

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☒ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all*

of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 5,872,132; 5,900,423; 6,113,944; 6,121,291; 6,133,289

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s): A091427

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR

314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☒ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s): 6,121,291; 6,133,289
Method(s) of Use/Code(s): U-286; U-358, U-431

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 5,872,132; 5,900,423; 6,113,944;
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): November 14, 2012; November 21, 2012

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☒ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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

/s/

KIMBERLY A SHILEY
06/27/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	**BRISDELLE™ (paroxetine) capsules, for oral use**
Applicant	Noven Therapeutics, LLC
Application/Supplement Number	NDA 204516
Type of Application	Original
Indication(s)	For the treatment of moderate to severe vasomotor symptoms associated with menopause (VMS)
Established Pharmacologic Class[1]	Selective serotonin reuptake inhibitor (SSRI)
Office/Division	ODE III/DBRUP
Division Project Manager	Kimberly Shiley
Date FDA Received Application	August 28, 2012
Goal Date	June 28, 2013
Date PI Received by SEALD	June 26, 2013
SEALD Review Date	June 27, 2013
SEALD Labeling Reviewer	Abimbola Adebowale
SEALD Division Director	Laurie Burke

PI = prescribing information

[1] The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item **(deficiency)**.
- **YES:** The PI **meets** the requirement for this item **(not a deficiency)**.
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Highlights (HL)

GENERAL FORMAT

NO 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment: *Margin between columns is < ½ inch. Increase to ½ inch.*

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

NO 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *Information under Drug Interactions heading in HL must reference (7.0 or the appropriate subsection under 7.0) in the FPI. We note that the references (4 and 5.7) currently included in HL under the Drug Interactions heading do not provide a list of clinically significant drug interactions in the FPI as described. Delete these two references if they are not applicable to this section.*

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required

Selected Requirements of Prescribing Information

• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*****
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

YES 12. All text must be **bolded**.

Selected Requirements of Prescribing Information

Comment:

NO 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment: *Heading in the Boxed Warning in HL is not centered.*

NO 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." in *italics* and centered immediately beneath the heading.

Comment: *Verbatim Statement in the Boxed Warning in HL is not centered.*

YES 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

YES 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.
Comment:

YES 24. Each contraindication is bulleted when there is more than one contraindication.
Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.
Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.
Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.
Comment:

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
Comment:

YES 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse

9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "*[see Warnings and Precautions (5.2)]*".

Comment:

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

YES 42. All text is **bolded**.

Comment:

YES 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

YES 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

Selected Requirements of Prescribing Information

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. 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:

YES 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment: *Do not need to italicize the statement at the beginning of Section 17.*

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

/s/

ABIMBOLA O ADEBOWALE
06/27/2013

ERIC R BRODSKY
06/27/2013
Eric Brodsky, SEALD labeling team leader, signing for Laurie Burke, SEALD Director

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	June 26, 2013
To:	Hylton V. Joffe, M.D. Director **Division of Bone, Reproductive and Urologic Products (DBRUP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Melissa Hulett, MSBA, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Twanda Scales, RN, MSN/Ed. Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Lynn Panholzer, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	BRISDELLE (paroxetine)
Dosage Form and Route:	Capsules
Application Type/Number:	204516
Applicant:	Noven Therapeutics

INTRODUCTION

On August 28, 2012, Noven Therapeutics (Noven) submitted for the Agency's review a New Drug Application (NDA) for paroxetine, 7.5 mg capsules for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause. On December 26, 2012 Noven submitted a Proprietary Name Request. On April 22, 2013 the Agency found the tradename Brisdelle acceptable.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the DBRUP on January 28, 2013 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for Brisdelle (paroxetine), 7.5mg capsules.

MATERIAL REVIEWED

- Draft Brisdelle (paroxetine) MG received on August 28, 2012 revised by the Review Division throughout the review cycle, and received by DMPP on June 18, 2013.
- Draft Brisdelle (paroxetine) MG received on August 28, 2012, revised by the Review Division throughout the review cycle, and received by OPDP on June 21, 2013.
- Draft Brisdelle (paroxetine) Prescribing Information (PI) received on August 28, 2012 revised by the Review Division throughout the review cycle, and received by DMPP on June 18, 2013.
- Draft Brisdelle (paroxetine) Prescribing Information (PI) received on August 28, 2012, revised by the Review Division throughout the review cycle, and received by OPDP on June 21, 2013.
- Approved Cymbalta (Duloxetine Delayed-Release Capsules) comparator labeling dated November 9, 2012.
- Approved Paxil (paroxetine hydrochloride Tablets and Oral Suspension) labeling dated December 18, 2012 (OPDP).

REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

CONCLUSIONS

The MG is acceptable with our recommended changes.

RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
06/26/2013

LYNN M PANHOLZER
06/26/2013

MELISSA I HULETT
06/26/2013

LASHAWN M GRIFFITHS
06/26/2013

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: June 24, 2013

To: Kim Shiley, RN
Regulatory Project Manager
Division of Bone, Reproductive, and Urologic Products (DBRUP)

From: Lynn Panholzer, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA 204516**
Brisdelle (paroxetine) Capsules

Background

This consult review is in response to DBRUP's January 28, 2013, request for OPDP's review of the package insert (PI), medication guide (MG), and carton and container labeling for Brisdelle (paroxetine) Capsules. OPDP reviewed the version of the draft PI and carton/container labels available in the DBRUP eRoom on June 18, 2013. Our comments on the PI are included directly on the attached, marked-up copy of the labeling. We have no comments on the carton/container labels (attached for reference). Our review of the MG was conducted jointly with the Division of Medical Policy Programs and will be filed under separate cover.

OPDP appreciates the opportunity to provide comments on this material. If you have any questions or concerns, please contact Lynn Panholzer at 301-796-0616 or lynn.panholzer@fda.hhs.gov.

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/s/

LYNN M PANHOLZER
06/24/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pediatric and Maternal Health Staff Memorandum

Date: June 17, 2013

From: Jeanine Best, MSN, RN, PNP, Team Leader – Maternal Health
Pediatric and Maternal Health Staff

Through: Lynne P. Yao, MD, OND Associate Director,
Pediatric and Maternal Health Staff

To: Division of Bone, Reproductive and Urologic Drug Products (DBRUP))

Drug: Brisdelle (paroxetine) capsules for oral use

NDA: 204516

Applicant: Noven Therapeutics, LLC

Subject: Pregnancy labeling

Materials Reviewed:

- Draft, revised Brisdelle labeling, dated June 6, 2013

Consult Question: Please provide guidance on whether we can abbreviate any of the information included in Sections 5.11 and 8.1, given that this product is for use only by menopausal women. We have labeled it as Category X because the indication (menopausal VMS) does not exist in pregnancy. However, the same drug is available in higher doses for psychiatric indications as Pexeva (NDA 21-299).

INTRODUCTION AND BACKGROUND

On August 28, 2012, Noven Therapeutics, LLC, submitted a 505(b)(2) application for Brisdelle (paroxetine mesylate) capsules for oral use, 7.5 mg, for the treatment of moderate to severe vasomotor symptoms associated with menopause. The Referenced Listed Drug is Paxil (paroxetine hydrochloride) tablets, NDA 20-031. Paroxetine is a selective serotonin reuptake inhibitor (SSRI).

The Division of Bone, reproductive, and urologic products (DBRUP) consulted the Pediatric and Maternal Health Staff (PMHS) – Maternal Health Team (MHT) on June 10, 2013, to provide input on pregnancy labeling for Brisdelle.

DISCUSSION

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in human milk is noted and presented in the label, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

Choice of a pregnancy category and inclusion of required risk statements are defined by the current labeling regulations at 21 CFR 201.57. Each category is defined by the findings from all available reproductive and developmental toxicity studies in animals and studies of drug use during human pregnancy. The pregnancy category definitions for pregnancy categories C, D, and X include a required consideration of both the potential risks and benefits of maternal drug use during pregnancy. The acceptability of clinical benefit to a woman for using a drug for a particular indication during pregnancy is weighed against the known and potential embryonal and fetal drug risks. Paroxetine is classified as a pregnancy category D for psychiatric indications because of human data demonstrating embryo-fetal harm; however, potential benefit exists for use in pregnant women for specific psychiatric indications. A pregnancy category X is the appropriate classification for Brisdelle due to the potential fetal farm and lack of potential benefit for use in pregnancy, as the indication of moderate to severe vasomotor symptoms does not occur in pregnant women.

CONCLUSIONS

PMHS-MHT agrees with the pregnancy category X classification for Brisdelle, as paroxetine can cause fetal harm and there is no potential benefit of Brisdelle treatment for a pregnant

woman because the condition of moderate to severe vasomotor symptoms associated with menopause does not exist during pregnancy. Furthermore, since the indication does not include a population of females of reproductive potential, a specific warning in labeling for females of reproductive potential is not necessary. A pregnancy contraindication and detailed information in subsection 8.1 Pregnancy is sufficient for providing pregnancy and potential embryo-fetal risk information for Brisdelle for the indication of treatment of moderate to severe vasomotor symptoms associated with menopause.

RECOMMENDATIONS

PMHS-MHT discussed Brisdelle pregnancy labeling with DBRUP at a June 11, 2013, labeling meeting and placed recommended labeling revisions in the DBRUP e-room (see Appendix A for PMHS-MHT recommended labeling revisions). We recommended revisions in the following sections of Brisdelle labeling:

- Highlights of Prescribing Information
- 4.4 Contraindications/Pregnancy
- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 17 Patient Counseling Information

Please note that PMHS-MHT reinserted the deleted subsections, 8.3 Nursing Mothers, and 8.4 Pediatric Use, as these subsections contain information for vulnerable populations; and therefore, should remain in all product labeling.

Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here.

Appendix A - PMHS - MHT Tracked-Changes Labeling Revisions

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/s/

JEANINE A BEST
06/17/2013

LYNNE P YAO
06/17/2013

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

CLINICAL INSPECTION SUMMARY

DATE: May 28, 2013

TO: Kim Shiley, Regulatory Project Manager
Ron Orleans, M.D., Medical Officer
Lisa Soule, M.D., Medical Team Leader
Division of Bone, Reproductive, and Urologic Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 204516

APPLICANT: Noven Therapeutics, LLC

DRUG: Mesafem® (paroxetine mesylate)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of vasomotor symptoms associated with menopause.

CONSULTATION REQUEST DATE:	October 26, 2012
CLINICAL INSPECTION SUMMARY DATE:	May 31, 2013
DIVISION ACTION GOAL DATE:	June 28, 2013
PDUFA DATE:	June 28, 2013

I. BACKGROUND:

The Applicant submitted this NDA to support the use of paroxetine mesylate for the treatment of vasomotor symptoms (VMS) in menopausal females.

The pivotal studies (Protocol N30-003 entitled "A Phase 3, Twelve-Week, Multicenter, Double-blind, Randomized, Placebo-controlled, Efficacy and Safety Study of Mesafem (Paroxetine Mesylate) Capsules in the Treatment of Vasomotor Symptoms Associated with Menopause" and Protocol N30-004 entitled "A Phase 3, Twenty-four Week, Multicenter, Double-blind, Randomized, Placebo-controlled, Efficacy and Safety Study of Mesafem (Paroxetine Mesylate) Capsules in the Treatment of Vasomotor Symptoms Associated with Menopause") were inspected in support of the indication. Protocol N30-003 is a 12-week, multi-center, double-blind, randomized, placebo-controlled study of Mesafem® in subjects with moderate to severe menopausal VMS. Protocol N30-004 is a 24-week, multicenter, double-blind, randomized, placebo-controlled study of paroxetine mesylate (7.5 mg) versus placebo in subjects with moderate to severe menopausal VMS.

The primary endpoints for both studies were the following:

- Mean change in frequency of moderate to severe vasomotor symptoms from baseline to Week 4
- Mean change in frequency of moderate to severe vasomotor symptoms from baseline to Week 12
- Mean change in severity of moderate to severe vasomotor symptoms from baseline to Week 4
- Mean change in severity of moderate to severe vasomotor symptoms from baseline to Week 12

Clinical sites 423, 314, 414, 338, and 438 below were selected based on higher levels of efficacy in comparison with most other sites. Sites were also selected for those conducting both protocols.

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ Site #/ # of Subjects (enrolled)	Inspection Dates	Final Classification
Nancy Campbell, M.D. 21820 Kingsland Blvd, Ste 100 Katy, TX 77450	N30-003/ 338/ 17	22 Feb – 6 Mar, 2013	NAI
Nancy Campbell, M.D. (as above)	N30-004/ 438/ 12		
Marvin Kalafer, M.D. 815 Greenwood Ave, Ste 12 Jenkintown, PA 19046	N30-003 323/ 6	19 Feb – 1 Mar, 2013	VAI. Pending final classification.
Marvin Kalafer, M.D. (as above)	N30-004 423/ 17		
Stephen Blank, M.D. 755 Mt Vernon Highway, Ste 300 Sandy Springs, GA 30328	N30-003/ 314/ 12	12 Feb – 8 Mar, 2013	NAI
Stephen Blank, M.D. (as above)	N30-004/ 414/ 15		

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

1. Nancy Campbell, M.D.
21820 Kingsland Blvd, Ste 100
Katy, TX 77450

a. What was inspected: At this site for Protocol N30-003, 29 subjects were screened, 17 subjects were randomized, and 17 subjects completed the study. For Protocol N30-004, 21 subjects were screened, 12 were randomized, and 12 completed the study. For Protocols N30-003 and N30-004, an audit of portions of the study records for all enrolled subjects was conducted. Signed informed consent forms were present for all subjects. Source records at the site were compared with line listings. Records reviewed included, but were not limited to, inclusion/exclusion criteria, Case Report Forms (CRFs), blinding procedures, medication diaries, adverse events, IRB, sponsor, and monitor communications, and test article accountability

b. General observations/commentary: A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.

c. Assessment of data integrity: The studies appear to have been conducted adequately, and the data submitted by this site may be used in support of the respective indication.

2. Marvin Kalafer, M.D.
815 Greenwood Ave, Ste 12
Jenkintown, PA 19046

a. What was inspected: At this site for Protocol N30-003, 16 subjects were screened, six subjects were enrolled, and six subjects completed the study. For Protocol N30-004, 34 subjects were screened, 17 subjects were enrolled, and 15 subjects completed the study.

For Protocol N30-003, an audit of the study records of four subjects randomized to the study was conducted. Line listings were compared with source data of subjects' responses to the various scales and questionnaires including those measuring the number of hot flashes and rating the severity of interference of the hot flashes with daily life. Other records reviewed included, but were not limited to, the informed consent forms for all subjects, Form FDA 1572s, financial disclosure forms, IRB and CRO communications, laboratory reports, concomitant medications, medical histories and physical examinations, electronic Case Report Forms (eCRFs), adverse events, compensation, and test article accountability.

Data regarding Patient Global Improvement and Body Mass Index were not verified as these data/source documents were not available at the site. Also not verified were data for the IWRS Confirmation of Discontinuation Emergent Signs and Symptoms Scale and the Columbia-Suicide Severity Rating Scale (C-SSRS) as these data were not provided with the line listings.

For Protocol N30-004, an audit of the study records of five subjects randomized to the study was conducted. Line listings were compared with source data of subjects' responses to the various scales and questionnaires including the Daily Hot Flash Diary and the Hot Flash Related Daily Interference Scale. Other records reviewed included, but were not limited to, the informed consent forms for all subjects, Form FDA 1572s, financial disclosure forms, IRB and CRO communications, laboratory reports, concomitant medications, medical histories and physical examinations, electronic Case Report Forms (eCRFs), adverse events, compensation, and test article accountability.

Not verified were data for the IWRS Confirmation of Suicidality Tracking Scale and IWRS Confirmation of Discontinuation Emergent Signs and Symptoms Scale as these data were not provided with the line listings.

b. General observations/commentary: A Form FDA 483 was issued at the conclusion of the inspection noting that sleep diaries for subjects were not reviewed in a timely manner, that documentation was lacking to demonstrate that at least four subjects were appropriately compensated for their participation in the study per the terms of the consent form, and that the consent form did not specify the amount of blood to be taken for subsequent analyses.

Of four sleep diaries reviewed for Protocol N30-003, all four were not reviewed by the clinical investigator until the following week (the protocol required that diaries be reviewed on a daily basis). Review of additional diaries indicated that a small percentage were not reviewed daily. Delay in review of sleep diaries would not significantly affect subject safety or the primary efficacy assessment.

The lack of documentation of appropriate subject compensation per the specifications of the consent form is an example of inadequate record keeping.

There is no regulatory requirement that the consent form specify the total amount of blood to be taken for analyses.

These observations (delayed diary review and inadequate documentation of compensation) do not affect the safety of the subjects or efficacy considerations.

Review of the Establishment Inspection Report (EIR) did indicate that test article reconciliation was inadequate since it could not be determined whether all unused drug returned to the site was forwarded to the sponsor for disposal.

For Protocol N30-004, Line Listing 8.01, Daily Hot Flash Diary, was compared with the Daily Hot Flash Compliance Report found on site. Of 182 hot flashes entered by Subject 423-023 between April 11, 2010, and March 17, 2011, there were at least 29 discrepancies with respect to when the hot flash occurred. Of these 29 discrepancies, 26 differed between one and eight seconds, and for the remaining three discrepancies, there was a difference of almost one hour (59:56-59:59). These time discrepancies were discussed with Dr. Orleans, the reviewing medical officer, who concurred that discrepancies in the time of reporting were of minimal significance given that the number and severity of hot flashes were reported correctly.

Also for Protocol N30-004, assessments of the Hot Flash Interference Scale by the clinical investigator were not documented as being performed daily as required by the protocol. For six Subjects (001, 007, 023, 025, 030, and 033), the assessment of the reports on 14 occasions by the clinical investigator occurred 27 to 196 days after the subject completed the survey.

c. Assessment of data integrity: Other than a lack of documentation of subject compensation and inadequate test article reconciliation as noted above, the studies appear to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. Stephen Blank, M.D.
755 Mt Vernon Highway, Ste 300
Sandy Springs, GA 30328

a. What was inspected: At this site for Protocol N30-003, 23 subjects were screened, 12 subjects were randomized, and 11 subjects completed the study. For Protocol N30-004, 29 subjects were screened, 15 were randomized, and 11 completed the study. For Protocols N30-003 and N30-004, the study records for those subjects completing the study were audited. Signed informed consent forms were present for all subjects. Other records reviewed included, but were not limited to, sponsor, monitor, and IRB communications, study training documentation, laboratory data, sleep and hot flash diaries, questionnaires, adverse events, and test article accountability.

b. General observations/commentary: A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.

c. Assessment of data integrity: The studies appear to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigator sites of Drs. Campbell, Blank, and Kalafer were inspected in support of this NDA. Drs. Campbell and Blank were not issued Form FDA 483s. The final classification for these inspections is No Action Indicated (NAI). Dr. Kalafer was issued a Form FDA 483. Review of the EIR for Dr. Kalafer's site indicated that test article reconciliation and documentation of subject compensation was inadequate. The preliminary classification for the inspection of Dr. Kalafer is Voluntary Action Indicated (VAI). Other than these deficiencies at Dr. Kalafer's site, the data generated by these three clinical sites and submitted by the sponsor appear adequate in support of the respective indication.

Note: The preliminary classification of VAI for the inspection of Dr. Kalafer's site is based on review of the EIR containing an outdated version of the Form FDA 483. An updated version (the version issued to the clinical investigator) will be submitted per communications with the field. An inspection summary addendum will be generated if conclusions change upon receipt and review of the updated Form FDA 483.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Janice Pohlman, M.D., M.P.H.
Team Leader
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/s/

ROY A BLAY
05/28/2013

JANICE K POHLMAN
05/28/2013

SUSAN D THOMPSON
05/28/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Final Label and Labeling Review

Date:	May 21, 2013
Reviewer:	Manizheh Siahpoushan, PharmD Division of Medication Error Prevention and Analysis
Acting Team Leader:	James Schlick, RPh, MBA Division of Medication Error Prevention and Analysis
Drug Name and Strengths:	Brisdelle (Paroxetine) Capsules 7.5 mg
Application Type/Number:	NDA 204516
Applicant/sponsor:	Noven Therapeutics, LLC
OSE RCM #:	2013-142-1

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the revised container labels for Brisdelle (Paroxetine) Capsules submitted on April 26, 2013 (Appendices A through C). Noven Therapeutics submitted revised container labels in response to:

- CMC comments pertaining to the established name and equivalency statement presentation in the November 9, 2012 Filing Communication Letter;
    - The established name for the drug substance should be displayed as (b) (4) on both the package insert and the carton and container labels when displayed in conjunction with the proprietary name.
    - The equivalency statement on the carton and container labels should read: "Each capsule contains (b) (4) paroxetine mesylate equivalent to 7.5 mg paroxetine (b) (4).
- Agency's March 15, 2013 letter concluding the proposed proprietary name, Brisdelle is acceptable.
- CMC's April 24, 2013 email requesting revisions to the labels and labeling regarding the established name and the storage conditions;
    - The established name of the product is paroxetine, per USP Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations, addressed in USP <1121> and effective May 1, 2013. Change all instances (b) (4) to "paroxetine".
    - Include "protect from humidity" or equivalent statement on carton and container labels for both configurations.
    - Change storage conditions to "Store at (b) (4)-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F)" for all configurations.

The Applicant's revised labels include:

- Updated artwork with the proprietary name Brisdelle.
- Agency's feedback regarding the established name and storage conditions.
- Recommendations in consideration of the draft Guidance for Industry: Safety consideration for Container Labels and Carton Labeling Design to Minimize Medication Errors (April 2013) and CDER MAPP 5021.1: Naming of Drug Products Containing Salt Drug Substances.

DMEPA previously reviewed the proposed labels and labeling under OSE Review # 2013-142 dated January 24, 2013. The recommendations made in that review were not forwarded to the Applicant.

2 MATERIALS REVIEWED

DMEPA reviewed the following items, submitted on April 26, 2013 (see Appendices A through C):

- (b) (4)
- Trade blister pack label
- Professional sample blister pack label

(b) (4)

Therefore, we looked at our previous review to ensure we provide the same recommendations for the revised container labels, when applicable (see Appendices D through F for the August 28, 2012 submission) .

3 CONCLUSIONS AND RECOMMENDATIONS

Based on our assessment of the revised container labels and carton labeling submitted on April 26, 2013 and our recommendations from the previous review (OSE Review #2013-142 dated Januray 24, 2013), DMEPA recommends the following be implemented prior to approval of this NDA:

3.1 COMMENTS TO THE APPLICANT

A. All Labels and Labeling

1. The finished dosage form is a component of the established name. Thus, we recommend that you relocate 'Capsules' to appear next to 'Paroxetine' and revise the presentation of 'Capsules' to have the same prominence (i.e., font size, color, and style) as Paroxetine.
2. Relocate the product strength (i.e., 7.5 mg) to follow the dosage form. Additionally, increase the prominence of the strength statement by increasing the font size. Thus, after revisions, the presentation of the proprietary name, established name, dosage form, and the product strength should appear as:

   Brisdelle
   (Paroxetine) Capsules
   7.5 mg
3. Remove or reduce the prominence of the flower type graphic that appears above the proprietary name as it competes in prominence with the proprietary name.
4. Remove (b) (4) that appear on all the labels as they distract from important information such as proprietary name, established name, dosage form, and product strength.

5. Reduce the prominence of the manufacturer's logo so that it does not compete with the prominence of the proprietary name.

B. [redacted]

C. Blister Label (trade)

1. Remove the statement [redacted] that appears next to the proprietary name. This statement appears promotional and clutters the label.
2. Delete the statement '[redacted] from the principal display panel as this statement already appears on the panel with the storage information.
3. Revise the presentation of the established name, dosage form, and product strength where they appear on all the panels of the blister label to appear as:

   (Paroxetine) Capsules
   7.5 mg per capsule

4. Relocate the NDC to appear in the top third portion of the label per 21 CFR 207.35(b)(3)(i).
5. Delete the '[redacted] statement and the [redacted] statement (i.e., [redacted]) that appear on the panel with the storage information. This information already appears on the principal display panel and clutters the area around the proprietary name, established name, and product strength.
6. Revise the blister pack design [redacted] with Day 1, Day 2, Day 3, …, Day 30. [redacted].
7. Remove [redacted]. Additionally, remove the statements [redacted]
8. Delete the statements [redacted] as well as the listed under these statements. [redacted]

D. Blister Labels (professional sample)

1. See comments C1 through C3.
2. Revise the blister pack design to replace [redacted] with Day 1, Day 2, Day 3, …, Day 7.
3. Delete the [redacted] statements that appear above the manufacturer's information on the panel with the storage information. This information already appears on this panel as well as the principal display panel, and clutters the label.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Marcus Cato, at 301-796-3905.

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/s/

MANIZHEH SIAHPOUSHAN
05/21/2013

JAMES H SCHLICK
05/21/2013

Clinical Consultation

FROM: Laleh Amiri-Kordestani, M.D.
Clinical Reviewer
Office of Hematology Oncology Products (OHOP)
Division of Oncology Products 1 (DOP1)

Elimika Pfuma, Pharm.D., Ph.D.
Clinical Pharmacology Reviewer
FDA/CDER/OTS/OCP/Division V

TO: Kim Shiley, R.N., RPM/DRUP 6-2117
Ron Orleans, M.D., Clinical Reviewer

SUBJECT: Paroxetine mesylate 7.5 mg capsules, NDA 204516

DATE CONSULT RECEIVED: February 4, 2013
DATE CONSULT COMPLETED: March 14, 2013

MATERIAL RECEIVED FOR REVIEW: Sponsor proposed paroxetine label

Requested Action
DRUP is currently reviewing NDA 204516 submitted by Noven, for paroxetine mesylate (7.5 mg capsules) for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause. DRUP requests DOP1 assistance with the following questions:

1. Do you anticipate any clinical impact on the effectiveness of tamoxifen if women with a history of or at high risk of breast cancer who are taking tamoxifen were to use paroxetine 7.5 mg concomitantly for VMS? It is anticipated that most women will continue their VMS treatment for several years.
2. Do you agree that the proposed labeling is appropriate and sufficient? If not, what language would you propose?

BACKGROUND

Currently, hormone (estrogen or estrogen/progestin) therapy is the only approved treatment for VMS associated with the menopause. If approved, paroxetine mesylate may be the first non-hormonal product approved for this indication. Because paroxetine is not a hormonal product, is likely to be used by women who have contraindications to hormonal therapy, such as those who have had breast cancer or are at high risk to develop

breast cancer. Some of these women may be candidates for or are taking tamoxifen therapy. Issues concerning the potential drug-drug interaction between paroxetine and tamoxifen (due to paroxetine's inhibitory effect on CYP2D6) were discussed at a 2006 AC meeting; however, the tamoxifen label does not discuss concomitant use with paroxetine. In the proposed paroxetine mesylate 7.5 mg label, the information about the interaction with Tamoxifen is listed under Highlights, Section 5.2 and Section 7.7.

• The Applicant proposes language stating that the efficacy of tamoxifen may be reduced when administered concomitantly with paroxetine, (b) (4)

• Section 5.2 and 7.7 of the proposed label state that some studies have shown that the efficacy of tamoxifen, as measured by the risk of breast cancer relapse/mortality, may be reduced when co-prescribed with paroxetine as a result of paroxetine's irreversible inhibition of CYP2D6. However, other studies have failed to demonstrate such a risk. (b) (4)

Response to Consult Request

Tamoxifen, a selective estrogen receptor modulator (SERM), has been a therapeutic agent for the treatment of breast cancer used in the past three decades. Tamoxifen is FDA approved for the following indications:

1. Metastatic Breast Cancer:
   In the treatment of metastatic breast cancer in women and men.
2. Adjuvant Treatment of Breast Cancer:
   Indicated for the treatment of node-positive and node-negative breast cancer in women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation.
   Indicated for the reduction of the occurrence of contralateral breast cancer.
3. Ductal Carcinoma in Situ (DCIS):
   Indicated to reduce the risk of invasive breast cancer in women with DCIS
4. Reduction in Breast Cancer Incidence in High Risk Women:
   Indicated to reduce the incidence of breast cancer in women at high risk for breast cancer. "High risk" is defined as women at least 35 years of age with a 5-year predicted risk of breast cancer ≥ 1.67%, as calculated by the Gail Model.

Paroxetine is an inhibitor of CYP2D6. CYP2D6 is believed to be the major enzyme involved in the formation of the tamoxifen active metabolite, endoxifen. In one trial, exdoxifen exposures were decreased by 64% when 10 mg/day of paroxetine was given with 20mg/day of tamoxifen compared to tamoxifen alone due to the drug interaction through CYP2D6 (PMID: 14652237). Endoxifen is believed to have a 100 fold greater affinity for the estrogen receptor and 30 – 100 fold greater potency than tamoxifen, *in vitro*.

1. Do you anticipate any clinical impact on the effectiveness of tamoxifen if women with a history of or at high risk of breast cancer who are taking tamoxifen were to use paroxetine 7.5 mg concomitantly for VMS? It is anticipated that most women will continue their VMS treatment for several years.

Response: No, the current evidence does not support the negative impact on the efficacy of tamoxifen. There are several clinical studies looking into the association of CYP2D6 and clinical outcome in patients with breast cancer. Unfortunately, data from randomized controlled trials are lacking.

Tamoxifen is known to be metabolized in the liver and gut wall in humans to several primary and secondary metabolites that have pharmacologic activity [PMID: 10430063, PMID: 14652237]. Tamoxifen itself has a weak affinity for the ER. Tamoxifen is known to be catalyzed by several enzymes including CYP450 enzymes, and undergoes extensive biotransformation into active and inactive metabolites. CYP2D6 is known to be a key enzyme responsible for the generation of an active tamoxifen metabolite, 'endoxifen'. There are some discrepant reports for the association between CYP2D6 genotype and clinical outcomes of tamoxifen therapy, probably because of the heterogeneity in sample collection or analysis, including differences in regimen of tamoxifen treatment [PMID: 21342038].

Many studies have investigated the CYP2D6 inhibitory potential of various medications. It has been hypothesized that concomitant use of CYP2D6 inhibitors may result in a poor clinical outcome in tamoxifen-treated patients with early or advanced breast cancer. The majority of evidence is generally based on results from in vitro studies examining the metabolism of a known substrate of CYP2D6 in the presence of CYP2D6 inhibitors using human liver microsomes. However, it is difficult to predict the in vivo effects when only using in vitro results. Several groups have reported the effects of concurrent CYP2D6 inhibitor use on the risk of breast cancer recurrence [PMID: 19690182, PMID: 20142325, PMID: 20848186, PMID: 20593233, PMID: 20880642, PMID: 20385997, PMID: 20823421]. Ahern et al. investigated 15 drugs inhibiting CYP2D6, and reported no association with breast cancer recurrence in the patients treated with tamoxifen; however, patients coadministrated paroxetine showed a higher odds ratio without statistical significance because of smaller sample size [PMID: 19690182]. In the report by Kelly et al. using 2430 patients treated with tamoxifen and a single SSRI, they reported that absolute increases of the period of overlapping use of paroxetine and tamoxifen were significantly associated with increases in the risk of death from breast cancer [PMID: 20142325]. By contrast, Azoulay et al. reported that concurrent use of strong CYP2D6 inhibitors was not associated with an increased incidence of breast cancer recurrence [PMID: 20848186]. There are some limitations to these studies, and the questions remain regarding the contribution of CYP2D6 inhibitors vs. the genotype to the observed results. Further investigation considering these issues is required.

2. Do you agree that the proposed labeling is appropriate and sufficient? If not, what language would you propose?

Response: We recommend that this information should not be included in the highlights section. We have the following recommendations:

(b) (4)

Laleh Amiri-Kordestani, MD
DOP1 Medical Reviewer

Patricia Cortazar, MD
DOP1 Medical Team Leader

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

/s/

LALEH AMIRI KORDESTANI
03/18/2013

PATRICIA CORTAZAR
03/18/2013

Consult NDA 204516
From: OND/DRUP
Date requested: 1-4-2013
Date Desired Completed: 2-1-2013
Medical reviewer: Lucas Kempf, MD Division of Psychiatric Products
Product: Paroxetine mesylate
Dosage: 7.5mg per day
Classification of Drug: non hormonal
Indication: vasomotor symptoms due to menopause

1. Background

General
LDMP (low dose mesylate of paroxetine) is an SSRI being developed for the treatment of moderate to severe VMS associated with menopause. The product contains 7.5 mg of paroxetine mesylate and is formulated as a capsule. Higher doses (10 to 60 mg) of paroxetine (Paxil® or Pexeva®) are approved for psychiatric indications and have been in use in the US since the initial approval of Paxil (paroxetine hydrochloride) in 1992.

Generally, antidepressant doses of paroxetine are in the range of 20 to 60 mg/day. Pexeva (paroxetine mesylate) has a chemical structure similar to paroxetine hydrochloride, the only difference being the associated salt. Pexeva was first approved for use in the US in 2003 at doses ranging from 10 to 60 mg/day, depending on the psychiatric indication.

There are no nonhormonal therapies currently approved for the treatment of VMS. LDMP is not approved and has no pending marketing applications outside of the United States.
Reference Listed Drug for 505(b)(2)
• NDA 20-031: Paroxetine Hydrochloride (Paxil)
• Route of administration Oral tablets
• Strength 10mg, 20mg, 30mg, 40mg
• GlaxoSmithKline

Reason for consult: To address suicidality in regards to this product.

2. Clinical Studies (Individual) Summaries

1. **Supportive Study N30-002**: “A Phase 2, Exploratory, Eight- Week, Multi-Center, Double-Blind, Randomized, Placebo-Controlled Efficacy and Safety Study of Mesafem (paroxetine mesylate) Capsules in the Treatment of Vasomotor Symptoms Associated with Menopause.”

101 subjects were randomized: 49 randomized to LDMP and 52 randomized to placebo.

2. **Pivotal Study N30-003:** “A Phase 3, Twelve-Week, Multicenter, Double-Blind, Randomized, Placebo-Controlled, Efficacy and Safety Study of Mesafem (Paroxetine Mesylate) Capsules in the Treatment of Vasomotor Symptoms Associated with Menopause.”

This was a 12 week study in 606 subjects. For inclusion in the study, subjects must have had 7-8 moderate or severe hot flashes per day and 50-60 moderate to severe hot flashes per week at baseline. There were 4 co-primary endpoints (Mean change in frequency and severity relative to placebo at 4 weeks and 12 weeks). In addition, if the frequency difference were less than 2 moderate or severe hot flashes per day, a responder analysis was required to determine a clinical meaningful response. There was a 12-day Placebo Run-in period. The weekly mean reduction in severity of moderate to severe hot flashes at Week 12 in Study N30-003 demonstrated a statistically significant difference from the placebo response.

3. **Pivotal Study N30-004:** “A Phase 3, Twenty-Four Week, Multicenter, Double-Blind, Randomized, Placebo-Controlled, Efficacy and Safety Study of Mesafem (Paroxetine Mesylate) Capsules in the Treatment of Vasomotor Symptoms Associated with Menopause.”

This was a 24 week study (168 days) in 570 subjects. There were four co-primary endpoints as in N30-003. A patient satisfaction anchored responder analysis was used to determine if these reductions in hot flash frequency were clinically meaningful. This analysis was based on the percentage of responders in each treatment group.

In addition, a co-primary endpoint of persistence of benefit to Week 24 was assessed using a responder analysis. A responder was defined as a subject whose frequency of moderate to severe hot flashes was reduced by 50% or more from baseline to Week 24. The proportion of subjects classified as responders was significantly greater in the LDMP group (48%) than in the Placebo group (36%; p=0.0066).

Safety

• A total of 1300 subjects were treated in the LDMP clinical program, of which 659 subjects received at least 1 dose of LDMP. Of these, 235 subjects in the LDMP group (218 in the Placebo group) completed 24 weeks (6 months) of treatment in Study N30-004. The percentage of subjects who completed the study was similar across treatment groups (86.8% and 85.3% in the LDMP and Placebo groups, respectively). A total of 84 subjects (13.2%) and 94 subjects (14.7%) discontinued the study in the LDMP and Placebo groups, respectively.

Suicidality

• There were no completed suicides reported in the LDMP clinical development program. There was 1 suicide attempt in 1 subject in the LDMP group (1/635; 0.2%) and none in the Placebo group (0/641; 0.0%). The patient took an overdose of medication in the setting of increased anxiety and depressed mood after an argument with her husband. She left several notes but was found by her husband and rushed to the

hospital. She was treated and released and appears to have misrepresented her hospitalization to the investigator at the next visit. It was not until her medical records from the hospital were received that it was discovered that she had a suicide attempt and was removed from the study. Her mood episode had resolved per the narrative report.
• One death occurred in a 55-year-old woman who experienced SAEs of cardiorespiratory arrest and coronary artery arteriosclerosis that led to death.

3. Consulting questions:

1. Comment on *"The appropriateness of the Applicant's evaluation of suicidality, including choice of instruments and mapping approach."*

Suicidality Scores
Summaries of Suicidality Scores were presented for the individual studies separately and for two pooled data sets (all controlled studies combined and all Phase 3 studies combined). Additionally, a subject listing of all suicidality score results was provided.

- For N30-002 and N30-004 suicidality was assessed using the Suicidality Tracking Scale (STS).
- For N30-003 and N30-005 suicidality was assessed using the Columbia Suicide Severity Rating Scale (C-SSRS).
  As stated per FDA's suicidality guidance document issued in September 2010, STS may be mapped to the preferred C-SSRS terms using the Columbia Classification Algorithm for Suicide Assessment (C-CASA).

The STS is a prospective rating scale that tracks treatment-emergent suicidal ideation and behaviors. It is an eight-item scale that can be administered either by a clinician or patient through self-report. Each STS item is scored on a 5-point Likert scale (0=not at all, 1=a little, 2=moderately, 3=very, and 4=extremely).

The applicant, instead of mapping to the C-CASA preferred terms, mapped both scales to dichotomous terms of yes or no for 2 categories of suicidal ideation and suicidal behavior.

The applicant's subscales from STS mapping to their understanding of the C-CASA include:
Excerpted from ISS:

• Suicidal Ideation subscale: sum of scores from items 2, 3, and 4, plus score from item 5 if ≤1.
• Suicidal behavior subscale: sum of scores from items 6, 7a, and 8, plus score from item 5 if >1.
• Total score

For summary purposes:
"Suicidal Ideation" will be set to "Yes" If responses for Q2, Q3, Q4 and Q5 are all <= 1 Else "Suicidal Ideation" will be set to "No".
"Suicidal Behavior" will be set to "Yes" If responses for Q5, Q6, Q7a and Q8 are all <= 1 Else "Suicidal Behavior" will be set to "No".

The subscales (i.e. Suicidal Ideation and Suicidal Behavior) from C-SSRS are.
• Suicidal Ideation:
1. Wish to be dead,
2. Non-specific active thoughts,
3. Active suicidal ideation with any methods (not plan) without intent to act,
4. Active suicidal ideation with some intent to act, without specific plan,
5. Active suicidal ideation with specific plan and intent and
6. Suicidal behaviors:
1. Actual attempt,
2. Interrupted Attempt,
3. Aborted Attempt,
4. Preparatory Acts or Behavior
For summary purposes:
"Suicidal Ideation" will be set to "Yes" If subjects have at least one occurrence of suicidal ideation Else "Suicidal Ideation" will be set to "No".
"Suicidal Behavior" will be set to "Yes" If subjects have at least one occurrence of suicidal behavior Else "Suicidal Behavior" will be set to "No".

The applicant did not follow the advice and mapped the STS to determinations of suicidal ideation and suicidal behavior for accounting purposes. They did not differentiate between a history of suicidality and treatment emergent suicidality, as is done in the C-SSRS. They erroneously report a high level of discontinuations due to suicidality rather than a "history of suicidality".

After reading the narratives and correcting for this error, there does not appear to be a higher rate of discontinuations due to treatment emergent suicidality.

2. Comment on *"Whether you agree with the Applicant's expert's conclusion that there does not appear to be a significant risk of suicidal ideation or behavior associated with use of paroxetine mesylate."*

Excerpted from the SSI report:

APPENDIX: EXPERT REPORT ON SUICIDALITY IN LDMP CLINICAL TRIALS
Expert Opinion by (b) (4)

My overall impression is that rates of suicidal ideation and behavior are in line with, or actually below, what may be expected in the general population of women of this age group over a period of nearly 6-months. I base my opinion on

the most recent published rates which suggest that on average 1% of adults reported making suicide plans in the past year, and 0.5% of the general adult population reports attempting suicide in the past year and on average the 3.7% of the adult population had suicidal thoughts in the last year. In addition, this rate appears to be actually even higher in females of the general age group (3.9% Crosby et al. 2011).

The exclusion and discontinuation criteria related to suicidal ideation and behavior were extremely conservative in these studies. It appears that the close follow up and ongoing evaluations with the STS scale identified fluctuations in individuals' suicidal ideations that would not have been recognized in general clinical practice, or even other suicide tracking scales. This likely lead to several adverse event filings and discontinuations that were out of proportion to the actual clinical significance of the ideations.

However, there were a few specific subjects of interest. There appears to have been one suicide attempt documented among all 4 studies: Subject 4-23- 014 who was randomized to LDMP. However, this case appears to be complicated. Based on the SAE report and hospital discharge summary, it was in a subject who was briefly hospitalized for an overdose with clonazepam, requip and metoprolol seeming precipitated by a family conflict. However, a possible secondary diagnosis of mastoiditis was originally believed to be the reason for admission by the treating clinician and this visit was not known to be for a suicide attempt and not considered to be a serious AE. The patient continued to receive study medication for an additional month before the complete story unfolded and the subject's study participation was ultimately terminated. At the time of termination the symptoms were completely resolved with a score of 0 of the STS.

Subject 4-05-013 had a significant increase in STS score from a baseline score of 2 to 22 at end of the randomized study period at Day 169. This case is also a somewhat confusing case as there was question as to whether the self-report assessment was accurately completed by the subject as per the study clinician's report. This report suggests the subject did not have an accident and she denied any suicidal behavior. There were 4 additional subjects (3 LDMP and 1 placebo) exhibiting a score of 5 on the STS at Day 169. Although there appears to be an uptick in reported suicidal ideation and behavior at the Day 169 visit, with a numerically larger number of subjects randomized to LDMP reporting suicidal ideation at this time point, the effects are not statistically significant. Considering that this effect was only seen at this single, late time point, makes me believe that this is more likely either a spurious finding or an artifact due to some other factor related to study termination. In sum, there appears to be little evidence to suggest any true, statistically significant increased risk of suicidal ideation or behavior associated with LDMP in the current sample. This together with existing literature showing no significant increase in suicidal ideation or behavior in mood and anxiety disorder patients in this age range treated with even higher doses of selective serotonin reuptake inhibitor medications, makes me confident that

these studies do not suggest a significant risk of suicidal ideation associated with LDMP 7.5 mg once daily in women with VMS associated with menopause. However, as is always the case, I would recommend ongoing surveillance.
[redacted] (b) (4) Date: 7/28/12

We agree that these studies do not demonstrate an increased risk of suicidal ideation or behavior for drug vs. placebo in these study populations. However, these populations excluded patients with a history of suicidal ideation, and investigators discontinued any patients whose STS became even mildly elevated. Additionally, as evidenced by study N30-003's frequent discontinuation of higher risk patients after the inclusion criteria were changed to exclude patients with history of suicidal ideation or behaviors, these studies are not a fully representative population. In conclusion, the one episode of suicidal behavior happened in the treatment arm so we agree with the need for ongoing surveillance.

3. Comment on "*Whether you believe labeling beyond the class labeling about suicidality (including a boxed warning) is warranted to address the risk of suicidality associated with this drug."*

We suggest that the labeling for this product should include the verbatim class language for the suicidality boxed warning and warnings in section 5. Warning and Precautions as presented in the submitted labeling.

We believe that the language in section 14 should reflect the fact that the study population excluded patients with a history of suicidal ideation or suicidal behavior. There is a high likelihood that physicians will use this product in patients that have comorbid depression and other psychiatric disorders, because of paroxetine's other indications. It should be clear in labeling that this low dose has not been studied for depression, as indicated in their proposed labeling. Labeling should also state that these studies excluded any high risk patients. Therefore, the studies are not informative regarding patients with depression or other psychiatric disorders.

We do not believe that there needs to be additional language in the Adverse Reactions section of labeling in regard to suicidality beyond the language they propose.

Thank you for the interesting consult. Please contact us for any further questions or clarifications.

Lucas Kempf, MD
Medical Reviewer

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

/s/

LUCAS B KEMPF
02/04/2013

ROBERT L LEVIN
02/04/2013

MITCHELL V Mathis
02/05/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 204516	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: TBD Established/Proper Name: paroxetine mesylate Dosage Form: capsules Strengths: 7.5 mg		
Applicant: Noven Therapeutics, LLC Agent for Applicant (if applicable):		
Date of Application: August 28, 2012 Date of Receipt: August 28, 2012 Date clock started after UN:		
PDUFA Goal Date: 6-28-2012	Action Goal Date (if different):	
Filing Date: 10-27-2012	Date of Filing Meeting: 10-23-2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 10		
Proposed indication(s)/Proposed change(s): treatment of moderate to severe vasomotor symptoms associated with menopause		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 076636	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**		X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***		X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:		X		Checked any paroxetine and found A091427 expired exclusivity, 11-1-2011

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		X		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			called Reviewer's Guide, sec 1.2
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**X**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**X**	
Applications in "the Program" (PDUFA V) (NME NDAs/Original BLAs)	**YES**	**NO**	**NA**	**Comment**
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			**X**	
• If yes, were all of them submitted on time?				
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?				
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?				
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			

Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)]. yes ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*				
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	ELECTRONIC

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*: ?			**X**	

Pediatrics	**YES**	**NO**	**NA**	**Comment**

PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?				
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	X			Full waiver
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]				
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***		X		
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels			

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

	☒ Immediate container labels (BLISTER) ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X			
Is the PI submitted in PLR format?[4]	X			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?				PENDING
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)				PENDING
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?				PENDING
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined?				

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If no, request in 74-day letter.				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	X			OSI filed DARRTS 10-30-2012 DNP consult pending
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 9-20-2010 ***If yes, distribute minutes before filing meeting***	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 5-29-2012 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** 12-13-2010, 5-13-2011 ***If yes, distribute letter and/or relevant minutes before filing meeting***	X			

ATTACHMENT

MEMO OF FILING MEETING

DATE: 10-23-2012

NDA #: 204516

PROPRIETARY NAME: TBD

ESTABLISHED/PROPER NAME: paroxetine mesylate

DOSAGE FORM/STRENGTH: capsules.7.5 mg

APPLICANT: Noven Therapeutics, LLC

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause

BACKGROUND: Applicant submitted application under 505(b)(2) regulatory pathway, relying, in part, on FDA's finding of safety for Paxil (paroxetine hydrochloride) tablets (GlaxoSmithKline NDA 020031), for which Noven does not have a right of reference. In addition, Noven is referencing information previously submitted within their NDA 021299 for Pexeva (paroxetine mesylate) tablets. Paroxetine mesylate 7.5 mg is an orally administered selective serotonin reuptake inhibitor (SSRI) submitted as an alternative to hormone therapy for the treatment of moderate to severe VMS associated with menopause.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kim Shiley	Y
	CPMS/TL:	Margie Kober	Y
Cross-Discipline Team Leader (CDTL)			
Clinical	Reviewer:	Ron Orleans	Y
	TL:	Lisa Soule	Y

Clinical Pharmacology	Reviewer:	Sayed Al Habet, filing Li Li, primary	Y Y
	TL:	MJ Kim	Y
Biostatistics	Reviewer:	Jia Guo	Y
	TL:	Mahboob Sobhan	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Leslie McKinney	Y
	TL:	Alex Jordan	N
Product Quality (CMC)	Reviewer:	Donna Christner, filing Caroline Strasinger, primary	Y Y
	TL:	Moo-Jhong Rhee	N
Biopharmaceutics	Reviewer:	Deepika Arora Lakhani	Y
	TL:	Angelica Dorantes	N
Facility Review/Inspection	Reviewer:	Vipul Dholakia	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Sarah Brody	Y
	TL:	Zach Oleszczuk	Y
OSE/DRISK (REMS)	Reviewer:	Cynthia LaCivita	N
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Roy Blay	Y
	TL:	Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees	Hylton Joffe, Director, DRUP Audrey Gassman, Acting Deputy Director, DRUP Julie Beitz, Director, ODE III Vicky Kusiak, Deputy Director, ODE III		Y Y Y Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the***	☒ YES Date if known: 3-4-2013 ☐ NO ☐ To be determined Reason:

reason. For example: o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

Comments:	

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO ☒ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**: Product Quality RPM to submit request	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☒ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Hylton Joffe

Date of Mid-Cycle Meeting: January 28, 2013

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day

	filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in "the Program")
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
(3) 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) 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, and.

(3) 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) 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, or

(3) 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 OND ADRA or OND IO.

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

/s/

KIMBERLY A SHILEY
11/08/2012

MARGARET M KOBER
11/08/2012

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Application: 204516

Application Type: New NDA

Name of Drug: paroxetine mesylate

Applicant: Noven Therapeutics, LLC

Submission Date: August 28, 2012

Receipt Date: August 28, 2012

1.0 Regulatory History and Applicant's Main Proposals

Paroxetine mesylate 7.5 mg is an orally administered selective serotonin reuptake inhibitor (SSRI) submitted for approval as an alternative to hormone therapy for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by November 30, 2012. The resubmitted PI will be used for further labeling review.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment: *Font type needs to be consistent throughout HL. Arial narrow not recommended.*

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*****

• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

YES 12. All text must be **bolded**.

Comment:

YES 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

YES 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

YES 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

YES 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

N/A 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment:

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

YES

24. Each contraindication is bulleted when there is more than one contraindication.
Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

NO 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: *BOXED WARNING is missing; subheading 9.2 should be changed to Abuse; add 9.3 Dependence; subheading 12.4 Special Populations should be changed to 12.6; 12.5 Drug Interactions not listed in TOC and should be changed to 12.7. 12.4, by guidance, is reserved for Microbiology and 12.5, for Pharmacogenomics.*

NO 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment: *WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS*

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action

12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

YES 42. All text is **bolded**.

Comment:

YES 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment: *Heading not centered in box.*

YES 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

YES 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. 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:

N/A 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

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

/s/

KIMBERLY A SHILEY
11/08/2012

MARGARET M KOBER
11/08/2012